Penicillin

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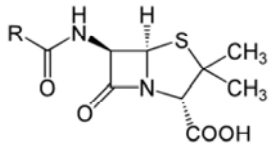
Penicillin (**PCN** or **pen**) is a group of antibiotics which include penicillin G (intravenous use), penicillin V (use by mouth), and procaine penicillin, and benzathine penicillin (intramuscular use). Penicillin antibiotics were among the first medications to be effective against many bacterial infections caused by staphylococci and streptococci. Penicillins are still widely used today, though many types of bacteria have developed resistance following extensive use.

About 10% of people report that they are allergic to penicillin; however, up to 90% of this group may not actually be allergic.[2] Serious allergies only occur in about 0.03%.[2] All penicillins are β-lactam antibiotics.

Penicillin was discovered in 1928 by Scottish scientist Alexander Fleming.[3] People began using it to treat infections in 1942.[4] There are several enhanced penicillin families which are effective against additional bacteria; these include the antistaphylococcal penicillins, aminopenicillins and the antipseudomonal penicillins. They are derived from *Penicillium* fungi.[5]

Penicillin



Penicillin core structure, where "R" is the variable group

Clinical data	
AHFS/Drugs.com	Micromedex Detailed Consumer Information (https://www.drugs.com/cons/penicillin-oral-injection-intravenous-intramuscular.html.html)
Pregnancy category	US: B (No risk in non-human studies) [1]
Routes of administration	Intravenous, intramuscular, by mouth
Legal status	
Legal status	℞ (Prescription only)
Pharmacokinetic data	
Metabolism	Hepatic
Biological half-life	between 0.5 and 56 hours
Excretion	Kidneys
ChemSpider	none
Chemical and physical data	
Formula	$C_9H_{11}N_2O_4S$
Molar mass	243.26 g·mol^{-1}

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Medical uses

The term "penicillin" is often used generically to refer to benzylpenicillin (penicillin G, the original penicillin found in 1928), procaine benzylpenicillin (procaine penicillin), benzathine benzylpenicillin (benzathine penicillin), and phenoxymethylpenicillin (penicillin V). Procaine penicillin and benzathine penicillin have the same antibacterial activity as benzylpenicillin but act for a longer period of time. Phenoxymethylpenicillin is less active against gram-negative bacteria than benzylpenicillin.[6][7] Benzylpenicillin, procaine penicillin and benzathine penicillin can be given by intravenous or intramuscular injections, but phenoxymethylpenicillin can be given by mouth because of its acidic stability.[8]

Susceptibility

While the number of penicillin-resistant bacteria is increasing, penicillin can still be used to treat a wide range of infections caused by certain susceptible bacteria, including Streptococci, Staphylococci, Clostridium, and Listeria genera. The following list illustrates minimum inhibitory concentration susceptibility data for a few medically significant bacteria:[9][10]

- *Listeria monocytogenes*: from less than or equal to 0.06 μg/ml to 0.25 μg/ml
- *Neisseria meningitidis*: from less than or equal to 0.03 μg/ml to 0.5 μg/ml
- *Staphylococcus aureus*: from less than or equal to 0.015 μg/ml to more than 32 μg/ml

Adverse effects

Common adverse drug reactions (≥ 1% of people) associated with use of the penicillins include diarrhoea, hypersensitivity, nausea, rash, neurotoxicity, urticaria, and superinfection (including candidiasis). Infrequent adverse effects (0.1–1% of people) include fever, vomiting, erythema, dermatitis, angioedema, seizures (especially in people with epilepsy), and pseudomembranous colitis.[11]

About 10% of people report that they are allergic to penicillin; however, 90% of this group are not actually allergic.[2] Serious allergies only occur in about 0.03%.[2]

Penicillin can also induce serum sickness or a serum sickness-like reaction in some individuals. Serum sickness is a type III hypersensitivity reaction that occurs one to three weeks after exposure to drugs including penicillin. It is not a true drug allergy, because allergies are type I hypersensitivity reactions, but repeated exposure to the offending agent can result in an anaphylactic reaction.[12]

Pain and inflammation at the injection site is also common for parenterally administered benzathine benzylpenicillin, benzylpenicillin, and, to a lesser extent, procaine benzylpenicillin.

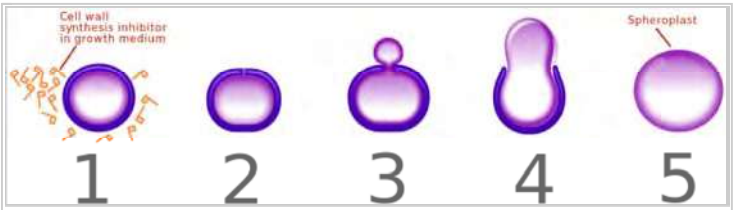
Although penicillin is still the most commonly reported allergy, less than 20% of people who believe that they have a penicillin allergy are truly allergic to penicillin;[13] nevertheless, penicillin is still the most common cause of severe allergic drug reactions. Significantly, there is an immunologic reaction to Streptolysin S, a toxin released by certain killed bacteria and associated with Penicillin injection, that can cause fatal cardiac syncope.[14]

Allergic reactions to any β-lactam antibiotic may occur in up to 1% of patients receiving that agent.[15] The allergic reaction is a Type I hypersensitivity reaction. Anaphylaxis will occur in approximately 0.01% of patients.[11] It has previously been accepted that there was up to a 10% cross-sensitivity between penicillin-derivatives, cephalosporins, and carbapenems, due to the sharing of the β-lactam ring.[16][17] Assessments in 2006 found no more risk for cross-allergy for second-generation or later cephalosporins than the first generation. However, as a general risk, research shows that all beta lactams have the intrinsic hazard of very serious hazardous reactions in susceptible patients. Only the frequency of these reactions vary, based on the structure.[18][19]

Papers in 2006 showed that a major feature in determining frequency of immunological reactions is the similarity of the side chains (e.g., first generation cephalosporins are similar to penicillins); this is why the β-lactams are associated with different frequencies of serious reactions (e.g., anaphylaxis).[20]

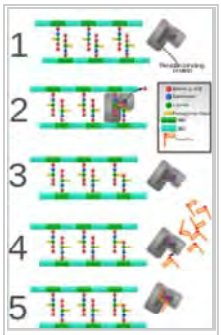
Mechanism of action

Bacteria constantly remodel their peptidoglycan cell walls, simultaneously building and breaking down portions of the cell wall as they grow and divide. *β*-Lactam antibiotics inhibit the formation of peptidoglycan cross-links in the bacterial cell wall; this is achieved through binding of the four-membered *β*-lactam ring of penicillin to the enzyme DD-transpeptidase. As a consequence, DD-transpeptidase cannot catalyze formation of these cross-links, and an imbalance between cell wall production and degradation develops, causing the cell to rapidly die.



Bacteria that attempt to grow and divide in the presence of penicillin fail to do so, and instead end up shedding their cell walls.

The enzymes that hydrolyze the peptidoglycan cross-links continue to function, even while those that form such cross-links do not. This weakens the cell wall of the bacterium, and osmotic pressure becomes increasingly uncompensated—eventually causing cell death (cytolysis). In addition, the build-up of peptidoglycan precursors triggers the activation of bacterial cell wall hydrolases and autolysins, which further digest the cell wall's peptidoglycans. The small size of the penicillins increases their potency, by allowing them to penetrate the entire depth of the cell wall. This is in contrast to the glycopeptide antibiotics vancomycin and teicoplanin, which are both much larger than the penicillins.[21]



Penicillin and other β-lactam antibiotics act by inhibiting penicillin-binding proteins, which normally catalyze cross-linking of bacterial cell walls.

Gram-positive bacteria are called protoplasts when they lose their cell walls. Gram-negative bacteria do not lose their cell walls completely and are called spheroplasts after treatment with penicillin.

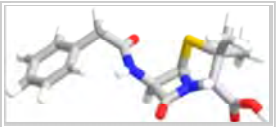
Penicillin shows a synergistic effect with aminoglycosides, since the inhibition of peptidoglycan synthesis allows aminoglycosides to penetrate the bacterial cell wall more easily, allowing their disruption of bacterial protein synthesis within the cell. This results in a lowered MBC for susceptible organisms.[22]

Penicillins, like other *β*-lactam antibiotics, block not only the division of bacteria, including cyanobacteria, but also the division of cyanelles, the photosynthetic organelles of the glaucophytes, and the division of chloroplasts of bryophytes. In contrast, they have no effect on the plastids of the highly developed vascular plants. This supports the endosymbiotic theory of the evolution of plastid division in land plants.[23]

The chemical structure of penicillin is triggered with a very precise, pH-dependent directed mechanism, effected by a unique spatial assembly of molecular components, which can activate by protonation. It can travel through bodily fluids, targeting and inactivating enzymes responsible for cell-wall synthesis in gram-positive bacteria, meanwhile avoiding the surrounding non-targets. Penicillin can protect itself from spontaneous hydrolysis in the body in its anionic form, while storing its potential as a strong acylating agent, activated only upon approach to the target transpeptidase enzyme and protonated in the active centre. This targeted protonation neutralizes the carboxylic acid moiety, which is weakening of the β-lactam ring N–C(=O) bond, resulting in a self-activation. Specific structural requirements are equated to constructing the perfect mouse trap for catching targeted prey.[24]

Structure

The term "penam" is used to describe the common core skeleton of a member of the penicillins. This core has the molecular formula R-$C_9H_{11}N_2O_4S$, where R is the variable side chain that differentiates the penicillins from one another. The penam core has a molecular weight of 243 g/mol, with larger penicillins having molecular weights near 450—for example, cloxacillin has a molecular weight of 436 g/mol. The key structural feature of the penicillins is the four-membered *β*-lactam ring; this structural moiety is essential for penicillin's antibacterial activity. The *β*-lactam ring is itself fused to a five-membered thiazolidine ring. The fusion of these two rings causes the *β*-lactam ring to be more reactive than monocyclic *β*-lactams because the two fused rings distort the *β*-lactam amide bond and therefore remove the resonance stabilisation normally found in these chemical bonds.[25]


Chemical structure of Penicillin G. The sulfur and nitrogen of the five-membered thiazolidine ring are shown in yellow and blue respectively. The image shows that the thiazolidine ring and fused four-membered *β*-lactam are not in the same plane.

History

Discovery

Starting in the late 19th century there had been many accounts by scientists and physicians on the antibacterial properties of the different types of moulds including the mould penicillium but they were unable to discern what process was causing the effect.[26] The effects of penicillium mould would finally be isolated in 1928 by Scottish scientist Alexander Fleming, in work that seems to have been independent of those earlier observations.[27] Fleming recounted that the date of his discovery of penicillin was on the morning of Friday 28 September 1928.[28] The traditional version of this story describes the discovery as a serendipitous accident: in his laboratory in the basement of St Mary's Hospital in London (now part of Imperial College), Fleming noticed a Petri dish containing Staphylococcus that had been mistakenly left open was contaminated by blue-green mould from an open window, which formed a visible growth.[29] There was a halo of inhibited bacterial growth around the mould. Fleming concluded that the mould released a substance that repressed the growth and caused lysing of the bacteria.[30]

Alexander Fleming, who is credited with discovering penicillin in 1928.

Once Fleming made his discovery he grew a pure culture and discovered it was a *Penicillium* mould, now known to be *Penicillium notatum*. Fleming coined the term "penicillin" to describe the filtrate of a broth culture of the *Penicillium* mould. Fleming asked C. J. La Touche to help identify the mould, which he incorrectly identified as *Penicillium rubrum* (later corrected by Charles Thom). He expressed initial optimism that penicillin would be a useful disinfectant, because of its high potency and minimal toxicity in comparison to antiseptics of the day, and noted its laboratory value in the isolation of *Bacillus influenzae* (now called *Haemophilus influenzae*).[29][31]

Sample of penicillium mould presented by Alexander Fleming to Douglas Macleod, 1935

Fleming was a famously poor communicator and orator, which meant his findings were not initially given much attention.[29] He was unable to convince a true chemist to help him extract and stabilize the antibacterial compound found in the broth filtrate. Despite the lack of a true chemist, he remained interested in the potential use of penicillin and presented a paper entitled "A Medium for the Isolation of Pfeiffer's Bacillus" to the Medical Research Club of London, which was met with little interest and even less enthusiasm by his peers. Had Fleming been more successful at making other scientists interested in his work, penicillin for medicinal use would possibly have been developed years earlier.[29]

Despite the lack of interest of his fellow scientists, he did conduct several experiments on the antibiotic substance he discovered. The most important result proved it was nontoxic in humans by first performing toxicity tests in animals and then on humans. His following experiments on penicillin's response to heat and pH allowed Fleming to increase the stability of the compound.[31] The one test that modern scientists would find missing from his work was the test of penicillin on an infected animal, the results of which would likely have sparked great interest in penicillin and sped its development by almost a decade.[29]

Medical application

In 1930, Cecil George Paine, a pathologist at the Royal Infirmary in Sheffield, attempted to use penicillin to treat sycosis barbae, eruptions in beard follicles, but was unsuccessful. Moving on to ophthalmia neonatorum, a gonococcal infection in infants, he achieved the first recorded cure with penicillin, on November 25, 1930. He then cured four additional patients (one adult and three infants) of eye infections, and failed to cure a fifth.[32][33][34]

Florey (pictured), Fleming and Chain shared a Nobel Prize in 1945 for their work on penicillin.

In 1939, Australian scientist Howard Florey (later Baron Florey) and a team of researchers (Ernst Boris Chain, Arthur Duncan Gardner, Norman Heatley, M. Jennings, J. Orr-Ewing and G. Sanders) at the Sir William Dunn School of Pathology, University of Oxford made progress in showing the *in vivo* bactericidal action of penicillin. In 1940, they showed that penicillin effectively cured bacterial infection in mice.[35][36] In 1941, they treated a policeman, Albert Alexander, with a severe face infection; his condition improved, but then supplies of penicillin ran out and he died. Subsequently, several other patients were treated successfully.[37]

Mass production

A technician preparing penicillin in 1943

By late 1940, the Oxford team under Howard Florey had devised a method of mass-producing the drug, but yields remained low.[37] In 1941, Florey and Heatley travelled to the US in order to interest pharmaceutical companies in producing the drug and inform them about their process.[37]

Florey and Chain shared the 1945 Nobel Prize in Medicine with Fleming for their work.

The challenge of mass-producing this drug was daunting. On March 14, 1942, the first patient was treated for streptococcal septicemia with US-made penicillin produced by Merck & Co.[38] Half of the total supply produced at the time was used on that one patient. By June 1942, just enough US penicillin was available to treat ten patients.[39] In July 1943, the War Production Board drew up a plan for the mass distribution of penicillin stocks to Allied troops fighting in Europe.[40] The results of fermentation research on corn steep liquor at the Northern Regional Research Laboratory at Peoria, Illinois, allowed the United States to produce 2.3 million doses in time for the invasion of Normandy in the spring of 1944. After a worldwide search in 1943, a mouldy cantaloupe in a Peoria, Illinois market was found to contain the best strain of mould for production using the corn steep liquor process.[41] In 1941–1944, Jasper H. Kane developed the practical, deep-tank fermentation method for production of large quantities of pharmaceutical-grade penicillin. Large-scale production resulted from the development of a deep-tank fermentation plant by chemical engineer Margaret Hutchinson Rousseau.[42] As a direct result of the war and the War Production Board, by June 1945, over 646 billion units per year were being produced.[40]

G. Raymond Rettew made a significant contribution to the American war effort by his techniques to produce commercial quantities of penicillin.[43] During World War II, penicillin made a major difference in the number of deaths and amputations caused by infected wounds among Allied forces, saving an estimated 12%–15% of lives. Availability was severely limited, however, by the difficulty of manufacturing large quantities of penicillin and by the rapid renal clearance of the drug, necessitating frequent dosing. Methods for mass production of penicillin were patented by Andrew Jackson Moyer in 1945.[44][45][46] Florey had not patented penicillin, having been advised by Sir Henry Dale that doing so would be unethical.[37]

Penicillin is actively excreted, and about 80% of a penicillin dose is cleared from the body within three to four hours of administration. Indeed, during the early penicillin era, the drug was so scarce and so highly valued that it became common to collect the urine from patients being treated, so that the penicillin in the urine could be isolated and reused.[47] This was not a satisfactory solution, so researchers looked for a way to slow penicillin excretion. They hoped to find a molecule that could compete with penicillin for the organic acid transporter responsible for excretion, such that the transporter would preferentially excrete the competing molecule and the penicillin would be retained.

The uricosuric agent probenecid proved to be suitable. When probenecid and penicillin are administered together, probenecid competitively inhibits the excretion of penicillin, increasing penicillin's concentration and prolonging its activity. Eventually, the advent of mass-production techniques and semi-synthetic penicillins resolved the supply issues, so this use of probenecid declined.[47] Probenecid is still useful, however, for certain infections requiring particularly high concentrations of penicillins.[11]

After World War II, Australia was the first country to make the drug available for civilian use. In the U.S., penicillin was made available to the general public on March 15, 1945.[48]

Penicillin was being mass-produced in 1944.


Dorothy Hodgkin determined the chemical structure of penicillin.

Structure determination and total synthesis

In 1945 the chemical structure of penicillin was determined using X-ray crystallography by Dorothy Crowfoot Hodgkin, who was also working at Oxford.[49] She later received the Nobel prize for this and other structure determinations.

Chemist John C. Sheehan at the Massachusetts Institute of Technology (MIT) completed the first chemical synthesis of penicillin in 1957.[50][51][52] Sheehan had started his studies into penicillin synthesis in 1948, and during these investigations developed new methods for the synthesis of peptides, as well as new protecting groups—groups that mask the reactivity of certain functional groups.[52][53] Although the initial synthesis developed by Sheehan was not appropriate for mass production of penicillins, one of the intermediate compounds in Sheehan's synthesis was 6-aminopenicillanic acid (6-APA), the nucleus of penicillin.[52][54][55] Attaching different groups to the 6-APA 'nucleus' of penicillin allowed the creation of new forms of penicillin.


Dorothy Hodgkin's model of penicillin's structure.

Developments from penicillin

The narrow range of treatable diseases or "spectrum of activity" of the penicillins, along with the poor activity of the orally active phenoxymethylpenicillin, led to the search for derivatives of penicillin that could treat a wider range of infections. The isolation of 6-APA, the nucleus of penicillin, allowed for the preparation of semisynthetic penicillins, with various improvements over benzylpenicillin (bioavailability, spectrum, stability, tolerance).

The first major development was ampicillin in 1961. It offered a broader spectrum of activity than either of the original penicillins. Further development yielded β-lactamase-resistant penicillins, including flucloxacillin, dicloxacillin, and methicillin. These were significant for their activity against β-lactamase-producing bacterial species, but were ineffective against the methicillin-resistant *Staphylococcus aureus* (MRSA) strains that subsequently emerged.

Another development of the line of true penicillins was the antipseudomonal penicillins, such as carbenicillin, ticarcillin, and piperacillin, useful for their activity against Gram-negative bacteria. However, the usefulness of the β-lactam ring was such that related antibiotics, including the mecillinams, the carbapenems and, most important, the cephalosporins, still retain it at the center of their structures.[56]

Production

Penicillin is a secondary metabolite of certain species of *Penicillium* and is produced when growth of the fungus is inhibited by stress. It is not produced during active growth. Production is also limited by feedback in the synthesis pathway of penicillin.


A 1957 fermentor (bioreactor) used to grow *Penicillium* mould.

α-ketoglutarate + AcCoA → homocitrate → L-α-aminoadipic acid → L-lysine + β-lactam

The by-product, L-lysine, inhibits the production of homocitrate, so the presence of exogenous lysine should be avoided in penicillin production.

The *Penicillium* cells are grown using a technique called fed-batch culture, in which the cells are constantly subject to stress, which is required for induction of penicillin production. The available carbon sources are also important: Glucose inhibits penicillin production, whereas lactose does not. The pH and the levels of nitrogen, lysine, phosphate, and oxygen of the batches must also be carefully controlled.

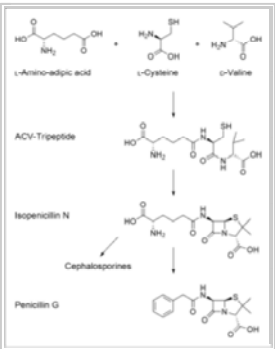
The biotechnological method of directed evolution has been applied to produce by mutation a large number of *Penicillium* strains. These techniques include error-prone PCR, DNA shuffling, ITCHY, and strand-overlap PCR.

Semisynthetic penicillins are prepared starting from the penicillin nucleus 6-APA.

Biosynthesis

Overall, there are three main and important steps to the biosynthesis of penicillin G (benzylpenicillin).

- The first step is the condensation of three amino acids—L-α-aminoadipic acid, L-cysteine, L-valine into a tripeptide.[57][58][59] Before condensing into the tripeptide, the amino acid L-valine must undergo epimerization to become D-valine.[60][61] The condensed tripeptide is named δ-(L-α-aminoadipyl)-L-cysteine-D-valine (ACV). The condensation reaction and epimerization are both catalyzed by the enzyme δ-(L-α-aminoadipyl)-L-cysteine-D-valine synthetase (ACVS), a nonribosomal peptide synthetase or NRPS.
- The second step in the biosynthesis of penicillin G is the oxidative conversion of linear ACV into the bicyclic intermediate isopenicillin N by isopenicillin N synthase (IPNS), which is encoded by the gene *pcbC*.[57][58] Isopenicillin N is a very weak intermediate, because it does not show strong antibiotic activity.[60]
- The final step is a transamidation by isopenicillin N N-acyltransferase, in which the α-aminoadipyl side-chain of isopenicillin N is removed and exchanged for a phenylacetyl side-chain. This reaction is encoded by the gene *penDE*, which is unique in the process of obtaining penicillins.[57]



Penicillin G biosynthesis

Members

Natural penicillins

- Penicillin G
- Penicillin K
- Penicillin N
- Penicillin O
- Penicillin V

β-lactamase-resistant

- Methicillin
- Nafcillin
- Oxacillin
- Cloxacillin
- Dicloxacillin
- Flucloxacillin

Aminopenicillins

- Ampicillin
- Amoxicillin
- Pivampicillin
- Hetacillin
- Bacampicillin
- Metampicillin
- Talampicillin
- Epicillin

Carboxypenicillins

- Carbenicillin
- Ticarcillin
- Temocillin

Ureidopenicillins

- Mezlocillin
- Piperacillin

See also

- Medicinal fungi
- Penicillinase

Notes

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- Penicillin (http://www.periodicvideos.com/videos/mv_penicillin.htm) at *The Periodic Table of Videos* (University of Nottingham)
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