

Blood transfusion

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Blood transfusion is generally the process of receiving blood or blood products into one's circulation intravenously. Transfusions are used for various medical conditions to replace lost components of the blood. Early transfusions used whole blood, but modern medical practice commonly uses only components of the blood, such as red blood cells, white blood cells, plasma, clotting factors, and platelets.

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Blood transfusion

Intervention



Plastic bag with 0.5–0.7 liters containing packed red blood cells in citrate, phosphate, dextrose, and adenine (CPDA) solution

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MeSH D001803

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- 12.1 Blood Transfusion Societies
- 12.2 Blood Establishment Alliances
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Medical uses

Historically, red blood cell transfusion was considered when the hemoglobin level fell below 10 g/dL or hematocrit falls below 30% (the "10/30 rule").^{[1][2]} Because each unit of blood given carries risks, a trigger level lower than that at 7–8 g/dL is now usually used as it has been shown to have better patient outcomes.^{[3][4]} The administration of a single unit of blood is the standard for hospitalized people who are not bleeding, with this treatment then followed with re-assessment and consideration of symptoms and hemoglobin concentration.^[3] Patients with poor oxygen saturation^[3] may need more blood.^[3] The advisory caution to use blood transfusion only with more severe anemia is in part due to evidence that outcomes are worsened if larger amounts are given.^[5] One may consider transfusion for people with symptoms of cardiovascular disease such as chest pain or shortness of breath.^[2] In cases where patients have low levels of hemoglobin but are cardiovascularly stable, parenteral iron is a preferred option based on both efficacy and safety.^[6] Other blood products are given where appropriate, such as clotting deficiencies.

Procedure

Before a blood transfusion is given, there are many steps taken to ensure quality of the blood products, compatibility, and safety to the recipient. In 2012, a national blood policy was in place in 70% of countries and 62% of countries had specific legislation that covers the safety and quality of blood transfusion.^[7]

Blood donation

Blood transfusions typically use sources of blood: one's own (autologous transfusion), or someone else's (allogeneic or homologous transfusion). The latter is much more common than the former. Using another's blood must first start with donation of blood. Blood is most commonly donated as whole blood intravenously and collecting it with an anticoagulant. In developed countries, donations are usually anonymous to the recipient, but products in a blood bank are always individually traceable through the whole cycle of donation, testing, separation into components, storage, and administration to the recipient. This enables management and investigation of any suspected transfusion related disease transmission or transfusion reaction. In developing countries the donor is sometimes specifically recruited by or for the recipient, typically a family member, and the donation occurs immediately before the transfusion.

Processing and testing

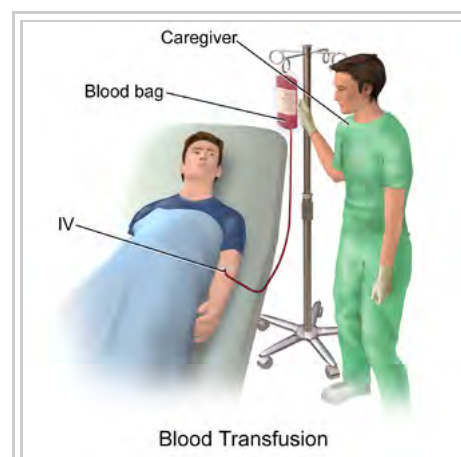


Illustration depicting intravenous blood transfusion

Donated blood is usually subjected to processing after it is collected, to make it suitable for use in specific patient populations. Collected blood is then separated into blood components by centrifugation: red blood cells, plasma, platelets, albumin protein, clotting factor concentrates, cryoprecipitate, fibrinogen concentrate, and immunoglobulins (antibodies). Red cells, plasma and platelets can also be donated individually via a more complex process called apheresis.

- The World Health Organization (WHO) recommends that all donated blood be tested for transfusion transmissible infections. These include HIV, Hepatitis B, Hepatitis C, *Treponema pallidum* (syphilis) and, where relevant, other infections that pose a risk to the safety of the blood supply, such as *Trypanosoma cruzi* (Chagas disease) and *Plasmodium* species (malaria).^[8] According to the WHO, 25 countries are not able to screen all donated blood for one or more of: HIV; Hepatitis B; Hepatitis C; or syphilis.^[9] One of the main reasons for this is because testing kits are not always available.^[9] However the prevalence of transfusion-transmitted infections is much higher in low income countries compared to middle and high income countries.^[9]
- All donated blood should also be tested for the ABO blood group system and Rh blood group system to ensure that the patient is receiving compatible blood.^[10]
- In addition, in some countries platelet products are also tested for bacterial infections due to its higher inclination for contamination due to storage at room temperature.^{[11][12]} Presence of Cytomegalovirus (CMV) may also be tested because of the risk to certain immunocompromised recipients if given, such as those with organ transplant or HIV. However, not all blood is tested for CMV because only a certain amount of CMV-negative blood needs to be available to supply patient needs. Other than positivity for CMV, any products tested positive for infections are not used.^[13]
- Leukocyte reduction is the removal of white blood cells by filtration. Leukoreduced blood products are less likely to cause HLA alloimmunization (development of antibodies against specific blood types), febrile non-hemolytic transfusion reaction, cytomegalovirus infection, and platelet-transfusion refractoriness.^[14]
- Pathogen Reduction treatment that involves, for example, the addition of riboflavin with subsequent exposure to UV light has been shown to be effective in inactivating pathogens (viruses, bacteria, parasites and white blood cells) in blood products.^{[15][16][17]} By inactivating white blood cells in donated blood products, riboflavin and UV light treatment can also replace gamma-irradiation as a method to prevent graft-versus-host disease (TA-GvHD).^{[18][19][20]}



A bag containing one unit of fresh frozen plasma

Compatibility testing

Before a recipient receives a transfusion, compatibility testing between donor and recipient blood must be done. The first step before a transfusion is given is to type and screen the recipient's blood. Typing of recipient's blood determines the ABO and Rh status. The sample is then screened for any alloantibodies that may react with donor blood.^[21] It takes about 45 minutes to complete (depending on the method used). The blood bank scientist also checks for special requirements of the patient (e.g. need for washed, irradiated or CMV negative blood) and the history of the patient to see if they have previously identified antibodies and any other serological anomalies.

A positive screen warrants an antibody panel/investigation to determine if it is clinically significant. An antibody panel consists of commercially prepared group O red cell suspensions from donors that have been phenotyped for antigens that correspond to commonly encountered and clinically significant alloantibodies. Donor cells may have heterozygous (e.g. K+k⁻), homozygous (K+k⁺) expression or no expression of various antigens (K-k⁻). The phenotypes of all the donor cells being tested are shown in a chart. The patient's serum is tested against the various donor cells. Based on the reactions of the patient's serum against the donor cells, a pattern will emerge to confirm the presence of one or more antibodies. Not all antibodies are clinically significant (i.e. cause transfusion reactions, HDN, etc.). Once the patient has developed a clinically significant antibody it is vital that the patient receive antigen-negative red blood cells to prevent future transfusion reactions. A direct antiglobulin test (Coombs test) is also performed as part of the antibody investigation.^[22]






























If there is no antibody present, an immediate spin crossmatch or computer assisted crossmatch is performed where the recipient serum and donor rbc are incubated. In the immediate spin method, two drops of patient serum are tested against a drop of 3–5% suspension of donor cells in a test tube and spun in a serofuge. Agglutination or hemolysis (i.e., positive Coombs test) in the test tube is a positive reaction and the unit should not be transfused.

If an antibody is suspected, potential donor units must first be screened for the corresponding antigen by phenotyping them. Antigen negative units are then tested against the patient plasma using an antiglobulin/indirect crossmatch technique at 37 degrees Celsius to enhance reactivity and make the test easier to read.

In urgent cases where crossmatching cannot be completed, and the risk of dropping hemoglobin outweighs the risk transfusing uncrossmatched blood, O-negative blood is used, followed by crossmatch as soon as possible. O-negative is also used for children and women of childbearing age. It is preferable for the laboratory to obtain a pre-transfusion sample in these cases so a type and screen can be performed to determine the actual blood group of the patient and to check for alloantibodies.

Compatibility of ABO and Rh system

This chart shows possible matches in blood transfusion between donor and receiver using ABO and Rh system.

		Donor							
		0-	0+	B-	B+	A-	A+	AB-	AB+
Receiver	AB+								
	AB-								
	A+								
	A-								
	B+								
	B-								
	0+								
	0-								

Adverse effects

In the same way that the safety of pharmaceutical products are overseen by pharmacovigilance, the safety of blood and blood products are overseen by haemovigilance. This is defined by the World Health Organization (WHO) as a system "...to identify and prevent occurrence or recurrence of transfusion related unwanted events, to increase the safety, efficacy and efficiency of blood transfusion, covering all activities of the transfusion chain from donor to recipient." The system should include monitoring, identification, reporting, investigation and analysis of adverse events near-misses and reactions related to transfusion and manufacturing.^[23] In the UK this data is collected by an independent organisation called SHOT (Serious Hazards Of Transfusion).^[24]

Transfusions of blood products are associated with several complications, many of which can be grouped as immunological or infectious. There is controversy on potential quality degradation during storage.^[25]

Immunologic reaction

- Acute hemolytic reactions** are defined according to Serious Hazards of Transfusion (SHOT) as "fever and other symptoms/signs of haemolysis within 24 hours of transfusion; confirmed by one or more of the following: a fall of Hb, rise in lactate dehydrogenase (LDH), positive direct antiglobulin test (DAT), positive crossmatch"^[26] This is due to destruction of donor red blood cells by preformed recipient antibodies. Most often this occurs due to clerical errors or improper ABO blood typing and crossmatching resulting in a mismatch in ABO blood type between the donor and the recipient. Symptoms include fever, chills, chest pain, back pain, hemorrhage, increased heart rate, shortness of breath, and rapid drop in blood pressure. When suspected, transfusion should be stopped immediately, and blood sent for tests to evaluate for presence of hemolysis. Treatment is supportive. Kidney injury may occur due to the effects of the hemolytic reaction (pigment nephropathy). In the USA in 2011 there were 48 episodes of acute hemolysis due to a mismatch in ABO blood type (1 in 495,207 blood components transfused) and 168 episodes of hemolysis due to other causes (1 in 124,525 blood components transfused).^[27] In the UK in 2014 there were 18 episodes of hemolysis due to other causes (1 in 147,972 blood components transfused).^[26]

- *Delayed hemolytic reactions* occur more than 24 hours after a transfusion,^[26] and occur more frequently (1 in 20,569 blood components transfused in the USA in 2011).^[27] They are due to the same mechanism as in acute hemolytic reactions. However, the consequences are generally mild and a great proportion of patients may not have symptoms. However, evidence of hemolysis and falling hemoglobin levels may still occur. Treatment is generally not needed, but due to the presence of recipient antibodies, future compatibility may be affected.
- *Febrile nonhemolytic reactions* are the most common type of blood transfusion reaction and occur due to the release of inflammatory chemical signals released by white blood cells in stored donor blood. This type of reaction occurs in about 7% of transfusions. Fever is generally short lived and is treated with antipyretics, and transfusions may be finished as long as an acute hemolytic reaction is excluded. This is a reason for the now-widespread use of leukoreduction – the filtration of donor white cells from red cell product units.^[14]
- *Allergic reactions* may occur when the recipient has preformed antibodies to certain chemicals in the donor blood, and does not require prior exposure to transfusions. Symptoms include hives, itching, low blood pressure, and respiratory distress which may lead to anaphylactic shock. Treatment is the same as for any other type 1 hypersensitivity reactions and includes administering intramuscular epinephrine, glucocorticoids, antihistamines, medications to keep the blood pressure from dropping, and mechanical ventilation if needed. A small population (0.13%) of patients are deficient in the immunoglobulin IgA, and upon exposure to IgA-containing blood, may develop an anaphylactic reaction.
- *Posttransfusion purpura* is a rare complication that occurs after transfusion of red cells or platelets and is associated with the presence antibodies in the patient's blood directed against the HPA (human platelet antigen) systems (only one case was reported in the UK in 2014).^[26] Recipients who lack this protein develop sensitization to this protein from prior transfusions or previous pregnancies, and develop thrombocytopenia about 5 to 12 days after subsequent transfusions. Treatment is with intravenous immunoglobulin.^[28]
- Transfusion-associated acute lung injury (TRALI) is a syndrome of acute respiratory distress, often associated with fever, non-cardiogenic pulmonary edema, and hypotension, which may occur as often as 1 in 2000 transfusions.^[29] Symptoms can range from mild to life-threatening, but most patients recover fully within 96 hours, and the mortality rate from this condition is less than 10%.^[30] Although the cause of TRALI is not clear, it has been consistently associated with anti-HLA antibodies. Because these types of antibodies are commonly formed during pregnancy, several transfusion organisations have decided to use only plasma from men for transfusion.^[31] TRALI is typically associated with plasma components rather than packed red blood cells (RBCs), though there is some residual plasma in RBC units.^[31]

Infection

The use of greater amount of red blood cells is associated with a high risk of infections. In those who were given red blood only with significant anemia infection rates were 12% while in those who were given red blood at milder levels of anemia infection rates were 17%.^[32]

On rare occasion, blood products are contaminated with bacteria. This can result in life-threatening infection, also known as transfusion-transmitted bacterial infection. The risk of severe bacterial infection is estimated, as of 2002, at about 1 in 50,000 platelet transfusions, and 1 in 500,000 red blood cell transfusions.^[33] Blood product contamination, while rare, is still more common than actual infection. The reason platelets are more often contaminated than other blood products is that they are stored at room temperature for short periods of time. Contamination is also more common with longer duration of storage, especially when exceeding 5 days. Sources of contaminants include the donor's blood, donor's skin, phlebotomist's skin, and from containers.

Contaminating organisms vary greatly, and include skin flora, gut flora, or environmental organisms. There are many strategies in place at blood donation centers and laboratories to reduce the risk of contamination. A definite diagnosis of transfusion-transmitted bacterial infection includes the identification of a positive culture in the recipient (without an alternative diagnosis) as well as the identification of the same organism in the donor blood.

Since the advent of HIV testing of donor blood in the 1980s, the transmission of HIV during transfusion has dropped dramatically. Prior testing of donor blood only included testing for antibodies to HIV. However, due to latent infection (the "window period" in which an individual is infectious, but has not had time to develop antibodies), many cases of HIV seropositive blood were missed. The development of a nucleic acid test for the HIV-1 RNA has dramatically lowered the rate of donor blood seropositivity to about 1 in 3 million units. As transmittance of HIV does not necessarily mean HIV infection, the latter could still occur, at an even lower rate.

The transmission of hepatitis C via transfusion currently stands at a rate of about 1 in 2 million units. As with HIV, this low rate has been attributed to the ability to screen for both antibodies as well as viral RNA nucleic acid testing in donor blood.

Other rare transmissible infections include hepatitis B, syphilis, Chagas disease, cytomegalovirus infections (in immunocompromised recipients), HTLV, and Babesia.

Inefficacy

Transfusion inefficacy or insufficient efficacy of a given unit(s) of blood product, while not itself a "complication" *per se*, can nonetheless indirectly lead to complications – in addition to causing a transfusion to fully or partly fail to achieve its clinical purpose. This can be especially significant for certain patient groups such as critical-care or neonatals.

For red blood cells (RBC), by far the most commonly transfused product, poor transfusion efficacy can result from units damaged by the so-called storage lesion – a range of biochemical and biomechanical changes that occur during storage. With red cells, this can decrease viability and ability for tissue oxygenation.^[34] Although some of the biochemical changes are reversible after the blood is transfused,^[35] the biomechanical changes are less so,^[36] and rejuvenation products are not yet able to adequately reverse this phenomenon.^[37] There has been controversy about whether a given product unit's age is a factor in transfusion efficacy, specifically about whether "older" blood directly or indirectly increases risks of complications.^{[38][39]} Studies have not been consistent on answering this question,^[40] with some showing that older blood is indeed less effective but with others showing no such difference; these developments are being closely followed by hospital blood bankers – who are the physicians, typically pathologists, who collect and manage inventories of transfusable blood units.

Certain regulatory measures are in place to minimize RBC storage lesion – including a maximum shelf life (currently 42 days), a maximum auto-hemolysis threshold (currently 1% in the US, 0.8% in Europe), and a minimum level of post-transfusion RBC survival *in vivo* (currently 75% after 24 hours).^[41] However, all of these criteria are applied in a universal manner that does not account for differences among units of product.^[42] For example, testing for the post-transfusion RBC survival *in vivo* is done on a sample of healthy volunteers, and then compliance is presumed for all RBC units based on universal (GMP) processing standards (of course, RBC survival by itself does not guarantee efficacy, but it is a necessary prerequisite for cell function, and hence serves as a regulatory proxy). Opinions vary as to the "best" way to determine transfusion efficacy in a patient *in vivo*.^[43] In general, there are not yet any *in vitro* tests to assess quality or predict efficacy for specific units of RBC blood product prior to their transfusion, though there is exploration of potentially relevant tests based

on RBC membrane properties such as erythrocyte deformability^[44] and erythrocyte fragility (mechanical).^[45]

Physicians have adopted a so-called "restrictive protocol" – whereby transfusion is held to a minimum – due in part to the noted uncertainties surrounding storage lesion, in addition to the very high direct and indirect costs of transfusions.^{[46][47][48]} Of course, restrictive protocol is not an option with some especially vulnerable patients who may require the best possible efforts to rapidly restore tissue oxygenation.

Although transfusions of platelets are far less numerous (relative to RBC), platelet storage lesion and resulting efficacy loss is also a concern.^[49]

Other

- A known relationship between intra-operative blood transfusion and cancer recurrence has been established in colorectal cancer.^[50] In lung cancer intra-operative blood transfusion has been associated with earlier recurrence of cancer, worse survival rates and poorer outcomes after lung resection.^{[51][52]}
- Transfusion-associated volume overload is a common complication simply due to the fact that blood products have a certain amount of volume. This is especially the case in recipients with underlying cardiac or kidney disease. Red cell transfusions can lead to volume overload when they must be repeated due to insufficient efficacy (see above). Plasma transfusion is especially prone to causing volume overload due to its hypertonicity.
- Hypothermia can occur with transfusions with large quantities of blood products which normally are stored at cold temperatures. Core body temperature can go down as low as 32 °C and can produce physiologic disturbances. Prevention should be done with warming the blood to ambient temperature prior to transfusions.
- Transfusions with large amounts of red blood cells, whether due to severe hemorrhaging and/or transfusion inefficacy (see above), can lead to an inclination for bleeding. The mechanism is thought to be due to disseminated intravascular coagulation, along with dilution of recipient platelets and coagulation factors. Close monitoring and transfusions with platelets and plasma is indicated when necessary.
- Metabolic alkalosis can occur with massive blood transfusions due to the breakdown of citrate stored in blood into bicarbonate.
- Hypocalcemia can also occur with massive blood transfusions due to the complex of citrate with serum calcium.
- Blood doping is often used by athletes, drug addicts or military personnel for reasons such as to increase physical stamina, to fake a drug detection test or simply to remain active and alert during the duty-times respectively. However a lack of knowledge and insufficient experience can turn a blood transfusion into a sudden death. For example, when individuals run the frozen blood sample directly in their veins this cold blood rapidly reaches the heart, where it disturbs the heart's original pace leading to cardiac arrest and sudden death.

Frequency of use

Globally around 85 million units of red blood cells are transfused in a given year.^[2]

In the United States, blood transfusions were performed nearly 3 million times during hospitalizations in 2011, making it the most common procedure performed. The rate of hospitalizations with a blood transfusion nearly doubled from 1997, from a rate of 40 stays to 95 stays per 10,000 population. It was the most common

procedure performed for patients 45 years of age and older in 2011, and among the top five most common for patients between the ages of 1 and 44 years.^[53]

According to the New York Times: "Changes in medicine have eliminated the need for millions of blood transfusions, which is good news for patients getting procedures like coronary bypasses and other procedures that once required a lot of blood." And, "Blood bank revenue is falling, and the decline may reach \$1.5 billion a year this year [2014] from a high of \$5 billion in 2008." Job losses will reach as high as 12,000 within the next three to five years, roughly a quarter of the total in the industry, according to the Red Cross.^[54]

History

Beginning with William Harvey's experiments on the circulation of blood, research into blood transfusion began in the 17th century, with successful experiments in transfusion between animals. However, successive attempts by physicians to transfuse animal blood into humans gave variable, often fatal, results.

Pope Innocent VIII is sometimes said to have been given "the world's first blood transfusion" by his Jewish physician Giacomo di San Genesio, who had him drink (by mouth) the blood of three 10-year-old boys. The boys subsequently died. The evidence for this story, however, is unreliable and may have been motivated by anti-semitism.^[55]

Early attempts

Animal blood

Working at the Royal Society in the 1660s, the physician Richard Lower began examining the effects of changes in blood volume on circulatory function and developed methods for cross-circulatory study in animals, obviating clotting by closed arteriovenous connections. The new instruments he was able to devise enabled him to perform the first reliably documented successful transfusion of blood in front of his distinguished colleagues from the Royal Society.

According to Lower's account, "...towards the end of February 1665 [I] selected one dog of medium size, opened its jugular vein, and drew off blood, until ... its strength was nearly gone. Then, to make up for the great loss of this dog by the blood of a second, I introduced blood from the cervical artery of a fairly large mastiff, which had been fastened alongside the first, until this latter animal showed ... it was overfilled ... by the inflowing blood." After he "sewed up the jugular veins," the animal recovered "with no sign of discomfort or of displeasure."

Lower had performed the first blood transfusion between animals. He was then "requested by the Honorable [Robert] Boyle ... to acquaint the Royal Society with the procedure for the whole experiment," which he did in December 1665 in the Society's *Philosophical Transactions*.^[56]



Richard Lower pioneered the first blood transfusion from animal to human in 1665 at the Royal Society.

The first blood transfusion from animal to human was administered by Dr. Jean-Baptiste Denys, eminent

physician to King Louis XIV of France, on June 15, 1667.^[57] He transfused the blood of a sheep into a 15-year-old boy, who survived the transfusion.^[58] Denys performed another transfusion into a labourer, who also survived. Both instances were likely due to the small amount of blood that was actually transfused into these people. This allowed them to withstand the allergic reaction.

Denys' third patient to undergo a blood transfusion was Swedish Baron Gustaf Bonde. He received two transfusions. After the second transfusion Bonde died.^[59] In the winter of 1667, Denys performed several transfusions on Antoine Mauroy with calf's blood. On the third account Mauroy died.^[60]

Six months later in London, Lower performed the first human transfusion of animal blood in Britain, where he "superintended the introduction in [a patient's] arm at various times of some ounces of sheep's blood at a meeting of the Royal Society, and without any inconvenience to him." The recipient was Arthur Coga, "the subject of a harmless form of insanity." Sheep's blood was used because of speculation about the value of blood exchange between species; it had been suggested that blood from a gentle lamb might quiet the tempestuous spirit of an agitated person and that the shy might be made outgoing by blood from more sociable creatures. Coga received 20 shillings to participate in the experiment.^[61]

Lower went on to pioneer new devices for the precise control of blood flow and the transfusion of blood; his designs were substantially the same as modern syringes and catheters.^[56] Shortly after, Lower moved to London, where his growing practice soon led him to abandon research.^[62]

These early experiments with animal blood provoked a heated controversy in Britain and France.^[59] Finally, in 1668, the Royal Society and the French government both banned the procedure. The Vatican condemned these experiments in 1670. Blood transfusions fell into obscurity for the next 150 years.

Human blood

The science of blood transfusion dates to the first decade of the 20th century, with the discovery of distinct blood types leading to the practice of mixing some blood from the donor and the receiver before the transfusion (an early form of cross-matching).

In the early 19th century, British obstetrician Dr. James Blundell made efforts to treat hemorrhage by transfusion of human blood using a syringe. In 1818 following experiments with animals, he performed the first successful transfusion of human blood to treat postpartum hemorrhage. Blundell used the patient's husband as a donor, and extracted four ounces of blood from his arm to transfuse into his wife. During the years 1825 and 1830, Blundell performed 10 transfusions, five of which were beneficial, and published his results. He also invented a number of instruments for the transfusion of blood.^[63] He made a substantial amount of money from this endeavour, roughly \$2 million (\$50 million real dollars).^[64]

In 1840, at St George's Hospital Medical School in London, Samuel Armstrong Lane, aided by Dr. Blundell, performed the first successful whole blood transfusion to treat haemophilia.

However, early transfusions were risky and many resulted in the death of the patient. By the late 19th century,



James Blundell, successfully transfused human blood in 1818.

blood transfusion was regarded as a risky and dubious procedure, and was largely shunned by the medical establishment.

Work to emulate James Blundell continued in Edinburgh. In 1845 the *Edinburgh Journal* described the successful transfusion of blood to a woman with severe uterine bleeding. Subsequent transfusions were successful with patients of Professor James Young Simpson after whom the Simpson Memorial Hospital in Edinburgh was named.^[65]

The largest series of early successful transfusions took place at the Edinburgh Royal Infirmary between 1885 and 1892. Edinburgh later became the home of the first blood donation and blood transfusion services.^[65]

Modern era

It was not until 1901, when the Austrian Karl Landsteiner discovered three human blood groups (O, A, and B), that blood transfusion was put onto a scientific basis and became safer.

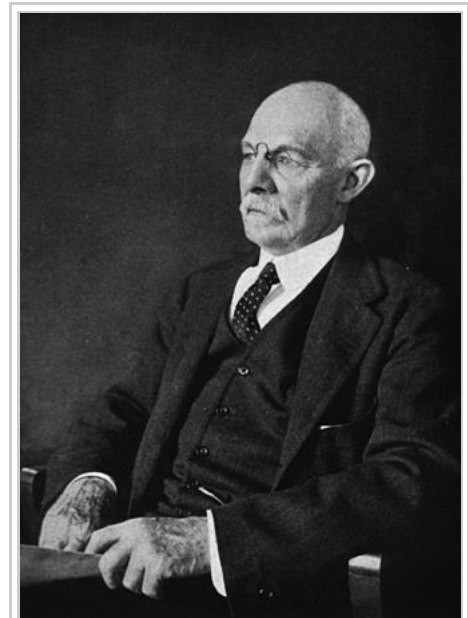
Landsteiner discovered that adverse effects arise from mixing blood from two incompatible individuals. He found that when incompatible types are mixed, an immune response is triggered and the red blood cells clump. The immunological reaction occurs when the receiver of a blood transfusion has antibodies against the donor blood cells. The destruction of red blood cells releases free hemoglobin into the bloodstream, which can have fatal consequences. Landsteiner's work made it possible to determine blood group and allowed a way for blood transfusions to be carried out much more safely. For this discovery he was awarded the Nobel Prize in Physiology and Medicine in 1930, and many other blood groups have been discovered since.

George Washington Crile is credited with performing the first surgery using a direct blood transfusion in 1906 at St. Alexis Hospital in Cleveland while a professor of surgery at Case Western Reserve University.^[66]

Jan Janský also discovered the human blood groups in 1907 which he classified blood into four groups I, II, III, IV. Titled in Czech "Hematologická studie u psychotiků". His nomenclature is still used in Russia and states of the former USSR, in which blood types O, A, B, and AB are respectively designated I, II, III, and IV.

Dr. William Lorenzo Moss's (1876–1957) Moss-blood typing technique of 1910 was widely used until World War II.^{[67][68]}

William Stewart Halsted, M.D. (September 23, 1852 – September 7, 1922) was an American surgeon who emphasized strict aseptic technique during surgical procedures, was an early champion of newly discovered anesthetics, and introduced several new operations, including the radical mastectomy for breast cancer. Halsted returned to New York in 1880 and for the next six years led an extraordinarily vigorous and energetic life. He operated at multiple hospitals, including Roosevelt Hospital, the College of Physicians and Surgeons, Charity Hospital, Emigrant Hospital, Bellevue Hospital and Chambers Street Hospital. He was an extremely popular, inspiring and charismatic teacher. In 1882 he performed one of the first gallbladder operations in the United States (a cholecystotomy performed on his mother on the kitchen table at 2 am). Halsted also performed one of



William Stewart Halsted, M.D., performed one of the first blood transfusions in the United States.

the first blood transfusions in the United States. He had been called to see his sister after she had given birth. He found her moribund from blood loss, and in a bold move withdrew his own blood, transfused his blood into his sister, and then operated on her to save her life.

Blood banks in WW1

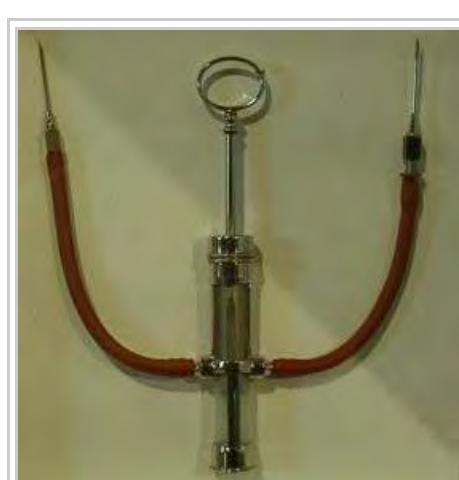
While the first transfusions had to be made directly from donor to receiver before coagulation, it was discovered that by adding anticoagulant and refrigerating the blood it was possible to store it for some days, thus opening the way for the development of blood banks. John Braxton Hicks was the first to experiment with chemical methods to prevent the coagulation of blood at St Mary's Hospital, London in the late 19th century. His attempts, using phosphate of soda, however, were unsuccessful.

The first non-direct transfusion was performed on March 27, 1914 by the Belgian doctor Albert Hustin, though this was a diluted solution of blood. The Argentine doctor Luis Agote used a much less diluted solution in November of the same year. Both used sodium citrate as an anticoagulant.^[69]

The First World War acted as a catalyst for the rapid development of blood banks and transfusion techniques. Canadian doctor and Lieutenant Lawrence Bruce Robertson was instrumental in persuading the Royal Army Medical Corps to adopt the use of blood transfusion at the Casualty Clearing Stations for the wounded. In October 1915, Robertson performed his first wartime transfusion with a syringe to a patient suffering from multiple shrapnel wounds. He followed this up with four subsequent transfusions in the following months and his success was reported to Sir Walter Morley Fletcher, director of the Medical Research Committee.^[70]



Dr. Luis Agote (2nd from right) overseeing one of the first safe and effective blood transfusions in 1914



World War II Russian syringe for direct inter-human blood transfusion.

Robertson published his findings in the *British Medical Journal* in 1916 and, with the help of a few like minded individuals (including the eminent physician Edward William Archibald who introduced the citrate anticoagulant method), was able to persuade the British authorities of the merits of blood transfusion. Robertson went on to establish the first blood transfusion apparatus at a Casualty Clearing Station on the Western Front in the spring of 1917.^[70] ^[71]

Oswald Hope Robertson, a medical researcher and U.S. Army officer was attached to the RAMC in 1917, where he was instrumental in establishing the first blood banks, in preparation for the anticipated Third Battle of Ypres.^[72] He used sodium citrate as the anticoagulant and the blood was extracted from punctures in the vein and was stored in bottles at British and American Casualty Clearing Stations along the Front. He also experimented with preserving separated red blood cells in iced bottles.^[71] Geoffrey Keynes, a British surgeon, developed a portable machine that could store blood to enable transfusions to be carried out more easily.

Expansion

The world's first blood donor service was established in 1921 by the secretary of the British Red Cross, Percy

Oliver. In that year, Oliver was contacted by King's College Hospital, where they were in urgent need of a blood donor.^[73] After providing a donor, Oliver set about organizing a system for the voluntary registration of blood donors at clinics around London, with Sir Geoffrey Keynes appointed as a medical adviser. Volunteers were subjected to a series of physical tests to establish their blood group. The London Blood Transfusion Service was free of charge and expanded rapidly in its first few years of operation. By 1925, it was providing services for almost 500 patients and it was incorporated into the structure of the British Red Cross in 1926. Similar systems were established in other cities including Sheffield, Manchester and Norwich, and the service's work began to attract international attention. Similar services were established in France, Germany, Austria, Belgium, Australia and Japan.^[74]

An academic institution devoted to the science of blood transfusion was founded by Alexander Bogdanov in Moscow in 1925. Bogdanov was motivated, at least in part, by a search for eternal youth, and remarked with satisfaction on the improvement of his eyesight, suspension of balding, and other positive symptoms after receiving 11 transfusions of whole blood. Bogdanov died in 1928 as a result of one of his experiments, when the blood of a student suffering from malaria and tuberculosis was given to him in a transfusion.^[75] Following Bogdanov's lead, Vladimir Shamov and Sergei Yudin in the USSR pioneered the transfusion of cadaveric blood from recently deceased donors. Yudin performed such a transfusion successfully for the first time on March 23, 1930 and reported his first seven clinical transfusions with cadaveric blood at the Fourth Congress of Ukrainian Surgeons at Kharkiv in September. However, this method was never used widely, even in Russia.



Alexander Bogdanov established a scientific institute to research the effects of blood transfusion in Moscow, 1925.

THE PRIME MINISTER HAS SAID: (Nov. 9, 1941)

"The Hazards of Great Battles lie before us"

Here is a warning all must heed. Adequate reserves of fresh blood, plasma and serum, *must* be available for giving transfusions to all 1944 battle casualties that need them. For this reason the Army Blood Transfusion Service calls for many thousands more blood donors of all groups. Will you help by giving a little of your blood? It is simple, painless and harmless, *but the lives of our wounded depend upon it* and thousands more blood donors are wanted.

WILL YOU enrol as a blood donor?

BRISTOL'S BLOOD TRANSFUSION CAMPAIGN
Feb. 12th to 26th

A.R.P. HEADQUARTERS, 35 BROADMEAD

ARMY BLOOD TRANSFUSION SERVICE

British poster encouraging people to donate blood for the war effort.

One of the earliest blood banks was established by Frederic Durán-Jordà during the Spanish Civil War in 1936. Duran joined the Transfusion Service at the Barcelona Hospital at the start of the conflict, but the hospital was soon overwhelmed by the demand for blood and the paucity of available donors. With support from the Department of Health of the Spanish Republican Army, Duran established a blood bank for the use of wounded soldiers and civilians. The 300–400 ml of extracted blood was mixed with 10% citrate solution in a modified Duran Erlenmeyer flask. The blood was stored in a sterile glass enclosed under pressure at 2 °C. During 30 months of work, the Transfusion Service of Barcelona registered almost 30,000 donors, and processed 9,000 liters of blood.^[76]

In 1937 Bernard Fantus, director of therapeutics at the Cook County Hospital in Chicago, established the first hospital blood bank in the United States. In creating a hospital laboratory that preserved, refrigerated and stored donor blood, Fantus originated the term "blood bank". Within a few years, hospital and community blood banks were established across the United States.^[77]

Frederic Durán-Jordà fled to Britain in 1938, and worked with Dr Janet Vaughan at the Royal Postgraduate Medical School at Hammersmith

Hospital to create a system of national blood banks in London.^[78] With the outbreak of war looking imminent in 1938, the War Office created the Army Blood Supply Depot (ABSD) in Bristol headed by Lionel Whitby and in control of four large blood depots around the country. British policy through the war was to supply military personnel with blood from centralized depots, in contrast to the approach taken by the Americans and Germans where troops at the front were bled to provide required blood. The British method proved to be more successful at adequately meeting all requirements and over 700,000 donors were bled over the course of the war. This system evolved into the National Blood Transfusion Service established in 1946, the first national service to be implemented.^[79]

Medical advances

A blood collection program was initiated in the US in 1940 and Edwin Cohn pioneered the process of blood fractionation. He worked out the techniques for isolating the serum albumin fraction of blood plasma, which is essential for maintaining the osmotic pressure in the blood vessels, preventing their collapse.

The use of blood plasma as a substitute for whole blood and for transfusion purposes was proposed as early as 1918, in the correspondence columns of the *British Medical Journal*, by Gordon R. Ward. At the onset of World War II, liquid plasma was used in Britain. A large project, known as 'Blood for Britain' began in August 1940 to collect blood in New York City hospitals for the export of plasma to Britain. A dried plasma package was developed, which reduced breakage and made the transportation, packaging, and storage much simpler.^[80]



Wounded soldier is given blood plasma in Sicily, 1943.



Charles R. Drew oversaw the production of blood plasma for shipping to Britain during WW2.

The resulting dried plasma package came in two tin cans containing 400 cc bottles. One bottle contained enough distilled water to reconstitute the dried plasma contained within the other bottle. In about three minutes, the plasma would be ready to use and could stay fresh for around four hours.^[81] Dr. Charles R. Drew was appointed medical supervisor, and he was able to transform the test tube methods into the first successful technique for mass production.

Another important breakthrough came in 1939–40 when Karl Landsteiner, Alex Wiener, Philip Levine, and R.E. Stetson discovered the Rhesus blood group system, which was found to be the cause of the majority of transfusion reactions up to that time. Three years later, the introduction by J.F. Loutit and Patrick L. Mollison of acid–citrate–dextrose (ACD) solution, which reduced the volume of anticoagulant, permitted transfusions of greater volumes of blood and allowed longer term storage.

Carl Walter and W.P. Murphy, Jr. introduced the plastic bag for blood collection in 1950. Replacing breakable glass bottles with durable plastic bags made from PVC allowed for the evolution of a collection system capable of safe and easy preparation of multiple blood components from a single unit of whole blood.

In the field of cancer surgery replacement of massive blood loss became a major problem. The cardiac arrest rate was high. In 1963, C. Paul Boyan and William S. Howland discovered that the temperature of the blood and the rate of infusion greatly affected survival rates, and introduced blood warming to surgery.^{[82][83]}

Further extending the shelf life of stored blood was an anticoagulant preservative, CPDA-1, introduced in 1979, which increased the blood supply and facilitated resource-sharing among blood banks.

As of 2006, there were about 15 million units of blood products transfused per year in the United States.^[84] By 2013, the number had declined to about 11 million units, due to the shift towards laparoscopic surgery and other surgical advances and studies that have shown that many transfusions were unnecessary. For example, the standard of care reduced that amount of blood transfused from 750 to 200 ml.^[85]

Special populations

Neonate

To ensure the safety of blood transfusion to pediatric patients, hospitals are taking additional precaution to avoid infection and prefer to use specially tested pediatric blood units that are guaranteed negative for Cytomegalovirus. Most guidelines recommend the provision of CMV-negative blood components and not simply leukoreduced components for newborns or low birthweight infants in whom the immune system is not fully developed.^[86] These specific requirements place additional restrictions on blood donors who can donate for neonatal use. vnv Neonatal transfusions typically fall into one of two categories:

- "Top-up" transfusions, to replace losses due to investigational losses and correction of anemia.
- Exchange (or partial exchange) transfusions are done for removal of bilirubin, removal of antibodies and replacement of red cells (e.g., for anemia secondary to thalasseмии and other hemoglobinopathies).^[87]

Massive trauma

A *massive transfusion protocol* is used for massive trauma resuscitation, when more than ten units of blood are needed. Packed red blood cells, fresh frozen plasma, and platelets are administered in lieu of crystalloids or whole blood.^[88] Typically higher ratios of fresh frozen plasma and platelets are given relative to packed red blood cells.^[88]

Unknown blood type

Because blood type O negative is compatible with anyone, it is often overused and in short supply.^[89] According to the American Association of Blood Banks, the use of this blood should be restricted to persons with O negative blood, as nothing else is compatible with them, and women who might be pregnant and for whom it would be impossible to do blood group testing before giving them emergency treatment.^[89] Whenever possible, the AABB recommends that O negative blood be conserved by using blood type testing to identify a less scarce alternative.^[89]

Religious objections

Objections to blood transfusions may arise for personal, medical, or religious reasons. For example, Jehovah's Witnesses object to blood transfusions due to their belief that blood is sacred. They have also highlighted

complications associated with transfusion.^[90]

Research into alternatives

Although there are clinical situations where transfusion with red blood cells is the only clinically appropriate option, clinicians look at whether alternatives are feasible. This can be due to several reasons, such as patient safety, economic burden or scarcity of blood. Guidelines recommend blood transfusions should be reserved for patients with or at risk of cardiovascular instability due to the degree of their anaemia.^{[91][92]} In these cases parenteral iron is recommended.

Thus far, there are no available *oxygen-carrying* blood substitutes, which is the typical objective of a blood (RBC) transfusion; however, there are widely available non-blood *volume expanders* for cases where only volume restoration is required. These are helping doctors and surgeons avoid the risks of disease transmission and immune suppression, address the chronic blood donor shortage, and address the concerns of Jehovah's Witnesses and others who have religious objections to receiving transfused blood.

A number of blood substitutes have been explored (and still are), but thus far they all suffer from many challenges. Most attempts to find a suitable alternative to blood thus far have concentrated on cell-free hemoglobin solutions. Blood substitutes could make transfusions more readily available in emergency medicine and in pre-hospital EMS care. If successful, such a blood substitute could save many lives, particularly in trauma where massive blood loss results. Hemopure, a hemoglobin-based therapy, is approved for use in South Africa.

Veterinary use

Veterinarians also administer transfusions to other animals. Various species require different levels of testing to ensure a compatible match. For example, cats have 3 known blood types, cattle have 11, dogs have 12, pigs 16 and horses have 34. However, in many species (especially horses and dogs), cross matching is not required before the *first* transfusion, as antibodies against non-self cell surface antigens are not expressed constitutively – i.e. the animal has to be sensitized before it will mount an immune response against the transfused blood.

The rare and experimental practice of inter-species blood transfusions is a form of xenograft.




See also

- Arnault Tzanck
- Blood transfusion in Sri Lanka
- Blood type (non-human)
- Xenotransfusion

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Further reading

- Tucker, Holly (2012). *Blood Work: A Tale of Medicine and Murder in the Scientific Revolution*. W. W. Norton & Company. ISBN 978-0393342239.

External links

- Cochrane Injuries Group (<http://injuries.cochrane.org/>), publishes systematic reviews of interventions for traumatic injury, which include evaluations of blood and blood substitute transfusions
- Cochrane Haematological Malignancies Group (<http://hm.cochrane.org/our-reviews>), publishes systematic reviews of interventions for haematological disorders and evaluations of blood and blood substitute transfusions.
- Transfusion Evidence Library (<http://www.transfusionevidencelibrary.com/>) searchable source of evidence for transfusion medicine.



Wikimedia Commons has media related to ***Blood transfusion***.

Blood Transfusion Societies

Blood Establishment Alliances

- Alliance of Blood Operators (<https://allianceofbloodoperators.org/about-abo/our-purpose.aspx>), an association of not for profit Blood Establishments.
- European Blood Alliance (<http://www.europeanbloodalliance.eu/>), an association of not for profit Blood Establishments.

Books

- Blood Groups and Red Cell Antigens. (<http://www.ncbi.nlm.nih.gov/books/NBK2261>) Free online book at NCBI Bookshelf ID: NBK2261
- Handbook of Transfusion Medicine (<http://www.transfusionguidelines.org.uk/document-library/documents/transfusion-handbook-5th-edition/download-file/5th%20Handbook%20of%20Transfusion%20Medicine.pdf>) Free book published in the UK 5th edition.

National Blood Transfusion Guidelines

- American Association of Blood Banks Clinical Practice Guidelines (<https://web.archive.org/web/20160202193620/http://www.aabb.org/sa/clinical-practice-guidelines/Pages/default.aspx>)
- Australian National Blood Authority Patient Blood Management Guidelines (<http://www.blood.gov.au/pbm-guidelines>)
- British Committee for Standards in Haematology (http://www.bcshguidelines.com/4_HAEMATOLOGY_GUIDELINES.html?dtype=Transfusion&dpage=0&sspage=0&ipage=0#gl)
- National Institute for Health and Care Excellence Blood Transfusion Guidance (<https://www.nice.org.uk/guidance/ng24>) UK Guidance for transfusion.
- Canadian Blood Transfusion Guidelines (<http://www.traqprogram.ca/index.php/en/guidelines-a-standards/canadian>)

- German Medical Association Guidelines (English) (http://www.bundesaerztekammer.de/fileadmin/user_upload/downloads/Querschnittsleitlinie_Gesamtdokument-englisch_07032011.pdf), published 2014.

Haemovigilance

- Serious Hazards of Transfusion (<http://www.shotuk.org/>) UK Haemovigilance Scheme.

Blood Transfusion Journals

- Transfusion (<http://www.blackwell-synergy.com/loi/trf>), ISSN 1537-2995 (<https://www.worldcat.org/search?fq=x0:jrn&q=n2:1537-2995>) (electronic) ISSN 0041-1132 (<https://www.worldcat.org/search?fq=x0:jrn&q=n2:0041-1132>) (paper). The official journal of the American Association of Blood Banks (AABB).
- Vox Sanguinis ([http://onlinelibrary.wiley.com/journal/10.1111/\(ISSN\)1423-0410](http://onlinelibrary.wiley.com/journal/10.1111/(ISSN)1423-0410)), ISSN 1423-0410 (<https://www.worldcat.org/search?fq=x0:jrn&q=n2:1423-0410>) (electronic). The official journal of the International Society of Blood Transfusion (ISBT).
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- ISBT Science Series ([http://onlinelibrary.wiley.com/journal/10.1111/\(ISSN\)1751-2824](http://onlinelibrary.wiley.com/journal/10.1111/(ISSN)1751-2824)), ISSN 1751-2824 (<https://www.worldcat.org/search?fq=x0:jrn&q=n2:1751-2824>) (electronic)
- Blood Transfusion (<http://www.bloodtransfusion.it/>), ISSN 1723-2007 (<https://www.worldcat.org/search?fq=x0:jrn&q=n2:1723-2007>). The Official Journal of Italian Society of Transfusion Medicine and Immunohaematology (SIMTI)

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