3. Blood transfusions and the immune system

The immune system never rests—its cells constantly patrol the circulation. Without the immune system, the body would be overwhelmed with infections. With it, blood transfusions must be performed with great care.

If incompatible blood is given in a transfusion, the donor cells are treated as if they were foreign invaders, and the patient's immune system attacks them accordingly. Not only is the blood transfusion rendered useless, but a potentially massive activation of the immune system and clotting system can cause shock, kidney failure, circulatory collapse, and death.

This chapter discusses the causes of transfusion reactions and how the hazards of blood transfusions are minimized.

How to launch an immune response against transfused red blood cells

Many of the adverse effects of blood transfusions are mediated by the recipient's immune system. In general, the formation of this and other immune responses occur in three stages:

- the immune system detects foreign material (antigen)
- the immune system processes the antigen
- the immune system mounts a response to remove the antigen from the body

The immune response varies tremendously, depending on the individual (the health of his or her immune system and genetic factors) and the antigen (how common it is and how "provocative" it is to the immune system).

Antigen detection

The red blood cells (RBCs) from one person may enter into the circulation of another person in two different ways, either by a blood transfusion or by pregnancy. The RBCs will appear foreign if they contain antigens that are not found on the patient's own RBCs.

Antigen processing

When the macrophage encounters an antigen, it engulfs it, digests it, and then presents the antigenic fragments on its cell surface together with MHCII (Major Histocompatibility Complex II).

A T helper cell binds to the antigen/MHCII on the macrophage, and the two cells interact. The macrophage secretes cytokines to stimulate the T cell, which in turn secretes cytokines to stimulate the growth and production of more T cells.

The T helper cell, now activated, leaves to activate a third type of cell, the B cell. Existing B cells are stimulated by the T cell to grow, divide, and produce genetically identical daughter cells. Some of the daughter cells become plasma cells that produce antibodies that are specific for the antigen that stimulated their production. The amount and type of antibody produced results from the interaction of T helper cells (which stimulate antibody production) and T suppressor cells (which inhibit antibody production). Other daughter cells remain as B cells in the circulation for many years. They serve as "memory cells", remembering the encounter with the antigen that stimulated their production.

Read a summary of antigen presentation to T cells in Janeway & Traver's Immunobiology

Immune response

If this is the first time the antigen has been encountered, a primary immune response is mounted. Usually there is a delay of several days, then IgM antibody is produced, followed by a switch to IgG antibody production. The initial IgM molecules bind the antigen weakly, but the subsequent IgG molecules are much better targeted. IgG continues to be produced long after the encounter with the antigen, providing long-lasting immunity.

If the immune system has encountered the antigen before, it will already be armed with primed B cells (memory cells) that accelerate the production of larger amounts of IgG (rather than IgM). This is called the secondary immune response. It is faster, more specific, and the production of the specific antibody may remain high for years. B cells may also undergo changes to further improve how the antibodies they produce bind to the antigen.

There are two main arms of immune response: humoral (using antibodies) and cellular (using immune cells). Severe immune-mediated transfusion reactions usually involve the humoral arm. In the case of a foreign red blood cell antigen, the patient's pre-existing antibodies bind to the antigen, coating the donor RBCs.

Some types of antibody may activate the complement cascade, a series of enzyme-driven reactions involving protein fragments. The cascade ends with the formation of a "membrane attack complex", a large molecule that punches a hole in the cell membrane. Other antibodies simply bind to the donor RBCs and cause them to clump together (agglutinate). The agglutinated cells may survive or may be prematurely removed from the circulation by the macrophages.

Otherwise, the fate of the incompatible RBCs largely rests in the hands of macrophages in the liver or the spleen. They remove the antibody-coated cells from the circulation and phagocytose them. Phagocytosis is aided by the macrophages having a receptor that binds to the antibodies and another receptor that binds to complement fragments. Therefore, incompatible RBCs are rapidly destroyed after antibody binding. In addition, this antibody response may cause dangerous hemolytic transfusion reactions as described below.

"Blood type and cross match"

To avoid a transfusion reaction, donated blood must be compatible with the blood of the patient who is receiving the transfusion. More specifically, the donated RBCs must lack the same ABO and Rh D antigens that the patient's RBCs lack. For example, a patient with blood group A can receive blood from a donor with blood group A (which lacks the B antigen) or blood group O (which lacks all ABO blood group antigens). However, they cannot receive blood from a donor with blood group B or AB (which both have the B antigen).

Before a blood transfusion, two blood tests known as a "type and cross match" are done. First, the recipient's blood type is determined, i.e., their ABO type and Rh D status. In theory, once the recipient's blood type is known, a transfusion of compatible blood can be given. However, in practice, donor blood may still be incompatible because it contains other antigens that are not routinely typed but may still cause a problem if the

recipient's serum contains antibodies that will target them. Therefore, a "cross match" is done to ensure that the donor RBCs actually do match against the recipient's serum.

To perform a cross match, a small amount of the recipient's serum is mixed with a small amount of the donor RBCs. The mixture is then examined under a microscope. If the proposed transfusion is incompatible, the donor RBCs are agglutinated by antibodies in the recipient's serum.

Play the blood typing game at:
NobelPrize.Org

Transfusion reactions: Immune-mediated

Immune-mediated transfusion reactions occur when incompatible blood products are transfused into a patient's circulation, triggering a response from the patient's immune system. The destruction of incompatible RBCs is called a hemolytic transfusion reaction, which may occur immediately (acute) or after a period of days (delayed). The destruction of incompatible donor white blood cells (WBCs) causes a febrile non-hemolytic transfusion reaction (FNHTR), and the destruction of incompatible donor platelets causes post-transfusion purpura (PTP).

The symptoms produced by these transfusion reactions are often similar, beginning with chills, fever, shaking, and aching. Some transfusion reactions are mild and resolve by themselves (e.g., FNHTR) whereas others can develop into a life-threatening reaction (e.g., acute hemolytic transfusion reaction).

The risks are minimized by using blood products only when necessary and, even then, using a specific blood component rather than whole blood. Also, all WBCs are now removed from donated blood; leukodepletion reduces the risk of certain infections as well as the risk of fever due to white blood cell incompatibility.

Hemolytic transfusion reaction: Red blood cell incompatibility

Hemolytic transfusion reactions (HTRs) are reactions in which donor RBCs are destroyed by antibodies in the recipient's circulation. They occur when antigen-positive donor RBCs are transfused into a patient who has preformed antibodies to that antigen. The donor RBCs may be destroyed immediately (a potentially serious reaction) or may have a shortened or even normal survival time (milder reactions).

Red blood cell incompatibility may also occur when the patient's RBC antigens are attacked by antibodies from the donor's plasma. This tends to be a minor problem because of the small amount of antibody present in the donated plasma, which is further diluted on transfusion into the recipient's circulation.

Acute hemolytic transfusion reaction

Acute hemolytic transfusion reactions occur within 24 hours of the transfusion and often occur during the transfusion. Ominously, the patient may report a "feeling of impending doom". They may also complain of a burning sensation at the site of the infusion, together with chills, fever, and pain in the back and flanks.

The severity of the reaction depends upon: (1) how much incompatible antigen was transfused—how much blood was given and the number of antigens per red blood cell; (2) the nature of the antigen - its size and location on the red blood cell membrane; and (3) the nature of the recipient's antibodies - the type (IgG or IgM) and subtype (IgG3) of antibody, the amount present in the circulation at the time of the transfusion, its avidity for binding to the antigen, and its ability to activate complement.

Intravascular hemolysis

The most severe reactions involve an intravascular hemolysis; the donor RBCs are destroyed by the recipient's antibodies while they are still inside blood vessels. Such reactions involve antibodies that strongly activate complement, which in turn lyses the donor RBCs. Hemoglobin is released into the plasma and excreted in urine (hemoglobinuria), turning the urine a dark brown color. Bilirubin, a metabolite of hemoglobin usually secreted into bile by the liver, instead accumulates in the blood causing jaundice. Massive activation of complement can cause shock, as can the large amounts of tissue factor released by RBC debris that triggers an uncontrollable clotting cascade (disseminated intravascular coagulation).

The most common cause of an acute intravascular hemolytic transfusion reaction is ABO incompatibility. The ABO blood group antigens are densely expressed on the RBC surface, and most people have adequate amounts of preformed antibodies that can not only bind to the RBCs but can also activate complement. Although routine typing and cross matching should prevent incompatible ABO blood group antigens from triggering this type of reaction, human error occasionally leads to the "wrong blood" being given during a transfusion.

Apart from anti-A and anti-B, other antibodies capable of intravascular hemolysis of transfused RBCs include anti-H produced in people with the Bombay blood group (see the H blood group), anti-Jk^a (see the Kidd blood group), and anti-P, P1, Pk (see the P blood group system).

Extravascular hemolysis

In extravascular hemolytic reactions, the donor RBCs are removed from the circulation by macrophages in the spleen and liver. The macrophages destroy the red blood cells inside these organs.

The donor RBCs may still be coated with the recipient's antibodies, but these antibodies do not trigger an immediate intravascular hemolysis. Instead, their presence (specifically, the Fc component of the antibody) is recognized by IgG-Fc receptors of macrophages, which aids the phagocytosis of the cells. Antibodies directed at antigens of the Rh blood group mediate this type of RBC removal.

Other types of antibody that bind to the donor RBCs may bind the complement component C3b without activating the entire cascade. This further aids the phagocytosis by macrophages that have C3b receptors. Such antibodies include those directed against antigens of the ABO, Duffy, and Kidd blood groups.

Because the extravascular destruction of RBCs is slower and more controlled than intravascular hemolysis, very little free hemoglobin is released into the circulation or excreted in the urine. The liver can keep up with the increased production of bilirubin, and jaundice rarely occurs. Therefore, the main symptoms of this type of reaction are fever and chills.

Delayed hemolytic transfusion reaction

Delayed hemolytic transfusion reactions may occur as soon as 1 day or as late as 14 days after a blood transfusion. The donor RBCs are destroyed by the recipient's antibodies, but the hemolysis is "delayed" because the antibodies are only present in low amounts initially.

The recipient's antibodies were formed during a previous sensitization (primary stimulation) with a particular antigen. However, by the time a cross match is done, the level of antibody in the recipient's plasma is too low to cause agglutination, making this type of reaction difficult to prevent. Likewise, during the blood transfusion the level of antibody is too low to cause an acute transfusion reaction.

However, during the blood transfusion, as the patient re-encounters the antigen, his or her immune system is stimulated to rapidly produce more antibodies (secondary stimulation). Over the following days, the recipient's antibodies bind to the donor RBCs, which are subsequently removed from the circulation by macrophages (extravascular hemolysis).

The clinical outcome depends upon the rate at which the patient can produce antibodies and hence destroy the donor RBCs. Usually, this type of reaction is much less severe than acute hemolytic reactions.

This type of transfusion reaction is associated with antibodies that target the Kidd and Rh antigens.

Febrile non-hemolytic transfusion reaction (FNHTR): White blood cell incompatibility

The most common transfusion reaction is a fever without signs of hemolysis. This is called a febrile non-hemolytic transfusion reaction (FNHTR). Most cases are mild—the patients may describe feeling hot and cold, their temperatures rise by at least 1°C, and they may have rigors. Only when other potentially severe causes of transfusion reactions have been excluded may FNHRT be diagnosed.

The cause is thought to be the patient's preformed antibodies attacking transfused WBCs, binding to their HLA antigens. Another factor might be that during the storage of blood units, WBCs release cytokines that may provoke a fever when the unit of blood is transfused into a patient.

The risk of FNHRT is reduced by removing WBCs from blood units prior to storage—a process known as leukodepletion. In addition, patients who receive multiple transfusions may be given an anti-pyretic before the transfusion to lessen fever symptoms.

Post transfusion purpura (PTP): Platelet incompatibility

Post transfusion purpura (PTP) is defined as a thrombocytopenia (low number of platelets) that occurs 5 to 10 days after a platelet transfusion. Patients are at risk of bleeding, and bleeding into the skin causes a purplish discoloration of the skin known as purpura.

PTP is caused by the recipient having a platelet-specific antibody that reacts with the donor platelets. The recipient's own platelets are also attacked. The platelet antigen HPA-1a appears to be most frequently targeted.

PTP is more common in women because pregnancy increases the likelihood of forming the platelet-specific antibody. It may also have formed after an earlier platelet transfusion. Treatment includes the use of intravenous immunoglobulin to neutralize the antibodies or to remove them from the plasma by plasmapheresis.

Allergic reactions: IgE anti-allergen antibodies

Some patients can have an allergic reaction after their blood transfusions—they report feeling itchy and break out into hives (urticaria). This is more common in patients who have a history of allergic conditions such as hay fever.

This type of allergic reaction happens when existing IgE antibody binds to its antigen and triggers the release of histamine from the patient's mast cells and basophils. In an allergic reaction to a blood transfusion, either the transfused blood contains IgE that binds to antigen from the recipient's blood, or the antibody is the recipient's own and binds to antigen in the transfused blood.

Fortunately, symptoms are usually mild and can be controlled by stopping the transfusion and giving antihistamines.

Anaphylaxis: IgA anti-plasma protein antibodies

Anaphylaxis is a life-threatening allergic reaction that can occur after only a few milliliters of blood have been transfused. The patient reports difficulty breathing and may be wheezing and coughing. There may also be nausea and vomiting in the absence of a fever. Other signs include low blood pressure, loss of consciousness, respiratory arrest, and circulatory shock. Urgent treatment is essential and includes giving epinephrine.

Usually the antigen that triggers the anaphylaxis is not known. In the case of patients with IgA deficiency, it is thought that the presence of IgA in the donor's plasma is the trigger. IgA-deficient patients have a mild immunodeficiency that may not have been diagnosed. Because they lack IgA, their immune systems can be sensitized to it. Although this type of transfusion reaction is rare in these patients, special precautions are taken to reduce their risk of exposure to IgA in blood products.

Transfusion associated lung injury (TRALI): Donor anti-leukocyte antibodies attack

Transfusion associated lung injury (TRALI) is a rare and occasionally fatal transfusion reaction characterized by a sudden onset of shortness of breath.

The underlying mechanism is not fully understood, but it is thought to involve the transfusion of donor plasma that contains antibodies that attack the recipient's WBCs. These donor antibodies bind to, and cause the aggregation of, the recipient's WBCs in the blood vessels that supply the lungs. The white cells release inflammatory mediators that increase the permeability of the lung capillaries, causing fluid to accumulate in the tissue of the lungs, a condition known as pulmonary edema for which supportive treatment is given.

Transfusion associated graft-versus-host disease (TA-GVHD): Donor T cells attack

Transfusion associated graft-versus-host disease (TA-GVHD) arises when transfused blood cells (the graft) attack the patient's own cells (the host). It is more common in immunocompromised patients whose immune systems fail to eliminate the transfused cells. Instead, the surviving donor T cells attack cells that bear HLA antigens.

This type of reaction becomes apparent about one week after the transfusion. Signs include a fever, characteristic skin lesions, and diarrhea. Blood tests reveal signs of bone marrow failure and liver malfunction.

To prevent TA-GVHD, special precautions are taken with high-risk patients. They only receive blood products that have been irradiated. This prevents all donor cells, including the T cells, from being able to divide and attack the host. In cases where TA-GVHD does develop, the outcome is grave. The patient usually dies several weeks after the blood transfusion.

Transfusion reactions: Non-immune

Not all of the problems that can arise during a blood transfusion are attributable to the immune system. Some are mechanical, especially in patients who need multiple blood transfusions. For example, blood that is not sufficiently warmed before transfusion can cause hypothermia. Also, the volume of blood that needs to be transfused may be too great for the patient's cardiovascular system, especially in elderly patients or patients with varying degrees of heart failure. In such cases, transfusion can cause volume overload and respiratory difficulty.

Metabolic disturbances can also occur, older or damaged RBCs release potassium, and transfusing such blood may cause hyperkalemia (an increased level of potassium) in the patient, putting them at risk of heart arrhythmias. In large amounts, citrate, a blood preservative that prevents clotting, can lower the level of calcium in the plasma (hypocalcemia), leading to muscle tremors and heart arrhythmias.

Finally, the risk of blood transfusions transmitting infectious diseases has been greatly reduced, but a small risk still remains. A virus can be passed on from the donor who is unaware that he or she has an infection. Infection may also occur after the blood has been donated; bacteria can contaminate blood products while they are being stored.

To minimize the risk of infection, blood donors are now screened, and people who are at risk of infectious diseases are excluded from donating blood. In addition, all donated blood is tested for infectious agents. Currently in the USA, blood is tested for HIV, hepatitis B virus, hepatitis C virus, syphilis, and HTLV types I and II, which are linked to leukemia. Since 2003, blood has also been screened for West Nile virus (WNV).