The Donation Process

There are three kinds of allogeneic blood donors:

- Voluntary unpaid donors
- Family or replacement donors
- Paid donors

In most high-income countries, where blood donation policy and infrastructure have been established, voluntary unpaid donors constitute the majority of blood donors. In low-income countries, however, family or replacement donors comprise the majority of blood donors. A replacement donor is an unpaid relative or family friend who donates to replace a unit issued from the blood bank after a patient has been given a transfusion [1, 2].

In the United States, two agencies regulate blood donations. The Food and Drug Administration (FDA) regulates it through its Code of Federal Regulations (CFR). The American Association of Blood Banks (AABB) provides guidelines for the blood donation process. Blood donation is unpaid and voluntary in the United States. Donors should be at least 17 years old, and parental permission is not required; however, some states allow 16-year-olds to donate blood with parental permission. The donor must provide identification, an address, and contact information prior to donation. Sufficient time must have elapsed since the last donation before a new donation can be done (e.g., >8 weeks for whole blood donation or >2 days for plasmapheresis or plateletpheresis procedures) [1, 2].

A health history questionnaire is used to screen donors who may not be suitable for donations. Individuals who are taking teratogenic medications such as...
isotretinoin or finasteride; those who have a history of high-risk behaviors for exposure to human immunodeficiency virus (HIV) infection, infectious hepatitis, malaria, Chagas disease, or variant Creutzfeldt-Jakob disease (vCJD); and those for whom the donation process may not be safe (e.g., pregnant women up to 6 weeks of postpartum period) are deferred, either permanently or temporarily depending on the identified risk factor.

The donor undergoes a brief physical examination and hemoglobin check. Donors who have acceptable physical examination criteria and a hemoglobin level greater than 12.5 gm/dL are accepted for donation. The blood donation occurs through one of two ways: whole blood collection or collection of a specific blood component through apheresis.

When whole blood is collected, it is obtained through venipuncture from one of the antecubital veins. Appropriate disinfection of the antecubital area is essential for avoiding introduction of skin bacteria into the collected blood. A large-bore needle such as a 16-gauge needle is used for venipuncture. Donors who weigh at least 110 lb (50 kg) can donate up to 525 mL of blood, but those who weigh less should donate proportionately less. The collected whole blood is subsequently separated into components via centrifugation.

Apheresis donation is accomplished through a single venipuncture. Whole blood is collected in the single-use collection system and the instrument utilizes centrifugation to separate the blood component of choice, red blood cells (RBCs), platelets, or plasma. After the target component is collected, the other blood components are returned to the donor through the same needle.

The collected blood is typed for ABO and Rh antigens and screened for unusual RBC antibodies. Donor blood is also extensively tested for some infectious agents (Table 29.1). Sometimes more than one method is used to screen for a specific infection to improve the detection of the infection. If the testing is positive, the test is repeated, and if confirmed on the second test, the unit is destroyed. The donor is notified of the positive result and deferred from future donations.

**Processing of Blood Components at the Collection and Processing Facility**

Donated blood undergoes several steps in processing before the various products are ready for issue from the collection and processing facility to hospital blood banks [5].

**FRACTIONATION:** If whole blood is collected, individual components (i.e., RBCs, platelets, and plasma) are separated through centrifugation. The centrifuged components are collected into satellite bags that are connected to the whole blood bag through plastic tubing. This “closed” system prevents contamination during the separation process.

**PRESERVATION:** The initial collection bag contains an anticoagulant/preservative solution, which is either CPD (citrate-phosphate-dextrose) or CPDA-1 (citrate-phosphate-dextrose-adenine). Citrate is the anticoagulant. Phosphate is necessary to
replenish 2,3-diphosphoglycerate (2,3-DPG) as decreased levels of 2,3-DPG shift the hemoglobin-oxygen dissociation curve to the left and oxygen release from hemoglobin to the hypoxic tissues is impaired. Dextrose is necessary for RBC energy. Glucose is converted to lactate through glycolysis, producing adenosine triphosphate (ATP) for the red blood cell, and adenine is necessary for ATP production.

Packed red blood cell (PRBC) units stored in CPDA-1 have a shelf life of 35 days, but additive solutions have more glucose and adenine, extending the shelf life to 42 days. The hematocrit of a CPDA-1 unit can be as high as 80%, but units prepared with an additive solution have a lower hematocrit between 55% and 65%. In situations where high post-transfusion hematocrits should be avoided, such as in patients with sickle cell disease, clinicians should consider the difference in hematocrit in their volume considerations. In general, 10 mL/kg of a unit with CPDA-1 is equivalent to 12 mL/kg of a unit prepared with additive solution.

PRE-STORAGE LEUKOREDUCTION: Blood components undergo leukocyte depletion, also called leukoreduction or leukofiltration, prior to storage and further processing, thus arriving at blood banks already leukoreduced, obviating the need to use bedside leukocyte filters. Pre-storage leukoreduction of a blood component has several advantages, including minimizing the occurrence of febrile non-hemolytic transfusion reactions, minimizing HLA (human leukocyte antigen) alloimmunization and platelet refractoriness, and prevention of transmission of leukotrophic viruses residing in white blood cells (WBCs), such as CMV or EBV (Epstein-Barr

| Microorganism(s) screened | Testing methodology | Year introduced |
|---------------------------|---------------------|-----------------|
| Syphilis                  | Serology            | 1950s           |
| Hepatitis B virus         | HbsAg (hepatitis B surface antigen) | 1971 |
|                           | Antibody against hepatitis B core antigen | 1986 |
|                           | NAT                 | 2009            |
| HIV types 1 and 2         | Anti-HIV 1/2 antibodies | 1985 |
|                           | NAT                 | 1999            |
| Hepatitis C               | Anti-HCV antibodies | 1990            |
|                           | NAT                 | 1999            |
| Human T-cell lymphotrophic virus (HTLV) I and II | Anti-HTLV antibodies | 1998 |
| West Nile virus           | NAT                 | 2003            |
| Trypanosoma cruzi (Chagas disease) | Anti-T. cruzi antibody | 2007 |
| Babesia microti           | Anti-B. microti antibody | 2012 |
|                           | NAT                 | 2012            |
| Zika virus                | NAT                 | 2016            |

NAT nucleic acid testing. The last column shows the year when American Red Cross incorporated routine testing of donated blood for the infectious agent [3, 4]. Universal screening of blood components for cytomegalovirus (CMV) is not routinely performed. However, some units are randomly screened for anti-CMV antibodies to maintain a source of CMV-seronegative units. (Indications for CMV-negative units will be discussed further below).
virus). In fact, leukoreduced blood components can be considered CMV-safe even if they have been obtained from a CMV-seropositive donor.

Post-storage leukoreduction may not have the above advantages as WBCs can still release cytokines or leukotropic viruses into the component solution during storage, and leukocyte fragments containing HLA may pass through bedside filters.

**BACTERIAL CULTURE OF PLATELET UNITS:** Regardless of the method of collection, platelet units are stored at room temperature (220–24 °C), which may facilitate bacterial growth in the platelet unit. In fact, bacterial sepsis in the recipient is most frequently associated with platelet transfusion. Most processing facilities have elected to culture platelet units prior to issuing them to blood banks to avoid transfusion-associated bacteremia or sepsis. Units that signal bacterial growth are discarded, and only those with negative growth at 2 days are issued to blood banks. This diminishes the already short, 7-day shelf life of platelets, and most units that reach the blood bank have only 5 days left before expiration [6].

**PATHOGEN INACTIVATION OF PLATELET UNITS:** This novel method is soon going to replace bacterial culturing of platelet units despite a labor-intensive process that involves injecting platelet units with amotosalen. Amotosalen-injected units are exposed to ultraviolet A rays, which leads to breakdown of psoralen-bound DNA of viruses, bacteria, and WBCs. Platelets do not have a nucleus and therefore are not affected by this process [6].

### Processing of Blood Components at the Hospital Blood Bank

**STORAGE and INFCTION CONTROL:** Table 29.2 summarizes the storage requirements and shelf lives for blood components [7, 8]. Figure 29.1 shows platelet storage at room temperature with gentle agitation.

When a PRBC unit leaves the blood bank, it must be used for transfusion within 4 hours or otherwise discarded to minimize infectious risk. PRBC units specific to recipients may also be frozen in a glycerol solution and stored at freezing temperatures up to 10 years.

| Blood component | Temperature | Shelf life |
|-----------------|-------------|------------|
| PRBC units      | At refrigerator shelf temperature of 1–6 degrees Celsius (°C) | 35 days – units stored in CPDA-1  
42 days – units stored in additive solution |
| Platelet units  | At room temperature of 20–24 °C with continuous gentle agitation | 5 days if the unit was cultured at the collection facility  
7 days if the unit underwent pathogen inactivation |
| FFP, cryoprecipitate | At freezing temperatures of ≤ −18 °C | Up to a year |

°C = degrees Celsius
Platelet units can be screened for presence of bacterial cell wall components prior to issuing to the patient. This strategy aims to reduce transfusion-transmitted bacterial infections.

**IRRADIATION:** Cellular blood components need to be irradiated prior to transfusing to certain patients to prevent transfusion-associated graft versus host disease (TA-GVHD). Irradiation prevents the donor T lymphocytes from proliferating in the recipient and launching a cellular immune attack on the recipient’s tissues. Gamma irradiation of the unit can be accomplished with an irradiator found in most blood banks. The expiry date of the PRBC units is reduced to 28 days after an irradiation or original expiration date, whichever is shorter. Irradiation also causes an efflux of potassium into the extracellular fluid in stored units, and that’s why irradiated units should be transfused as soon as possible to avert hyperkalemia in patients at risk, such as newborns [9]. Pathogen-inactivated units do not need to be irradiated as they have already received ultraviolet A irradiation [7, 8].

Cellular blood products should be irradiated for the following transfusions [10]:

- Intrauterine transfusions.
- Transfusions given to newborns or infants younger than 4 months of age (some centers irradiate only for transfusions given to low-birth-weight preterm infants).
- Transfusions from blood-related donors.
- Transfusions following hematopoietic stem cell transplantation.
- Transfusions given to individuals with congenital immunodeficiency.
- Transfusions given to patients receiving chemotherapy or radiation treatment for cancer.
- Transfusions given to patients receiving intense immunosuppressive treatment.
- Transfusions of HLA-matched blood components.
- All granulocyte transfusions.
- All cellular transfusions need to be irradiated in homogenous populations where there is very little HLA variability. For example, the Japanese population is relatively homogenous, and there is very little HLA variability, and cases of TA-GVHD have occurred even after transfusions from unrelated donors to immunocompetent individuals [11].
WASHING: Washing is a process that aims to reduce the plasma component of cellular blood components such as PRBC units or platelet units. The indications for this processing include severe or multiple allergic reactions in the recipient. The goal is to reduce exposure to the inciting allergen in the plasma. The washing process itself is accomplished by infusing 1–2 liters of normal saline into the unit and then centrifuging the unit to remove the supernatant. The process unfortunately leads to loss of the cellular product as well, and up to 20% of the RBC yield and 33% of the platelet yield are also lost. This process is labor-intensive, takes time, and reduces the expiry to 24 hours for PRBCs and 4 hours for platelet units and therefore should not be ordered unless there is a strong indication for its use [7, 8].

Blood Components

Packed Red Blood Cells

Source

PRBC units can be obtained via centrifugation of the whole blood or via erythrocytapheresis. PRBC units generally weigh between 250 and 350 mL [7].

Young Versus Old Blood

Several changes occur in the RBCs as the PRBC unit ages. ATP and 2,3-DPG are depleted towards the end of the 2nd week of storage, and the intracellular potassium leaks into the unit storage solution. In most stable patients, this does not cause any clinical problems as the extracellular potassium in the solution is minimal and the depleted ATP and 2,3-DPG are restored within hours. In vulnerable populations such as newborns and patients with severe cardiopulmonary conditions, however, PRBC units stored less than 7–10 days are preferred to avoid hyperkalemia [10].

Pretransfusion Testing

RBCs carry several carbohydrate or protein antigens that may be present or absent in different individuals. Antigens that are perceived as “non-self” and thus provoke an immune reaction in an individual are called “blood groups.” The major blood groups are the ABO and the RhD antigens.

ABO antigens are carbohydrate antigens. Individuals lacking a certain ABO antigen develop antibodies “naturally” without prior exposure via transfusion. The theory is these antibodies develop during infancy after exposure to antigens carried through exposure to gut bacteria. Antibodies against RhD antigen, however, require previous exposure to the antigen. Therefore an RhD-negative individual receiving
RhD-positive blood transfusion or an RhD-negative woman pregnant with an RhD-positive fetus develops antibodies against the Rh antigen. These antibodies could initiate a strong hemolytic reaction in a subsequent exposure, either via transfusion or during pregnancy.

The blood bank technician types the recipient’s blood for ABO and RhD antigens and screens for auto- and alloantibodies. This screen is an indirect antiglobulin test using the Coombs reagent to identify antibodies present in the recipient’s serum. This combined testing is referred to as a “type and screen.”

The technician then runs a crossmatch of the donated blood and the recipient’s sample. In major crossmatch, donor’s RBCs are tested in the presence of recipient serum. If the recipient has antibodies against the donor RBC antigens, an agglutination occurs which can be detected visually. In minor crossmatch, donor serum is tested against recipient RBCs [12].

**Volume and Rate**

The typical transfusion volume of PRBCs for most stable patients is 10–12 mL/kg which can be given over 2 hours. Stable patients usually require one to two units depending upon body weight. Patients with active bleeding may require higher volumes of transfusion or more frequent transfusions to replenish ongoing losses. Patients receiving chronic blood transfusions such as thalassemia major or sickle cell disease may receive higher volumes of 12–15 mL/kg. Newborn infants with severe anemia are usually given higher volumes up to 15 mL/kg.

Transfusion can be delivered much faster if the patient has developed acute anemia due to active bleeding or severe hemolysis. Transfusions should be given slowly to patients who have very low hemoglobin levels due to chronic anemia to avoid precipitating heart failure. Since the transfusion time cannot be extended over the abovementioned 4-hour limit, smaller aliquots of 5–6 mL/kg of body weight should be given in such cases [13].

**Indications**

**Basic Principles**

The hemoglobin inside RBCs carries oxygen from the lungs to capillaries where oxygen is released into the tissues. In situations with low hemoglobin levels, compensatory mechanisms, such as oxygen dissociation curve shift, may be sufficient to maintain adequate tissue oxygenation. The basic indication for PRBC transfusion is treatment of severe anemia that disrupts oxygen delivery to tissues. Many other factors, such as the patient’s age, comorbidities, acuity of the condition, and availability of other treatment options for anemia, may affect this indication [13, 14].

Both the public and the medical community have had legitimate concerns about adverse effects of transfusion. These include not only infection transmission and
acute transfusion reactions but also HLA alloimmunization, alloantibody formation, and transfusion-related immunomodulation. Inappropriate transfusions expose patients to adverse effects, incur unnecessary costs, and waste an otherwise precious resource that could have benefited another patient in need of transfusion. Therefore, the decision to transfuse should include the following considerations of clinical transfusion:

1. Transfuse only and only if it is absolutely necessary.
2. Avoid transfusing for arbitrary “triggers.”
3. Transfuse only as much as needed. If one unit will achieve the clinical goal, a second unit does not need to be given.

PRBC transfusions should not be given as a volume expander unless the patient is actively hemorrhaging, as a substitute for iron, vitamin B12, or erythropoietin which can be administered pharmacologically, to help with wound healing or to satisfy a patient’s or physician’s desire to have a certain numerical hemoglobin value.

PRBC Transfusion Indications by Disease Category

Chronic anemias secondary to deficiencies of iron, folic acid, vitamin B12, or erythropoietin should be ideally managed by replacing the deficient hematopoietic substance. Such children with chronic anemia can tolerate very low levels of hemoglobin, and it is not unusual for severe anemia to be discovered during a routine blood count check. For such asymptomatic patients, transfusion could be held even for hemoglobin levels as low as 5 gm/dL. Patients with hemoglobin levels below 5 gm/dl or those who have symptoms and signs related to severe anemia such as headache, pre-syncpe, syncope, or heart failure should receive a transfusion. The transfusion should be undertaken very slowly and in small volumes in such patients. Typically the volume for transfusion is 5–6 mL/kg given over 3 hours, with careful monitoring of cardiovascular status. If the etiology of the anemia is due to iron, folic acid, or vitamin B12, supplementation should be started in addition to the transfusion. If the patient is found to be deficient in erythropoietin, renal function should be evaluated and recombinant erythropoietin administration begun [13, 14].

The acute onset of severe anemia, however, will not have allowed development of compensatory mechanisms seen in chronic anemias, and patients may require transfusion at higher initial hemoglobin levels. These patients can be transfused more rapidly especially if there is a concern that the severe anemia is leading to shock. Patients with such severe acute anemia include those with active hemorrhage (gastrointestinal, vaginal, surgical, or traumatic) and those with acute hemolysis (secondary to thrombotic thrombocytopenic purpura, glucose-6-phosphate dehydrogenase deficiency, or autoimmune hemolytic anemia (AIHA)).

Note that in patients with AIHA, the blood bank may require more time to investigate the involved antibody and to crossmatch units. Because rapidly evolving
severe anemia could easily decompensate, patients with severe anemia may not be able to wait for perfectly matched blood. In such situations, even an incompatible unit may be transfused. Slow transfusion, warming the patient and the unit in the presence of cold antibodies, providing fluids, and immunosuppressive therapy such as steroids may slow the hemolysis and provide the patient with a more stable hemoglobin until the autoimmune hemolysis is controlled.

Patients with hemoglobinopathies, severe red cell enzyme defects and red cell membranopathies, congenital dyserythropoietic anemia (CDA), and myelodysplastic syndrome may need to receive transfusion on a scheduled, chronic basis. In patients with ineffective erythropoiesis (i.e., thalassemia, CDA), PRBC transfusions aim to maintain hemoglobin at a higher level to suppress expanded erythropoiesis and thereby prevent medullary expansion. The aim is to achieve a pretransfusion or nadir hemoglobin of 9–10 gr/dL in such patients. Transfusions could be given at 15–18 mL/kg every 3–6 weeks based on patient characteristics. In patients with hereditary spherocytosis, the abnormal RBCs are broken down in the spleen, while severe anemia results in extramedullary hematopoiesis in the spleen and further splenomegaly, leading to a vicious cycle of hemolysis causing anemia causing splenomegaly causing more hemolysis and more severe anemia. The aim of the transfusion is to break this cycle by both elevating the hemoglobin and thus suppressing extramedullary erythropoiesis and providing red blood cells that will not be destroyed in the spleen.

In patients with sickle cell disease (SCD), PRBC transfusion is given to decrease the hemoglobin S concentrations below 20–50% depending upon the indication for transfusion. Reducing the HbS% significantly reduces the sickling process. Transfusion in SCD can either be given on a chronic basis such as in patients with a history of stroke or on an acute basis, such as those presenting with acute chest syndrome. Simple transfusions may be adequate for acute anemia or increased hemolysis. However, in the setting of stroke, severe ACS or multi-organ failure exchange transfusions are preferred to more rapidly reduce the HbS percentage. Exchange transfusions can be performed using an automated instrument or manually where the patient undergoes a phlebotomy of 5 mL/kg and receives 12 ml/kg of PRBC in additive solution (10 mL/kg if the PRBC solution is prepared only with CPDA-1).

Patients undergoing myelosuppressive chemotherapy or radiation treatment for pediatric cancers usually receive PRBC transfusions when their hemoglobin drops to 7–8 gm/dL. The anemia in these patients does not respond to erythropoietic substances such as iron or erythropoietin, and the use of recombinant erythropoietin in patients with pediatric cancers is controversial because of the risk of inducing tumor growth. Myelosuppression after chemotherapy or radiation therapy usually takes 2–3 weeks (longer in some cases) to recover. By the time the bone marrow has recovered, the next cycle of myelosuppressive therapy starts.

Patients with critical illness with stable cardiopulmonary status can usually be transfused at hemoglobin levels as low as 7 gm/dL. Past studies have shown that transfusing at higher hemoglobin levels does not impart any clinical benefit and could even be harmful [15].
Platelets

Source

Platelet units can be collected as either random donor platelets (RDP), which are obtained via centrifugation of a whole blood donation, or single donor units (SDU), which are obtained via apheresis. RDP units have a volume of ~50 mL and contain at least 55 billion platelets per unit, but the larger apheresis units have a volume of 200–250 mL and contain at least 300 billion platelets per unit. Blood processing centers in the United States have largely shifted to collecting apheresis platelets, and the platelets obtained from whole blood donations are usually discarded. If obtained, however, 4–6 RDP units are usually pooled into one random donor unit (RDU) [16, 17].

Pretransfusion Testing

In general, there is no pretransfusion testing for platelets other than the recipient blood type as platelets should be plasma compatible. Many blood banks issue platelet units without regard to ABO compatibility between the donor and recipient. However, platelets do carry ABO antigens and, if transfused to a recipient with a major incompatibility, may lead to “platelet refractoriness,” meaning an unexpectedly low rise in the platelet count after transfusion. Although platelet refractoriness might have other causes, most experts recommend attempting transfusion with ABO-identical platelet units prior to embarking on a search for other causes, such anti-HLA antibodies.

Platelets are also contaminated with minute amounts of RBCs, increasing the risk of Rh-sensitization if a unit obtained from an Rh-positive donor is transfused to an Rh-negative recipient. Female Rh-negative patients of reproductive age should receive Rh-negative units or anti-D injections to avoid sensitization after a transfusion of Rh-positive platelet unit.

Volume and Rate

Most experts do not recommend transfusing more than six random donor units or one single apheresis unit at a time. Platelet transfusions can be given over 30–60 minutes. Slower transfusion compromises post-transfusion platelet count and activity.

Indication

The decision to transfuse platelets depends on the patient’s clinical condition, the status of plasma phase coagulation, the platelet count, the cause of the thrombocytopenia, and the functional capacity of the patient’s own platelets. In the face of decreased production and platelet counts less than 10,000–20,000/µL, the risk of
severe, spontaneous bleeding is increased markedly, and, in the absence of immune-mediated thrombocytopenia (ITP), transfusion should be considered. Under certain circumstances, especially with platelet dysfunction or when receiving anticoagulation treatment, transfusions at higher platelet counts may be necessary to prevent or treat bleeding [17–19].

**Plasma-Based Components**

**Source**

The two most commonly used plasma-based blood components are fresh frozen plasma (FFP) and cryoprecipitate. FFP is obtained either through plasma apheresis or via separation of the plasma component of a whole blood collection. Cryoprecipitate is manufactured from the precipitated portion of plasma thawed at 1–6 °C [16].

**Pretransfusion Testing**

Although a pretransfusion crossmatch testing is not necessary, the plasma should be compatible with the recipient’s ABO antigens. Individuals with AB blood type can universally donate plasma to all recipients, whereas individuals with O blood type can donate only to recipients with group O.

**Volume and Rate**

Both FFP and cryoprecipitate can be given in a rapid transfusion over 30–60 minutes. FFP is given at a dose of 10–15 ml/kg.

Cryoprecipitate dosing is as follows:
- 1 cryoprecipitate unit for every 5 kg to raise the fibrinogen by 100 mg/dL [20].

**Indication**

The indication for FFP is replacement of plasma coagulation factors in the setting of active bleeding associated with multiple clotting factor deficiencies. In most hereditary factor deficiencies, such as factor VIII deficiency or vWD, commercially prepared concentrates contain higher concentrations of these factors and, because of viral inactivation, impose less infectious risk and are more appropriate than FFP.

FFP units are the blood components most commonly transfused for inappropriate indications. Such inappropriate use may involve the treatment of prolongation of prothrombin time (PT) or activated partial thromboplastin time (aPTT) in the absence of clinical bleeding or for supplementation of volume or albumin or
replacement of coagulation factors for which individual factor concentrates are readily available.

Cryoprecipitate contains four important coagulation factors: factor VIII, von Willebrand factor, factor XIII, and fibrinogen. Specific concentrates for each of these individual factors now are available, thus decreasing the utilization of cryoprecipitate as a treatment for specific clotting factor deficiencies; however, it is still commonly used to replenish fibrinogen in states such as disseminated intravascular coagulation (DIC), as the fibrinogen solution is not easily available and is more expensive.

**Granulocytes**

Granulocyte transfusions had fallen out of favor because of severe side effects including ARDS but are now making a comeback for severely neutropenic patients with severe sepsis. The complications and availability are still significant issues with the use of this blood component. Granulocyte donors receive granulocyte colony-stimulating factor injections and/or steroids to increase blood granulocyte numbers prior to donation [16].

With better supportive care over the past 10 years, the need for granulocytes in neutropenic patients with severe bacterial infections has decreased. Indications still remain for severe bacterial or fungal infections unresponsive to vigorous medical therapy in either newborns or older children with bone marrow failure or patients with neutrophil dysfunction. Newer mobilization schemes using G-CSF and steroids in donors result in granulocyte collections with at least 50 billion neutrophils. This may provide a better product for patients requiring granulocyte support.

**Adverse Effects of Transfusion**

Transfusion of blood components can be associated with either acute or delayed complications. Acute transfusion reactions manifest themselves either during the transfusion of the unit or soon after the transfusion is completed, and reactions occurring within 24 hours after the start of the transfusion are included within this category. Delayed adverse complications are usually referred to as “post-transfusion complications” and occur within days, months, or years after the transfusion [13, 20–22].

Signs and symptoms of acute transfusion reactions vary based on type of reaction but include skin manifestations such as urticaria or angioedema; respiratory symptoms such as wheezing, tachypnea, dyspnea, or hypoxia; cardiovascular symptoms such as hypotension, tachycardia, and shock; inflammatory signs and symptoms such as fever and rigors; or pain in the back or flank. In the event of a suspected transfusion reaction, the transfusion should immediately be stopped when such signs and symptoms occur in a patient being transfused. The patient should be
urgently evaluated, and appropriate supportive care (oxygen, intravenous fluids, medications etc.) should be provided. Patients with mild allergic reactions limited to skin (i.e., urticaria only) can resume the transfusion with the same unit once the reaction subsides and the patient is stable. Further investigation is not necessary. For all other reactions, the involved unit should be returned to the blood bank for cross-match and a microbiologic culture, and patient specimens should be obtained for a laboratory investigation. Such investigations aim to exclude mostly a hemolytic reaction (direct Coombs test, indirect bilirubin level, complete blood counts, plasma and urine hemoglobin), but a blood culture should also be obtained if bacterial infection is suspected.

**Acute transfusion reactions include the following:**

**ACUTE HEMOLYTIC TRANSFUSION REACTION:** This reaction can occur as a result of a clerical error, where incompatible RBCs are transfused because of an error in sampling, crossmatch, or patient identification. It can also occur because of previously undetected alloantibodies in the recipient. The responsible antibody may be either immunoglobulin (Ig) M or immunoglobulin G (IgG) in the case of anti-A- or anti-B-related acute intravascular hemolysis. Complement-fixing IgG antibodies can also cause acute hemolysis in the case of anti-Kidd or anti-Kell antibodies.

Hemolytic antibodies cause lysis of red blood cells through complement activation. This results in hemoglobinemia and hemoglobinuria. The complement activation also triggers the kinin-bradykinin system, releases anaphylatoxins, and causes release of further inflammatory cytokines. The severe storm of physiologic changes following a hemolytic transfusion reaction can cause fever and rigors; back, flank, or chest pain; nausea and vomiting; dark urine; respiratory difficulty; and hypotension which could progress to shock. The patient may complain of feeling “impending doom,” meaning feeling like he/she is going to die. The clinical picture can be confused with an infectious process due to fever or with an allergic reaction because of wheezing and shortness of breathing. Laboratory investigations show evidence of disseminated intravascular coagulation, acute renal failure, positive direct Coombs test, indirect hyperbilirubinemia, presence of free hemoglobin in the plasma and hemoglobinuria, and presence of schistocytes and spherocytes on the smear.

**Transfusion-Related Acute Lung Injury (TRALI) and Transfusion-Associated Circulatory Overload (TACO)**

TRANSFUSION-RELATED ACUTE LUNG INJURY (TRALI) AND TRANSFUSION-ASSOCIATED CIRCULATORY OVERLOAD (TACO): TRALI is caused by anti-neutrophil or anti-HLA (human leukocyte antigen) antibodies in the donor plasma that interact with the neutrophils in the recipient’s pulmonary circulation. This interaction results in neutrophil activation, altered vascular
permeability, and capillary leak syndrome in the pulmonary capillaries. The end result is pulmonary edema. TRALI presents with respiratory distress associated with hypoxia within 6 hours after the start of transfusion, accompanied by radiographic findings of acute pulmonary edema. Other causes of pulmonary edema should be excluded to be able to make the diagnosis of TRALI. Clinically, physicians have to distinguish between TRALI and TACO, which has a similar clinical and radiographic presentation. TACO is associated with elevations in brain-natriuretic peptide (BNP) in the serum and responds promptly to diuretics and fluid restriction, whereas TRALI is associated with normal BNP levels and does not respond to diuretics or fluid administration.

Acute hemolytic transfusion reaction, bacterial contamination and sepsis, and allergic reactions can also cause respiratory symptoms; therefore, a full transfusion reaction investigation needs to be undertaken in the patient who develops tachypnea, dyspnea, wheezing, or hypoxia during or soon after a transfusion. Blood culture should be sent from the patient, and the suspected unit (if available) should be sent to the blood bank for crossmatch and bacterial culture.

In situations where other causes of respiratory distress have been excluded, there is a high probability of TRALI. In such situations, the diagnosis can be verified by testing the donor for antibodies against HLA or neutrophil antigens and testing the recipient for HLA and neutrophil antigen specificities. If an antibody is detected in the donor along with a corresponding antigen in the recipient, the diagnosis of TRALI can be confirmed.

Patients who develop TRALI require respiratory support and critical care. Fortunately the event is self-limited, and the patient recovers within a few days in most cases. In a few cases, however, the patient dies of TRALI, which in fact is the number 1 cause of transfusion-related death in the United States.

The donor implicated in a case of TRALI should be deferred from donations. Interestingly, TRALI occurs mostly in units with a large plasma content such as platelet units or FFP. Multigravid women donors have higher incidence of implicating antibodies, and exclusion of such donors can decrease the incidence of TRALI. In fact, some countries now collect only male plasma, and this practice has led to a fall in the incidence of TRALI.

Allergic Reactions

ALLERGIC REACTIONS: are usually triggered by plasma proteins and thus are more common with FFP or platelet transfusions. Clinically, allergic reactions can be mild (with only urticarial skin reaction); moderate (respiratory symptoms secondary to angioedema of the airway or bronchospasm); or
severe (hypotension and shock along with respiratory ± skin manifestations). Moderate to severe reactions are called “anaphylaxis” if truly mediated by IgE and “anaphylactoid reactions” if mediated through other antibodies. For example, IgG4 antibodies cause this reaction by binding to Fc receptors on mast cells and basophils.

Mild allergic reactions are the most common transfusion reactions. As described above, STOP the transfusion and assess the patient in the event of an allergic reaction. If the reaction is limited to skin manifestations only and resolves upon treatment with antihistamines, the unit may be restarted at a slower rate. Note that mild reactions usually appear late during the course of the transfusion and are not generalized. If an urticarial reaction occurred immediately after start of a transfusion, it should not be considered as a “mild” reaction. Rapidity of onset predicts the severity of the reaction. Do not restart the unit if there is perioral swelling or laryngospasm, even if the urticarial rash has cleared.

The treatment for moderate to severe allergic reactions includes epinephrine and steroids.

1:1000 epinephrine solution (1 mg/mL) is administered subcutaneously at a dose of 0.2 to 0.5 mL for adults and 0.1 mL for every 10 kg of body weight for children. The dose may be repeated every 15–30 minutes as needed.

Patients who have had multiple reactions can be given premedications, such as hydrocortisone and antihistamines. Patients who have had an anaphylactic reaction should be investigated for IgA deficiency or haptoglobin deficiency. If such a deficiency is discovered, patients can be given transfusions from IgA deficient or haptoglobin-deficient donors. If no such deficiency is discovered, and the patient is going to receive a cellular unit such as PRBC or a platelet unit, then the units should be “washed,” meaning the cells are suspended in a saline solution and the plasma is removed by centrifugation.

**Febrile Non-hemolytic Transfusion Reaction (FNHTR)**

Fever is defined as temperature >38 °C or a rise in temperature >1 °C or >2 °F in the 4 hours after the start of transfusion. Shaking chills may accompany fever. In FNHTR, the patient does not have any other signs or symptoms, and specifically there is no hypotension, and laboratory investigations exclude bacterial contamination or hemolytic transfusion reaction. The cause of this reaction is cytokine accumulation in the plasma compartment of the unit. This was a common transfusion reaction in the past, but since the introduction of pre-storage leukocyte filtration, the incidence has decreased significantly. Treatment includes antipyretics.
Transfusion-Associated Graft Versus Host Disease (TA-GVHD)

TRANSFUSION-ASSOCIATED GRAFT VERSUS HOST DISEASE (TA-GVHD): This is a rare complication thanks to implementation of irradiation when indicated. The graft versus host disease reaction takes place particularly in the skin, bone marrow, liver, and gut, giving rise to symptoms and signs of fever, erythematous rash that progresses to desquamation, diarrhea, and liver dysfunction or failure. The mortality is as high as 90% after TA-GVHD [10].

Transfusion Avoidance

Blood transfusion is a life-saving therapeutic modality, but like all therapeutic measures, it should only be used for appropriate indications. Blood transfusion is an expensive limited resource, associated with numerous adverse effects. Some patients and families may wish to avoid transfusion because of religious or personal beliefs. Therefore, the clinician should be familiar with transfusion-sparing strategies and should employ them in an effort to avoid or at least to minimize transfusion exposure [23].

Blood conservation in children undergoing surgery can be achieved through several modalities:

1. Preoperative hemoglobin level can be increased by using erythropoiesis-stimulating agents and iron supplementation, either orally or parenterally.
2. Autologous blood transfusion can be given to the patient. This involves preoperative autologous blood donation, reinfusion of shed blood during surgery, and acute normovolemic hemodilution.
3. Operative blood losses can be reduced using anti-fibrinolytic agents, such as tranexamic acid.
4. Rates of postoperative transfusion can be reduced by using transfusion algorithms.

Setting Evidence-Based Clinical Guidelines

Hospital committees that oversee blood component use should set evidence-based guidelines to help clinicians decide when and how much to transfuse. For example, most children who are not actively bleeding and who are stable from a cardiopulmonary point can tolerate hemoglobin levels as low as 7 gm/dL. Increasing absolute reticulocyte counts can help anticipate erythropoietic recovery and can help avoid transfusion. If the anemia is related to the deficiency of a substance that can be easily replaced (iron, vitamin B12, erythropoietin, etc.), replacement of the deficient substance is preferable to transfusion.
The amount that will be delivered should also be decided upon judiciously. Whenever possible, the patient should be exposed to as few units as possible. Consider the two cases below:

- Case #1: A 15-year-old girl who presented to the hospital with syncope and was later found to have a hemoglobin level of 7.5 gm/dL is suffering from heavy menstrual bleeding. The patient still has active bleeding, is tachycardic, and is hypotensive. The patient has been started on intravenous fluids, intravenous estrogen, and intravenous iron. The attending clinician also wants to transfuse PRBC to this patient who weighs 50 kg. The calculation for 12 mL/kg of PRBC yields 600 mL. The two matching PRBC units available at the hospital blood bank have 300 mL and 350 mL of volume each.

- Case #2: A 15-year-old girl who is receiving chemotherapy for Hodgkin lymphoma was found to have a hemoglobin of 7.2 gr/dL with an absolute reticulocyte count of 10,000/mm3. The patient is clinically stable. She will be discharged home after a PRBC transfusion and is expected to return in a week for her subsequent chemotherapy visit. The patient weighs 50 kg. The calculation for 12 mL/kg of PRBC yields 600 ml. The hospital blood bank has two units available, one with a volume of 300 mL and the other 350 mL.

The case #1 absolutely needs an acute increase in her hemoglobin level as she is symptomatic with active bleeding. Although the intravenous iron will increase the hemoglobin, a clinically significant rise will not occur until at least a week after the start of the iron treatment. The initial hemoglobin of 7.5 gr/dL may be an underestimate of the patient’s actual hemoglobin, which possibly is much lower. This patient should be given both units totaling 650 mL, and the hemoglobin should be monitored closely.

The case #2 is clinically stable but has a low (<40,000) reticulocyte count, and therefore a spontaneous recovery is not expected soon. The patient will return to the clinic 1 week later, and by that time, the patient’s hemoglobin may be even lower. A PRBC transfusion therefore may be needed, but since the goal here is only to elevate the hemoglobin to a safer level, transfusing only one unit should be adequate. The clinician may ask for the larger unit of 350 mL to be given. Since there is no active bleeding, it is acceptable to repeat the blood counts in 1 week’s time.

**Intravenous Iron**

Occasional patients who do not respond well to oral iron supplementation, either because of malabsorption of iron or poor tolerance of oral iron, may benefit from intravenous iron therapy. Although parenteral iron therapy has long been available, the severe adverse effect (i.e., anaphylaxis) profile of heavy-molecular-weight iron dextran has made intravenous iron therapy unpopular in pediatric hematology practice. In recent years, newer and safer intravenous iron preparations have become
available, such as sodium ferric gluconate, iron sucrose, low-molecular-weight iron dextran, and ferumoxytol.

**Recombinant Erythropoietin**

The most important erythropoiesis-stimulating agent is erythropoietin (EPO), a glycoprotein hormone secreted from kidney cells. EPO was first purified and characterized in 1977 by Miyake et al. The hormone induces erythropoiesis by stimulating erythroid progenitors and precursors in the bone marrow. The molecule is made up of 165 amino acids. The secreted protein is heavily glycosylated, with ~40% of its mass composed of carbohydrate. The human EPO gene was cloned in 1983, allowing for clinical development of recombinant human EPO (rhEPO). Epoetin alfa (Epogen; Procrit; Eprex) is a commonly used form of rhEPO in the United States. Darbepoetin alfa is a hyperglycosylated analog of rhEPO that has a longer half-life. Major clinical uses of EPO include replacement therapy in anemia associated with chronic renal failure, malignancy, prematurity, or HIV infection. It can also be used to increase hemoglobin above physiological levels prior to a surgery or in situations where blood transfusion is not allowed [24, 25].

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