The first documented transfusion of blood in humans occurred in 1667, but it was not until almost 300 years later that transfusion became a therapeutic practicality. Landsteiner’s landmark discovery in the early 1900s of blood groups and agglutinating antibodies was the key that unlocked this therapeutic pathway. The development of anticoagulants, blood preservatives, and sterile collection sets in the middle of the 20th century made blood banking possible by enabling the collection and preservation of donor blood for later use.

In the past few decades, the complexity of blood banking and blood component therapy has virtually exploded. The recognition of both infectious and noninfectious complications of transfusion led to numerous practice changes involving blood donor screening, component production and modification, compatibility testing, and blood utilization. The menu of blood component options and therapeutic services has progressively expanded, along with efforts to establish evidence-based guidelines for their optimal use. Specialized recommendations have been developed for supporting specific patient populations such as immunosuppressed patients, chronic transfusion recipients, hematopoietic cell transplant recipients, and neonates. In the United States, all blood establishments (blood banks and transfusion services) are regulated by the US Food and Drug Administration (FDA). FDA regulations govern all aspects of blood collection, component processing, storage, compatibility testing, and administration. The FDA requires blood establishments to comply with highly stringent quality assurance standards that ensure control of processes and restrict variability. The AABB (formerly known as the American Association of Blood Banks) issues accreditation standards and recommendations that further establish the standard of practice in the US.

Today, Transfusion Medicine is itself a Board-recognized clinical specialty. In addition to overseeing the complex donor center and transfusion service operations, Transfusion Medicine physicians are increasingly important participants in the clinical care team. Transfusion Medicine specialists can guide the selection of therapeutic options to best support a patient’s medical needs, and coordinate the supply and delivery of these blood components and therapeutic services. This chapter serves as an introduction to blood components and transfusion services available in the United States.

**BLOOD DONATION AND COLLECTION**

**Donor Selection**

In the United States (US), donor eligibility criteria are established and enforced by the FDA and to a lesser degree by the American Association of Blood Banks (AABB). Donor selection is undertaken with two goals in mind: to protect the health of the donor by ensuring that a donation does not place the donor at risk, and to protect the recipient by ensuring that the donor meets all health and screening criteria so that the risk of transmitting infectious agents or causing other adverse events is minimized. In the US, most fresh blood products are from unpaid volunteers. These donors have decreased risk of transmitting infectious agents, especially in the “window period,” when screening tests fail to detect infection. Paying donors for fresh transfusion products was stopped after studies in the 1970s showed that paid donors had a much higher prevalence of hepatitis. Commercial plasma-derivative manufacturers still use paid donors, but comply with FDA-approved donor eligibility criteria and employ pathogen reduction processes during manufacturing that reduce infectious risks, as discussed later in this chapter.

**Donor Identification and Registration**

Donor registration must accurately identify the potential donor, including name, birthdate, address, and phone number, so the donor can be traced if needed. Records must link donors to all prior donations and test results and be kept for at least 10 years.

**Donor Information**

The donor must be given educational material describing signs and symptoms of AIDS and activities associated with increased risk of acquiring human immunodeficiency virus (HIV). The donor must be informed that testing may not detect all infections, and that individuals who have engaged in risk behavior should not donate.

**Donor Health History**

Information to be elicited is defined by the FDA and the AABB. The medical history is obtained by a trained interviewer, or donors may complete an FDA-approved self-administered questionnaire on paper or a computer. Responses are then reviewed with the donor by qualified staff. The history includes a review of current health, ensuring that the donor feels well, is free of signs of infection, and that his or her cardiovascular status can tolerate an acute blood volume loss of 10% to 15%. The donor is questioned about recent exposures to blood, potential exposure to HIV or hepatitis, sexual contact with individuals at risk for HIV, needle sharing by the donor or sexual partners, travel to or residence in areas endemic for malaria or variant Creutzfeldt-Jakob disease, medications, and immunizations.

The donor must meet certain requirements of age and vital signs. The hemoglobin must be at least 12.5 g/dl. Donor weight must be sufficient so that the donation constitutes no more than a 15% loss of blood volume. There must be no arm stigmata of parenteral drug abuse.

**Informed Consent**

The donor must sign the health history form verifying that all questions were answered truthfully, that the donation process is understood, and that he consents to testing for infectious agents transmitted by transfusion, including HIV and hepatitis.

**Additional Donor Criteria for Specific Components**

Donors may be eligible to donate some blood components but not others.

**Medications That Impact Therapeutic Effectiveness of Particular Blood Components**

Acetylsalicylic acid (ASA) irreversibly acetylates platelet cyclooxygenase and inhibits platelet aggregation.
hemostasis is restored, however, if ASA-inhibited platelets are mixed with untreated platelets. After a single dose of aspirin, ASA-exposed platelets are inhibited for the rest of their lifespan, but platelets produced after clearance of the drug restore hemostatic function. Therefore, platelets from donors who have taken ASA are acceptable as long as 48 hours have elapsed from the last dose. Platelets donated within 2 days of ASA ingestion are acceptable for use if mixed with platelets from unexposed donors.

Nonsteroidal anti-inflammatory drugs (NSAIDs) may impair platelet function, but the effects of many are reversible—that is, platelet function is restored once the platelets are removed from the offending drug. Therefore, individuals taking reversible NSAIDs can donate platelets for transfusion. Individuals who are taking irreversible NSAIDs, however, or other irreversible antiplatelet agents (e.g., ticlopidine) are not eligible to donate platelets for transfusion.  

Warfarin reduces levels of functional blood clotting factors (see Chapter 5). Transfusable plasma units or cryoprecipitate cannot be made from donors taking this medication.  

**TRALI Mitigation Strategies for “High Plasma Volume” Components**  

Studies in the early 2000s indicated that blood products containing a large volume of plasma (e.g., plasma and apheresis platelet units) were associated with a higher per unit risk of transfusion-related acute lung injury (TRALI) compared to components containing small amounts of plasma (e.g., red cell units and cryoprecipitate). Furthermore, plasma or platelet units containing donor antibodies to white blood cell (HLA and neutrophil) antigens were implicated in a substantial proportion of TRALI cases. In an attempt to reduce the frequency of TRALI, the AABB recommended in 2006 that blood collection agencies take steps to reduce production of high plasma volume products from donors with an increased likelihood of having WBC antibodies.

Women with a history of pregnancy are at highest risk of being immunized to WBC antigens. Therefore, in response to AABB recommendations, many blood collection facilities have stopped making transfusable plasma components from women with a history of pregnancy or from all women. Whole blood collections are still accepted from these women, but the plasma portion of their collections is used only for cryoprecipitate production and/or manufacturing into plasma derivatives. It has been more challenging to exclude women with a history of pregnancy from plateletpheresis donations, as the platelet supply is difficult to sustain. Some blood collection facilities exclude multiparous women as platelet donors or screen them for the presence of HLA antibodies.

**Directed Donations**  

A directed donation (DD) is a donation in which the donor directs his/her donated blood product to a specific designated patient. The donation must usually be ordered by the recipient’s doctor. DD programs exist primarily for emotional reasons, although these programs are required to be offered in certain states. In these programs, patients anticipating the need for blood can select who their donors will be. The donor is often a family member or acquaintance of the recipient. DDs are not of medical benefit when an established blood supply exists but can be useful in rare circumstances when specific characteristics of the donor’s blood are medically needed (e.g., for rare HLA or blood types obtained from family members). Directed donors must meet all regular donation criteria; however, exceptions can be made if rare types are needed. Data show DDs are no more safe than regular community donations from an infectious disease perspective. Directed donors are more likely to be first-time donors, who have a higher incidence of HIV and HCV than repeat blood donors. DDs theoretically may have higher risk of causing transfusion complications such as (1) hemolytic disease of the newborn in future pregnancies after a woman has received blood from her husband or his relatives, (2) TRALI in a mother to child transfusion, or (3) transfusion-associated graft-versus-host disease (TA-GVHD) from a related family donation. Directed donations from blood relatives are irradiated to prevent TA-GVHD.

**BLOOD COLLECTION PROCESS**  

Phlebotomy and collection of blood proceed only if the donor is deemed suitable pre-donation screening. Blood is collected in accordance with established standards and is collected either manually or with an automated collection device.

**Whole Blood (Manual) Collection**  

The phlebotomy site is swabbed with a disinfectant. Blood is collected in a primary plastic collection bag with a large bore needle allowing rapid flow and mixture with anticoagulant. The volume drawn is standardized for the collection bag used (either 450 or 500 ml). The blood draw is controlled by scales that discontinue flow when the desired weight is collected. Blood and anticoagulant are mixed gently during the collection. Specimen tubes for testing are also procured. Because most whole blood units will be separated into components, the primary bag has one or two attached satellite bags allowing separation of components in a sterile closed system. The collection tubing is heat-sealed into segments that are left attached to provide samples for cross-matching. The whole blood is transported to a laboratory where it can be separated into its components (red cells, plasma, platelets).

**Blood Component Separation**  

Whole blood is centrifuged to sediment the red blood cells (RBCs) (Fig. 21.1). Most of the supernatant “platelet-rich plasma” is pushed off into an attached sterile satellite bag. The bag containing platelet-rich plasma may then be centrifuged at a higher rate to sediment platelets. Most of the plasma is then removed into a third satellite bag. This leaves behind a platelet pellet which is then resuspended in 40 to 70 ml of residual plasma resulting in a platelet concentrate. If platelet concentrates are not going to be produced from the donation, the initial centrifugation of the whole blood is done at high speed, and the plasma is removed directly from the red blood cells and frozen. Further processing of plasma and red cell components is discussed later in this chapter.

**Terminology**  

The whole blood in the original collection bag (450 or 500 ml) is referred to as one whole blood unit, and each component made from that unit is defined as one “unit” of that component. Because a whole blood unit constitutes approximately 10% of a donor’s blood volume, each component can be considered roughly 10% replacement therapy for an adult patient.

“Closed” versus “Open” Systems  

If blood component manipulation is done without opening the system to air (closed system), all components may be stored to the limit of their viability. If the bag or tubing is entered, however, the system is considered potentially open to air/bacteria, and the product outdates in 4 hours if stored at room temperature or 24 hours if refrigerated. Devices using high-temperature welds can steriley attach additional containers or tubing to the original unit in a way that prevents entry of bacteria. With these “sterile connection devices,” blood components may be split into aliquots, filtered, or otherwise manipulated without loss of shelf life.
Automated Blood Collection and Separation Devices: Apheresis

The word apheresis is derived from a Greek word that means to separate or to take away. Initially, it referred to a manual process in which whole blood was withdrawn from the donor and centrifuged, the plasma retained, and the red cells returned to the donor. In 1914, Abel experimentally removed plasma from anephric dogs, and replaced it with crystalloid. It was not until the advent of plastic bags that manual apheresis could be used routinely in humans. Between 1950 and 1980, manual apheresis was the primary source of plasma for fractionation.

In the 1970s and 1980s automated cell separator devices changed the approach to apheresis. This technology has become the routine collection method for many blood components and is used in the treatment of many diseases.

In discontinuous centrifugal devices, anticoagulated blood is collected into a spinning disposable bowl. Centrifugal force causes red cells to move to the outside of the bowl, and platelet-rich plasma moves to the inside. White blood cells (WBCs) (buffy coat) settle in between. With optical detectors, the desired component is pumped into an attached plastic blood bag. The remaining components are returned to the donor.

Continuous flow devices continuously subject incoming blood to a centrifugal force, establishing a standing cell gradient. The fraction(s) to be removed is pumped into a bag, and the rest is reinfused continuously. The extracorporeal blood volume is lower than with the discontinuous technique, and the procedure is faster. An increasing proportion of blood components are being collected using automated cell separation. These devices can collect multiple unit-equivalents of red cells, plasma, or white cells from one donation. Apheresis is the main source of plasma for fractionation because multiple units of plasma may be obtained without red cells and possible resultant iron deficiency. Apheresis technology is now used to collect the majority of platelets in the US and in many regions apheresis platelets have entirely replaced platelets derived from whole blood units.

Apheresis platelets have several advantages. Up to three therapeutic platelets doses (equivalent to 18 whole blood–derived platelet units) can be obtained from one apheresis donation. This minimizes possible recipient exposure to infectious agents. If a donor is large enough, it is possible to obtain two RBC unit-equivalents from one apheresis donation, returning plasma, platelets, and saline to the donor to minimize volume loss. Some apheresis devices can be programmed to collect any desired combination of red cells, plasma, or platelet products from the same donation. Apheresis technology is also used for therapeutic plasma exchange (TPE) and for collection of peripheral blood hematopoietic progenitor cells (HPCs) or donor lymphocytes, as discussed later in this chapter and in Chapter 102.

Membrane filtration can be combined with apheresis to collect plasma. Blood is pumped over a membrane with a specific pore size that permits passage of plasma but not cells. Such devices have been used to collect plasma for fractionation or to perform TPE.

Complications of Donation

Most people easily tolerate blood donation but occasional problems arise, the most common of which are from venipuncture, consisting of bruises, soreness, and hematoma. These complications may be striking but usually resolve spontaneously. Nerve irritation and/or injury (0.02% to 0.9%) and arterial puncture (0.003% to 0.01%) are less common. Donors normally compensate for volume loss by increasing heart rate and vascular resistance, but 2% to 7% of donors experience vasovagal reactions, with syncope occurring in 0.1% to 0.3%. Fatigue (8%), nausea, and vomiting (1.1%) are also seen. Apheresis donors can develop transient symptomatic hypocalcemia (tingling or muscle cramps) from the citrate infused when anticoagulated blood components are returned to them. These symptoms are treated by slowing the flow of the device and or giving the donor oral calcium supplements. Apheresis donors can develop transient symptomatic hypocalcemia (tingling or muscle cramps) from the citrate infused when anticoagulated blood components are returned to them. These symptoms are treated by slowing the flow of the device and or giving the donor oral calcium supplements. Intravenous calcium infusions are needed only during prolonged apheresis procedures such as these for HPC collection.
Donor Testing

Every blood donation undergoes a series of tests to determine its suitability for transfusion. In the United States, the following tests must be performed on every unit collected: ABO group and Rh type, red cell antibody screen, serologic tests for infectious markers including hepatitis B surface antigen (HBsAg), antibodies to hepatitis B core (HBc) antigen, hepatitis C, HIV-1 and -2, human T-cell lymphotropic virus (HTLV)-I and -II, and syphilis, and nucleic acid tests for HIV-1 RNA, HCV RNA, and West Nile virus RNA. In 2010 the FDA recommended one-time testing of allogeneic donors for antibodies to T. cruzi (the causative agent of Chagas disease). Donor testing is discussed more fully later in this chapter.

Blood components are not released for transfusion unless all donor tests for infectious markers are negative. This extensive testing results in a delay of 24 to 48 hours from the time of collection until an RBC component can be released for transfusion. Platelet products are typically not available until 36 to 48 hours after collection because of additional bacterial testing (see Bacterial Contamination).

RED BLOOD CELL PRESERVATION AND STORAGE

RBCs are collected and stored in solutions that maintain their viability.

Anticoagulant/Preservative Solutions

Blood banking was not practical until anticoagulant and preservative solutions capable of preserving red cells in viable form were developed.

Citrated anticoagulant is used for essentially all transfusable blood components today. It chelates ionized calcium in blood, blocking calcium-dependent coagulation steps. After transfusion, citrate is readily metabolized by the liver.

During World War I, a sodium citrate and glucose solution was developed that permitted blood storage for several days. This citrated blood was used to treat shock in British and American soldiers. During World War II, it was found that the addition of citric acid (acid citrate dextrose [ACD]) preserved RBCs for 21 days. Continued efforts resulted in citrate phosphate dextrose (CPD) solution, a modified ACD, with added NaH₂PO₄ and a higher pH. Stored in CPD, red cell phosphate and 2,3-diphosphoglycerate (2,3-DPG) are maintained at higher levels than in ACD; however, RBC viability was still only 21 days.

In the 1950s, it was noted that red cells that had lost their adenosine triphosphate (ATP) did not survive well during storage. Nakao showed that ATP content and posttransfusion viability of aged red cells could be improved by the addition of adenine, which allows the RBCs to maintain the adenine nucleotide pool. Simon et al. described the maintenance of red cell ATP levels using preservatives containing glucose and low concentrations of adenine, leading to the adenine-supplemented anticoagulants now in use. CPDA-1, which is CPD fortified with adenine, became available in the United States in 1978. It had been used extensively in Europe for several years before then. Initial concerns about potential toxicity of adenine proved to be unfounded. CPDA-1 is now a common anticoagulant-preservative and allows storage of RBC concentrates for 35 days.

Packed Red Cells versus Red Cells in Additive Solutions

After whole blood is collected into CPD or CPDA-1, the red cells may be centrifuged, allowing removal of most of the plasma (“packed RBCs”). Approximately 20% of the anticoagulant-containing plasma must be left to provide metabolic substrate for RBCs during storage. Another approach to red cell preservation involves more complete removal of the anticoagulated plasma from the red cells (“dry pack”), followed by resuspension of the red cells in 100 ml of an additive solution. Such additive solutions contain saline, adenine, and glucose, with or without mannitol to decrease hemolysis. The storage of RBCs in additive solutions is extended to 42 days. RBCs in additive solution are now the most common preparations for transfusion. RBCs collected in any of the anticoagulants and preservatives must be stored at 1° to 6°C to maintain optimum function.

Changes in Red Cells during Storage

Stored liquid RBCs undergo biochemical and structural changes that have major influences on their viability and function after transfusion.

Structural Changes

A number of red cell changes contribute to decreased cell viability after storage. RBCs are normally disc shaped. Soon after storage they become spherical with surface projections (spherocytosis). Later defects include loss of membrane lipids and protein, as well as alterations in structural proteins. Loss of membrane deformability correlates with viability. The more severe membrane changes are irreversible and probably contribute to decreased posttransfusion RBC survival.

Blood bag plasticizers appear to influence membrane stability. Red cells are stored in polyvinyl chloride (PVC) bags that contain the plasticizer di-2-ethylhexylphthalate (DEHP). Morphologic deterioration is greater in RBCs stored in containers that do not have DEHP, with increased hemolysis and loss of deformability, suggesting that DEHP has a direct membrane stabilizing effect. Adding DEHP can both prevent and repair deterioration of stored red cells, with many of the spherical cells reverting to normal discoid morphology. However, concerns have been raised about potential toxic effects of DEHP. Efforts are being made to find alternatives to DEHP.

Biochemical Changes

During storage, red cells metabolize glucose, producing lactic and pyruvic acid, resulting in lower pH and decreased glycolysis. As glycolysis slows, RBC ATP content falls. Because human RBCs contain no enzymes to synthesize adenine or other purines de novo, the nucleotide pool gradually becomes exhausted. In the presence of adenine, ATP may be regenerated. Understanding this has led to prolonged RBC storage by the addition of exogenous adenine and inorganic phosphate, both of which improve the cells’ ability to regenerate ATP.

Red cells lose potassium and gain sodium during storage. This is because the Na⁺-K⁺ gradient is normally maintained by a Na⁺-K⁺ ATPase that does not function well at 4°C. Gamma irradiation of red cells to prevent graft-versus-host disease (GVHD) (see section GVHD) doubles the rate of potassium leakage. Red cells reabsorb potassium after transfusion.

Red Cell 2,3-Diphosphoglycerate

Another significant change in stored RBCs is 2,3-DPG depletion, which decreases RBC oxygen delivery. In blood preserved in ACD, 2,3-DPG drops to below 50% within 48 hours. In CPD, CPDA-1, and additive solution–stored red cells, 2,3-DPG is better maintained but is still depleted after about 2 weeks. Studies show that if RBCs are cooled down rapidly to 17 to 18 degrees C within 1 hour after collection, the fall of 2,3-DPG can be delayed.
significant. 2,3-DPG levels improve rapidly within the first 6 hours after transfusion, and return to near-normal levels within 24 hours.48,52

The clinical implications of transfusion of blood with decreased 2,3-DPG content is controversial.32,53 The oxygen dissociation curve of cells that are 2,3-DPG-depleted is shifted to the left, resulting in increased hemoglobin oxygen affinity and decreased tissue oxygenation. These changes are thought to be of limited clinical significance because the stored red cells rapidly regain their 2,3-DPG in the circulation. In select patients, such as those in shock, lower RBC 2,3-DPG levels may have a negative effect. However, the acidosis that may be present in such patients shifts the oxygen dissociation curve to the right. Because of such compensatory mechanisms, the need for blood specifically altered to preserve or reconstitute red cell 2,3-DPG has not been demonstrated.

Rejuvenating Solutions
A number of chemical agents—dihydroxyacetone,54 pyruvate,55 phosphoenolpyruvate,56 and inosine57—are capable of maintaining near-normal red cell 2,3-DPG content during storage, or of replenishing 2,3-DPG after storage. Although none of these chemicals are likely to be used in transfusion because of their side effects, studies with these agents have resulted in the development of rejuvenating solutions.

Rejuvenating solutions contain pyruvate, inosine, glucose, phosphate, and adenosine, and may be added to red cells up to 3 days after the expiration date. Treatment with rejuvenating solutions corrects the metabolic defects of the red cell, with a return to normal levels of ATP and 2,3-DPG. These rejuvenated red cells may either be washed and transfused within 24 hours or frozen for later use.5 Such rejuvenated red cells have a normal survival and oxygen affinity.58-60 In practice, rejuvenation is rarely performed.

In Vivo Recovery of Stored Red Cells
After transfusion of stored blood, red cells that have developed lethal degrees of damage are removed promptly from the circulation of the recipient. Red cells that survive the first 24 hours after transfusion have normal survival thereafter.61,62 Therefore, the criterion by which the adequacy for transfusion of banked blood is assessed is the proportion of transfused red cells that remain in circulation at 24 hours after transfusion. Generally, 75% survival at 24 hours is considered evidence of adequate viability; the anticoagulant systems in current use readily achieve this goal. Work to develop optimal additive solutions capable of maintaining red cell ATP and 2,3-DPG levels and to prolong red cell storage time continues.

Clinical Implications of Stored Blood
Whether the age of transfused blood affects clinical outcomes is highly controversial, with many studies coming to different conclusions.63,64 For a variety of complex methodologic reasons, the ability of even well-designed randomized controlled trials to demonstrate significant clinical differences based on the age of transfused blood has been questioned.65

Frozen Red Cells
Red cell freezing is a labor-intensive process that is used primarily for storing rare blood types or prolonged storage of autologous red cells in the event of planned or postponed surgery. Glycerol is gradually added to the red cells as a cryoprotectant to a final concentration of 40% (weight/volume). The cells are then frozen at −65°C or colder for up to 10 years. Immediately after thawing, an automated cell processor must be used to wash the glycerol from the cells. The washed cells are resuspended in isotonic saline and glucose. In most cases, postthaw storage is limited to 24 hours because an open system is used to process the cells.7 However, a closed system maintaining sterility has been developed and RBCs processed in this manner can be stored in a refrigerator for up to 2 weeks after thawing.66,67

Potential new technologies for RBC biopreservation are now under investigation, such as hypothermic storage and lyophilization. Hypothermic red cell storage potentially maintains higher levels of 2,3-DPG but still requires improvements. Lyophilization of red cells potentially would allow stable, indefinite, room temperature storage and would be ideal for remote storage and military applications. These methods have still not been sufficiently developed.68

PLATELET PREPARATION AND STORAGE

Preparation of Platelet Concentrates
Platelets, like erythrocytes, are actively metabolizing cells and require specific conditions for their preparation and storage to optimally maintain viability and function.69,70 They are prepared for transfusion either as platelet concentrates from whole blood or by apheresis. Although the preparation differs, both products are stored under the same conditions.

Platelet concentrates may be prepared from whole blood collected into bags with satellites (Fig. 21.1). The anticoagulants in current use, CPD and CPDA-1, are satisfactory for preparation of platelet concentrates. The whole blood is kept at room temperature and must be processed within 8 hours of collection. The unit of whole blood is centrifuged at low speed at room temperature, and the supernatant, platelet-rich plasma is expressed into a satellite bag. The supernatant is centrifuged again to further concentrate the platelets. Most of the supernatant platelet-poor plasma is expressed, and after 1 hour, the platelets are gently resuspended in the remaining plasma (50 to 60 ml). Approximately 60% to 75% of the donor platelets, or a minimum of 5.5 × 1010 platelets/unit, are recovered.71

In Europe and Canada, whole blood platelet concentrates are prepared from the buffy coat.2 Briefly, the whole blood unit is spun inverted at high speed, and the platelet-poor plasma and theuffy coat are withdrawn, each into its own satellite bag. Theuffy coat is then centrifuged at low speed to separate the platelets from the red and white cells. The functional quality of these platelets is comparable to those prepared by the American method.71 Platelet concentrates prepared from buffy coat contain fewer white cells than those prepared from platelet-rich plasma, although filtration is necessary to meet the European standards for leukoreduced products. In some European countries, platelet concentrates are pooled, resuspended in an additive solution, and filtered before storage.72 In the United States and Canada, the pooling of platelets before storage has been evaluated73,74,75; currently, only one system has been FDA-approved for this use in the US.76

Apheresis (Pheresis) Platelets
In the US the majority of platelets are collected from single donors by apheresis using the automated collection devices described earlier.7 Platelets collected in this way must contain at least 3 × 1011 platelets in approximately 300 ml of plasma by AABB standards. This is equal to about six whole blood platelet concentrates. With improved apheresis technology many platelets collections are so abundant that they can be split into multiple products that still meet the 3 × 1011 requirement. Apheresis platelets are leukocyte-reduced by the collection technology. Because the procedure
Platelet Storage and Functional Integrity

Platelet products must be kept under specific conditions to ensure optimal recovery and function. Unlike red cells, platelets stored at 4°C undergo shape changes and lose their viability. Platelet survival and function are optimized by storage at room temperature (20° to 24°C). During storage, platelets metabolize glucose to lactate and hydrogen, which are buffered by bicarbonate present in the plasma, resulting in a release of CO₂. The nature of the bag in which platelet concentrates are stored is important. The plastics used in the early era of platelet transfusion were made of PVC and plasticizers and were not permeable to O₂ and CO₂. In these bags, stored platelets become depleted of oxygen, resulting in a shift from oxidative to glycolytic metabolism, with increased lactate generation, decreased pH, and decreased platelet viability. As the pH decreases below 6.2, platelets undergo shape change, are damaged, and show reduced in vivo recovery. The platelets could not be stored for longer than 72 hours in the PVC bags. The plastic blood bags currently in use are more gas permeable. This permits continued oxidative metabolism and prolongation of storage time.

Despite this, however, platelet viability is maintained for up to 7 days in the new plastic containers. Storage of platelet concentrates at room temperature is currently approved for only 5 days in the US because of the risk of bacterial growth. Viability is best preserved if the platelets are gently agitated during storage. Platelets must be stored in sufficient plasma to maintain a pH greater than or equal to 6.2.

Even under optimum storage conditions, platelets, like red cells, develop a storage lesion. After storage at room temperature, the changes that occur in the platelets include decreased aggregation in response to single platelet agonists such as adenosine diphosphate, and reduction in adenosine diphosphate and ATP content both in granules and in the metabolic pool. Beta-thromboglobulin and platelet factor-4 are released, and both dense and alpha-granules are depleted. There is increased surface expression of P-selectin (CD62), a molecule derived from the alpha-granule membrane of the resting platelet. Platelets may develop morphologic changes and impaired responses to hypotonic shock. It has been difficult, however, to correlate the clinical response to platelet transfusions with specific in vitro findings.

The in vivo effectiveness of stored platelets is dependent on the recovery of transfused platelets in the circulation of recipients. This has been assessed through platelet recovery and survival studies in normal volunteers using autologous radiolabeled platelets. Platelet recovery is the percentage of transfused platelets that are found in circulation immediately after transfusion. Even when fresh platelets are transfused, only about two thirds of the transfused platelets are recovered in the circulation; the remaining 30% to 40% are pooled in the spleen. At the end of storage, mean platelet recovery is approximately 40% to 50%. After the initial recovery, there is little difference in survival of fresh versus stored platelets; both show a half-life of 3 to 5 days in healthy adults. In patients, however, the observed recovery and survival of transfused platelets are often substantially lower than these figures (as discussed in the section Dosage and Expected Response).

The in vivo hemostatic efficacy of transfused platelets is difficult to assess. The use of bleeding times in thrombocytopenic patients as an indicator of function is not of value because of great variability in technique and lack of reproducibility of results.

PREPARATION OF PLASMA COMPONENTS

Plasma is obtained from whole blood donations and apheresis collections. The plasma may be used for transfusion, further processed by the blood center into cryoprecipitate, or sent to commercial facilities for manufacturing into plasma derivatives.

Plasma Components for Transfusion

Plasma components such as FFP and cryoprecipitate are produced from individual volunteer blood donations and are briefly described here. As noted earlier, transfusable plasma units are not typically made from donors with an increased likelihood of having antibodies to WBC (e.g., women or women with a history of pregnancy); this strategy reduces the TRALI risk associated with plasma transfusion.
Fresh Frozen Plasma, Plasma Frozen within 24 Hours (FP24)

Fresh frozen plasma (FFP) is prepared by separating citrated plasma from whole blood and freezing it within 8 hours of collection or by freezing citrated apheresis plasma within 6 hours of collection. Each unit of FFP prepared from whole blood contains approximately 200 ml of plasma. Apheresis plasma may be packaged into 200- or 400-ml bags. FFP may be stored at −18°C or below for up to 1 year. Under these conditions, there is minimal loss of activity of the labile coagulation factors V and VIII. One milliliter of FFP contains approximately one unit of coagulation factor activity. After thawing, FFP may be stored in the refrigerator for up to 24 hours before use.

A product called “Plasma frozen within 24 hours after phlebotomy” (FP24) has largely replaced FFP production in the United States. As discussed earlier, TRALI mitigation strategies have restricted the donations from which transfusable plasma units can be made. In order to maintain a sufficient supply of plasma components for transfusion, most blood collection facilities in the US are labeling their plasma units as “Plasma frozen within 24 hours after phlebotomy” rather than “FFP.” This labeling permits blood centers to make transfusable plasma units from donations that reach the component processing facility more than 8 hours after collection. The content of FP24 is identical to that of FFP except that the Factor VIII content may be reduced to 80% that of FFP.109,110,111 This Factor VIII content is more than sufficient for the therapeutic applications in which plasma is utilized, e.g., trauma, liver disease, warfarin reversal, etc. Therefore, FFP and FP24 are typically used interchangeably.112

Liquid Plasma, Thawed Plasma

Liquid plasma is a term for plasma that is separated from whole blood and stored at 1°C to 6°C without freezing. Thawed plasma is a term for FFP or FP24 that is thawed and stored in the refrigerator for up to 5 days after thawing. The only significant difference between these products and FFP/FP24 is the content of the labile coagulation factors (V and VIII).

After 5 days of refrigerated storage, Factor VIII and V levels are at about 65% to 75% of their original levels. After 28 days’ storage, Factor VIII activity is approximately 40% of normal and Factor V levels approximately 50% to 60% of normal. Other coagulation factors, including fibrinogen, ADAMTS 13, and factors II, VII, IX, X, and XIII, are generally stable under refrigerated storage conditions.112,113,114-116,117

Liquid plasma or thawed plasma should not be used for clotting factor replacement in patients who have specific deficiencies of factor V or VIII. However, these products can be used for plasma replacement in massively bleeding patients, as these products will still maintain clinically hemostatic factor levels in the patient (i.e., 30% of normal). Because Vitamin K-related factors are not labile coagulation factors, they are present at about 65% to 75% of normal. One milliliter of FFP contains approximately 80 to 100 mg of fibrinogen.118,119

Plasma, Cryoprecipitate Reduced

This is the supernatant remaining after removal of cryoprecipitate from FFP (see “Cryoprecipitated Antihemophilic Factor”). Storage conditions are the same as for FFP. This product is deficient in fibrinogen, Factor VIII, von Willebrand factor (vWF), and factor XIII. Cryoprecipitate-reduced plasma was initially thought to be superior to FFP for treatment of TTP because of its lower vWF content. Randomized studies have verified that this fluid is therapeutically effective for TTP; however, it is not superior to FFP.115

Cryoprecipitated Antihemophilic Factor

Cryoprecipitated AHF, or cryoprecipitate, is an extract of FFP that is enriched in high-molecular-weight plasma proteins.

It is prepared by thawing one unit of FFP at 1°C to 6°C. Under these conditions, the high-molecular-weight proteins remain as a precipitate. The precipitated protein is concentrated by centrifugation, and all except approximately 15 ml of supernatant is removed. The remaining 15 ml and the precipitate are refrozen. Each unit of this cryoprecipitate contains approximately 80 to 120 units of Factor VIII and at least 150 mg of fibrinogen. It also contains factor XIII, fibronectin, and the high-molecular-weight multimers of vWF.

Cryoprecipitate was originally developed for the treatment of hemophilia A. It is no longer the treatment of choice for that disorder, because less infectious alternatives are available. At the present time, cryoprecipitate is most often used for correction of hypofibrinogenemia (<100 mg/dl) in bleeding patients. Cryoprecipitate has also been used topically, along with thrombin and calcium, as a “fibrin glue.” However, commercial products that are much more effective as topical hemostatic or sealant agents are now available. A commercial fibrinogen concentrate for intravenous infusion is available, but as of April 2012 this product was approved in the US only for treatment of congenital fibrinogen deficiency.

The typical dose of cryoprecipitate of one unit per 5 to 10 kg can be expected to raise the recipient’s fibrinogen level by approximately 70 mg/dl.120 Multiple units of cryoprecipitate are often pooled before administration.

Commercial Plasma Derivatives

Commercial plasma derivatives are made from pooled plasma collected from hundreds or thousands of donors. In the United States, paid plasmapheresis donors provide most of the plasma derivatives, but excess (“recovered”) plasma from volunteer whole blood donations is used also. Plasma units are pooled and fractionated into a number of purified proteins. The most commonly used fractionation procedure is based on Cohn’s cold ethanol fractionation process, developed in the 1940s.119 As the temperature, ionic strength, pH, and ethanol concentration are varied, plasma can be separated into several fractions. Fraction I contains factor VIII and fibrinogen, fraction II contains the immunoglobulins, and fraction V contains albumin. Fractions III and IV contain a number of other coagulation factors and proteins. Although other approaches such as ion-exchange chromatography have been applied to the preparation of certain plasma products, Cohn’s method remains the standard.

Because the plasma pools used for the production of plasma derivatives are derived from many donors, contamination with infectious agents is common. All plasma derivatives are treated by methods demonstrated to inactivate HIV, HCV, and hepatitis B virus (HBV), such as prolonged heat and treatment with organic solvents and detergents, which inactivates lipid-coated viruses. Pooled plasma products, however, could still transmit infectious agents that lack a lipid coat and that are resistant to heat. Human parvovirus B19 is one such agent. The FDA requires screening for, and exclusion of, donations that contain high titer of the B19 virus,120 but low levels of B19 virus can still be present in the pools. Many plasma derivatives undergo additional purification steps such as affinity chromatography, precipitation, or nanofiltration that would further reduce their contamination by infectious agents.119,121

There are many commercial plasma derivatives available. Some examples are described in the following.

Solvent/Detergent-treated Plasma

Solvent/detergent-treated plasma is made from hundreds or thousands of units of FFP that are then thawed, pooled, subjected to treatment with organic solvents and detergents, filtered, and refrozen.122 The product was developed to reduce the risk...
of transmitting enveloped viruses, such as HIV, HCV, and HBV. It appears to be therapeutically equivalent to FFP.\textsuperscript{122} A version of this product introduced in the US in the late 1990s was withdrawn after reports of thromboembolic complications. European versions of this product, however, are in current use and have a good safety record. In contrast to individual plasma units, this pooled plasma product has not been associated with transfusion-related acute lung injury (TRALI), presumably because of dilution of antibodies from individual donors during plasma pooling.

**Coagulation Factor Concentrates**

The coagulation factor concentrates, both the recombinant products and those made from plasma, are discussed in detail elsewhere as part of the management of inherited or acquired coagulation disorders (see Chapters 53 and 54). Recombinant coagulation products are used when available; these include Factors VIII, IX, and VIIa. Some factors are available only as plasma-derived concentrates, including fibrinogen and protein C.

**Immunoglobulins**

Intramuscular immune globulin preparations are prepared from pooled plasma by cold ethanol fractionation. They contain dimeric and polymeric IgG, artifacts of the fractionation procedure, which are capable of nonspecifically activating complement by both the classic and alternative pathways. This mechanism probably explains the major adverse effects that occur if these products are administered intravenously.\textsuperscript{117} Products labeled for intramuscular use must therefore not be given intravenously.

Intravenous immune globulin preparations (IVIGs) are produced by various chemical modifications designed to decrease the aggregation of IgG. Nonspecific complement activation is reduced, whereas the ability of the Ig molecules to interact with pathogenic organisms and complement is retained. Many of these products may also be administered subcutaneously.

Nonspecific immune globulin preparations contain a broad spectrum of antibodies naturally present in the donor population. They are most often used for treatment of primary immunodeficiency or as immune modulators.\textsuperscript{123} Immune globulins against a particular target are derived from the plasma of donors selected for high concentrations of antibodies to that target. Such preparations include Rh immune globulin, hepatitis B immune globulin, and Varicella zoster immune globulin.

IVIGs have been associated with some adverse reactions, including renal failure, hemolysis, and thrombotic events. Both IM and IV immune globulin products should be used with caution in patients with IgA deficiency, because they may contain small quantities of IgA.

**BLOOD COMPONENT MODIFICATION**

**Leukocyte Reduction**

When whole blood is separated by centrifugation, WBCs sediment at the interface between red cells and platelet-rich plasma. Therefore, WBCs typically contaminate both red cell and platelet components, with concentrations of WBCs approximately $10^9$/product. WBCs in blood components can mediate febrile transfusion reactions, stimulate HLA alloimmunization in transfusion recipients, and transmit some cell-associated pathogens such as cytomegalovirus (CMV).\textsuperscript{124} Therefore, it is desirable to remove WBCs from transfusable blood components.

Historically, several methods have been used to reduce the number of WBCs in transfusable blood components. Relatively nonspecific methods were used initially, including saline washing of red cells or physical separation of the WBC layer (buffy coat) from the RBCs.\textsuperscript{124} Later, microaggregate filters were used to remove WBCs after centrifugation.\textsuperscript{125} These methods resulted in white cell reduction of 70% to 90% and were effective in preventing most febrile reactions to red cells. Freezing and deglycerolization of red cells have also been used to remove WBCs and result in approximately 2-log WBC removal. Ultimately selective leukoreduction filters were developed that can reduce WBCs from blood components by 3 or more logs. These synthetic fiber filters remove WBCs by a combination of mesh density, chemical attraction, and active adhesion.\textsuperscript{124} All leukocyte-reduced red cells are now produced using these special filters and, by FDA criteria, have less than $5 \times 10^6$ WBCs/unit and at least 85% of the original RBC component.

Leukofiltration of RBC components may be performed at the blood collection center, in the hospital transfusion service, or at the bedside. Filtration prior to storage reduces WBC breakdown products in the blood component and there is some evidence that RBC viability is better preserved. The clinical importance of these benefits has not been demonstrated.\textsuperscript{124} In practice, most RBC leukofiltration is performed by blood collection centers within the first few days after collection.

Apheresis platelets usually contain very few WBCs and usually qualify as leukoreduced ($<5 \times 10^6$ WBCs) without the need for filtration. In contrast, whole blood–derived platelet concentrates contain large numbers of WBCs, and many of the febrile transfusion reactions to these products appear to be due to cytokines produced by the WBCs in these products during storage.\textsuperscript{126,127–129} Therefore, removal of WBCs from whole blood–derived platelet concentrates before storage is beneficial. One system is approved in the US that allows prestorage leukocyte reduction and pooling of whole blood platelets.

The use of leukoreduced products has evolved over the last decade or two. Initially these products were indicated for patients with a history of febrile, nonhemolytic transfusion reactions, to reduce the risk of HLA alloimmunization, and as an alternative to cytomegalovirus (CMV) antibody screening of donors to reduce the risk of transfusion-transmitted CMV. Now the use of leukoreduced products has become nearly universal, although the medical necessity of universal leukoreduction remains somewhat controversial.\textsuperscript{130}

**Washed Products**

Saline washing with automated cell washers can be used to reduce the amount of plasma in cellular blood products. These washers are capable of removing approximately 99% of plasma proteins from red cell products.\textsuperscript{2} Although cell washing was previously used also for leukocyte reduction, it is no longer used for this purpose. Today, washing is primarily used to reduce incompatible plasma and also prevent severe allergic reactions (which are thought to be triggered by donor plasma proteins). Washing is also used to reduce RBC supernatant potassium, which may be required prior to massive or rapid infusion of stored RBC to neonates. Washing on an automated cell processor takes 30 to 45 minutes/unit. Because the washing procedure is usually performed in an “open” system, the red cells have only a 24-hour shelf life after washing. A closed processing system has been developed that may permit longer storage of washed cells.\textsuperscript{66} Although many facilities perform red cell washing, few offer washed platelets. Use of automated cell washers to wash platelets has been described.\textsuperscript{2} However, in practice, it may be difficult to ensure adequate platelet recovery and viability after washing.

**Irradiation of Blood Products**

Gamma irradiation of cellular blood components is used to prevent transfusion-related GVHD by impairing the proliferative capacity of lymphocytes in the blood component. The recommended dose
for the irradiation of blood and blood products is 2500 cGy at the center of the irradiation field, with a minimum dose of 1500 cGy at any point in the field.\textsuperscript{5,131} This dose of radiation has no significant adverse effect on red cell, platelet, or granulocyte function. However, there are changes in the red cell membrane that result in an increased loss of potassium from the cell, limiting the storage time of red cell concentrates to 28 days.\textsuperscript{46,47} The amount of accumulated free potassium in the supernatant of irradiated red cells may be clinically important in massive transfusion, especially in the neonate.\textsuperscript{132} It may be desirable to irradiate proximate to transfusion, or wash stored irradiated RBCs if massive transfusion of irradiated products is required for a patient at risk for hyperkalemia. The dose of irradiation used for cellular blood components is not sufficient to inactivate pathogens.\textsuperscript{132} The irradiation doses required for pathogen inactivation would irreparably damage blood components.

**ALTERNATIVES TO ALLOGENEIC DONOR BLOOD**

**Autologous Blood**

Autologous blood donation is blood donated by a patient, intended for transfusion back into the same patient. Blood collected for autologous use is not released to other patients.

Use of a patient’s own (autologous) blood may reduce or eliminate the need for allogeneic blood. There are three types of autologous blood collection procedures. In preoperative autologous donation (PAD), patients donate one or more units of blood to a bank during the weeks preceding an elective procedure. In acute normovolemic hemodilution (ANH), blood units are collected in the operating room immediately prior to surgery. In autologous blood cell salvage, blood lost during or after a surgical procedure is salvaged for reinfusion.

**Preoperative Autologous Donation**

Preoperative blood donation (PAD) is most often used for patients who are expected to require transfusion during elective surgery. It is also used in patients for whom crossmatch-compatible blood cannot otherwise be made available, as in patients with rare blood groups or with multiple alloantibodies. For autologous collections, the donor eligibility criteria are not as stringent as for allogeneic donors. The key consideration is whether the patient can tolerate the acute withdrawal of a unit of whole blood representing 10% to 15% of their blood volume. Patients with significant cerebral or cardiac disease should be evaluated before they are enrolled in a PAD program. Children are also eligible for autologous blood donation, but the volume of blood collected and anticoagulant used must be adjusted to body weight.

An autologous donor may donate blood every 3 days as long as the donor’s hemoglobin remains at or above 11 g/dl. An “aggressive” donation schedule stimulates a more substantial endogenous erythropoietin response, with the potential for more autologous units collected or a higher patient hemoglobin at surgery.\textsuperscript{134} In most instances, the units of blood are stored in the liquid state for up to 35 to 42 days. They may be frozen if a longer interval between donation and surgery is required, but this significantly increases the cost and is not routinely recommended.\textsuperscript{135,136}

All autologous collections must be tested for ABO group and Rh type. The units must be labeled For Autologous Use Only. If autologous blood is to be transfused at an institution that is not the collecting facility, the blood unit must be tested for transfusion-transmitted infectious diseases.\textsuperscript{2} Units with reactive infectious disease tests must be labeled with biohazard labels. Regulators permit the use of autologous units with positive infectious disease tests. However, some hospitals do not accept such units because of concerns related to the risk of accidental transfusion of the unit into the wrong patient.

PAD is not necessarily beneficial to the patient. There is a reported 12-fold increase in the number of autologous donors hospitalized after a donation compared to allogeneic donors, with an increased risk in the elderly.\textsuperscript{137} Iron supplementation is recommended, but may not be sufficient to prevent anemia, especially if the last unit of autologous blood is collected <7 days preoperatively. This anemia may increase the patient’s likelihood of requiring transfusion.\textsuperscript{138} PAD is expensive and the logistics of collecting and shipping the blood in the desired timeframe are complex. Autologous blood may be wasted or transfused unnecessarily, particularly if collected for procedures in which transfusion is rarely needed.\textsuperscript{139,140}

Transfusion complications such as bacterial contamination, febrile nonhemolytic transfusion reactions (FNHTRs), allergic reactions, and volume overload can occur with autologous transfusion.\textsuperscript{141} The possibility of an accident or error such as the transfusion of the wrong unit or an allogeneic unit into the autologous donor/patient has been reported to be as high as 1.2%.\textsuperscript{142} The cost-effectiveness of PAD is has been questioned, given its high cost, risks, and limited benefit.\textsuperscript{143}

**Acute Normovolemic Hemodilution**

The second approach to autologous blood procurement involves the withdrawal of blood immediately before the surgical procedure and replacing the blood with crystalloid, colloid, or both, thereby acutely lowering the patient’s hematocrit.\textsuperscript{139,144} The blood lost during surgery is therefore relatively dilute, reducing total red cell loss. The higher hematocrit blood withdrawn immediately prior to surgery is used for transfusion. Patients most likely to benefit from this maneuver are those with anticipated large surgical blood losses who can tolerate low intraoperative hematocrits.\textsuperscript{145,146}

Units collected by ANH can be stored at room temperature for up to 8 hours or at 1°C to 6°C for up to 24 hours.\textsuperscript{147} The blood so collected does not undergo any storage-related changes. The relative efficacy of ANH in comparison to other blood conservation techniques has been debated.\textsuperscript{146,148,149} The cost of ANH is significantly less than that of PAD because there is little incremental cost associated with collecting the blood and no required testing.\textsuperscript{149}

**Intraoperative and Postoperative Salvage and Reinfusion**

A third approach to autologous transfusion is the collection and retransfusion of blood lost during or after surgery.\textsuperscript{2,150} Perioperative salvage has been shown to be effective in reducing the need for allogeneic blood in a variety of surgical procedures. The AABB publishes Standards for Perioperative Autologous Blood Collection and Administration, which provide guidance for use of these blood conservation options.\textsuperscript{147}

There are two basic techniques available. Intraoperatively, an anticoagulated vacuum suction device can be used to collect blood from the surgical field and deliver it to a centrifuge-like device that washes the shed blood with saline before it is reinfused. Only red cells are salvaged by this method (platelets and plasma are lost). There has been concern about the safety of reinfusing materials suctioned from obstetric, cancerous, or contaminated surgical fields. Published experience to date, however, suggests that reinfusion of salvaged cells after processing with leukoreduction filters may be safe in these settings.\textsuperscript{151} Postoperatively, blood shed into joints or body cavities can be collected into sterile containers. The salvaged material must be filtered to remove fat and particles, and may then be reinfused either directly or after washing. The shed fluid contains red cell stroma, free hemoglobin, activated clotting factors, and fibrin degradation products.
It appears that there is not an increased risk associated with infusion of unwashed shed blood if the volume reinfused is limited to approximately 1 L. There is little value to salvaging shed blood in settings where the volume of fluid drained from the surgical site is small or has a low hematocrit. Because these devices are expensive, patient selection is important.152

### Erythropoiesis Stimulating Agents

Erythropoiesis stimulating agents (ESA) have been used to stimulate red cell production in patients, either to increase the number of units that can be collected preoperatively, or to increase preoperative red cell mass.153 The use of epoetin alfa has been approved to facilitate autologous blood donation in the European Union, Canada, and Japan, but not in the United States.154 Epoetin alfa has also been approved for perioperative use in anemic patients (Hgb ≤13 g/dl) in the US and Canada.

### Artificial Oxygen Carriers

Some aspects that make the artificial oxygen carriers particularly appealing include: the prospect of being free of most or all of the infectious risks of allogeneic blood; no need to perform blood grouping and cross-match; extended shelf life and possibility of storage at room temperature; the potential for a virtually unlimited supply; and the possibility of development of homogeneous and standardized products with controlled characteristics optimized to achieve the goal of oxygen delivery without raising all other complexities of allogeneic blood.155–161 No artificial oxygen carrier is currently approved by the FDA for clinical human use in the US. Perfluorocarbon (PFC) emulsions boost oxygen delivery by increasing the amount of dissolved oxygen. Use of these oxygen carriers must be coupled with oxygen and increased FiO2 to further increase the amount of dissolved oxygen. The PFCs that reached clinical trials include Fluosol-DA (Alpha Therapeutics, Los Angeles, CA) and Oxygent (Alliance Pharmaceutical Corporation, San Diego, CA). Fluosol-DA was initially used to improve oxygen delivery to the heart muscle during percutaneous transluminal coronary angiography, but it was subsequently withdrawn because of difficulties in storage and preparation, and lack of utilization in angioplasty.

Hemoglobin-based oxygen carriers (HBOCs) increase the oxygen delivery by increasing total hemoglobin. Despite being an effective oxygen carrier, vasoconstriction (initially attributed to extravasation of the HBOC to interstitial space and scavenging nitric oxide)161, hypertension, and renal, pancreatic, and liver injury have been described as complications. Approaches such as purification, polymerization, cross-linking, conjugating with other macromolecules, and encapsulating in vesicles or other nanoparticles have been pursued to minimize toxicity and associated complications in subsequent generations of HBOCs.162

A 2008 meta-analysis of 16 trials on 5 different HBOCs indicated that regardless of the individual product or indication studied, HBOCs are associated with significantly higher risk of death (relative risk of 1.30) and myocardial infarction (relative risk of 2.71) compared to the controls.163,164,165 A new generation of products is in development as “oxygen bridges” until anemia management via compensatory erythropoiesis with production of cellular hemoglobin can be achieved with the use of ESA and intravenous iron therapy.

### USE OF BLOOD COMPONENTS

Table 21.1 lists the blood components available for clinical use and briefly summarizes the indications for the use of each. The use of each component is discussed in detail in the following sections.

### Patient Informed Consent

Although approximately 14 million units of RBCs are transfused in the United States each year, their efficacy has never been demonstrated in well-designed trials. For purposes of obtaining the patient’s informed consent, the treating physicians and patient must understand that not all is known about the relative risks and benefits of blood transfusion.

The elements of transfusion consent comprise: a discussion of blood transfusion risks166,167 and benefits; alternatives to blood; an opportunity to ask questions; and patient consent.168 Consent should occur as far in advance of transfusion as possible, so that alternatives to allogeneic blood such as autologous blood can be made available. Some states have legislated that alternatives to allogeneic blood be offered to patients whenever there is a reasonable possibility that a blood transfusion may be necessary. It should also be noted that blood transfusion has been legislated to be a medical service not subject to commerce and trade laws, thus excluding the principle of implied warranty and granting blood banks immunity from strict product liability.169

### Patient Blood Management

Of the estimated 39 million discharges in the US in 2004, 5.8% (2.3 million) were associated with blood transfusion.170 The rate of blood transfusion more than doubled from 1997 to 2009. Increased provider awareness of the costs associated with blood transfusion171 and recognition of the potential negative outcomes have stimulated initiatives in Patient Blood Management.172 Blood Management has been defined as the appropriate use of blood and blood components, with a goal of minimizing their use. This goal has been motivated historically by: 1) known blood risks; 2) unknown blood risks; 3) preservation of the national blood inventory; and 4) constraints from escalating costs.172

Patient-focused blood management173 is an evidence-based approach that is multidisciplinary (transfusion medicine specialists, surgeons, anesthesiologists, and critical care specialists) and multiprofessional (physicians, nurses, pump technologists, and pharmacists). Preventative strategies are emphasized to identify, evaluate, and manage anemia174,175 (e.g., pharmacologic therapy176 and reduced iatrogenic blood losses from diagnostic testing)176; to optimize hemostasis (e.g., pharmacologic therapy177 and point of care testing)178; and to establish decision thresholds (e.g., guidelines) for the appropriate administration of blood therapy (the impact of these activities on blood transfusion outcomes is illustrated in Figure 21.2).172,179,180

In the US, the Joint Commission (TJC) developed Patient Blood Management Performance Measures which have been placed in their Topic Library. These are available to be used as additional patient safety activities and/or quality improvement projects by provider institutions.181

Patient Blood Management strategies for patients undergoing cardiac surgery have been shown to be safe and effective in reducing transfusion, while at the same time delivering high-quality outcomes. One institution reported that only 11% of patients undergoing cardiac surgeries received blood transfusions; this program ranked first in their state for lowest risk-adjusted mortality.182

### RED CELL TRANSFUSION

The main indication for RBC transfusion is inadequate oxygen delivery as a result of anemia and, in some cases, hypovolemia. Wound healing is not impaired in the presence of anemia, and transfusion does not improve wound healing. Patients with chronic diseases should never be transfused simply because of mild asymptomatic anemia or as part of supportive care.
provides insight into the circumstances in which transfusion may serve as an absolute indicator of transfusion need. However, approximately 3.5 to 4 g/dl. and an oxygen extraction ratio of 50% occur at a hemoglobin of approximately 6 to 7 g/dl. The heart is the principal organ at risk in acute anemia. In a normal heart, increased lactate production and an oxygen extraction ratio of 50% occur at a hematocrit of approximately 3.5 to 4 g/dl. In a model of coronary stenosis, the anaerobic state occurs at a hemoglobin of approximately 7 g/dl.

**Indications for Red Blood Cell Therapy**

The therapeutic goal of a blood transfusion is to improve oxygen delivery according to the physiologic need of the recipient. The usual response to an acute reduction in hemoglobin in the normovolemic state is to increase cardiac output to maintain adequate oxygen delivery. The heart is the principal organ at risk in acute anemia. In a normal heart, increased lactate production and an oxygen extraction ratio of 50% occur at a hematocrit of approximately 3.5 to 4 g/dl. In a model of coronary stenosis, the anaerobic state occurs at a hemoglobin of approximately 6 to 7 g/dl. No single number, either extraction ratio or hemoglobin, can serve as an absolute indicator of transfusion need. However, the use of a physiologic value in conjunction with clinical assessment of the patient status would permit a rational decision regarding the appropriateness of transfusion before the onset of hypoxia or ischemia.

**Literature on mortality in surgical patients refusing transfusion provides insight into the circumstances in which transfusion may be of benefit. In a review of 16 reports of the surgical outcomes in Jehovah’s Witness patients who underwent major surgery without blood transfusion, mortality associated with anemia occurred in only 1.4% of the 1,404 operations. A more detailed analysis of 61 studies of Jehovah’s Witness patients found that, with the exception of three patients who died after cardiac surgery, all deaths attributed to anemia occurred in patients with hemoglobin ≤ 5 g/dl. In one large study of surgical patients refusing transfusion, the risk of death was found to be higher in patients with cardiovascular disease than in those without. A subsequent analysis found that although the risk of death was low in patients with postoperative hemoglobin levels of 7.1 to 8.0 g/dl, morbidity occurred in 9.4%; the odds of death in patients with a postoperative hemoglobin level ≤ 8 g/dl increased 2.5 times for each gram decrease in hemoglobin level.

A large retrospective study of elderly patients who underwent surgical repair of hip fracture found that transfusion of patients with hemoglobin levels ≥ 8 g/dl did not influence 30-day or

**TABLE 21.1**

<table>
<thead>
<tr>
<th>Component</th>
<th>Composition</th>
<th>Volume</th>
<th>Indications and Expected Benefit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whole blood</td>
<td>RBC and plasma (approx. Hct, 40%); WBCs; platelets&lt;sup&gt;a&lt;/sup&gt;</td>
<td>500 ml</td>
<td>To increase red cell mass and plasma volume; plasma deficient in labile clotting factors V and VII; for hypovolemic anemia, massive transfusion, or exchange transfusion in neonates.</td>
</tr>
<tr>
<td>Packed RBCs</td>
<td>RBC and reduced plasma (approx. Hct, 75%); WBCs; platelets&lt;sup&gt;a&lt;/sup&gt;</td>
<td>250 ml</td>
<td>To increase red cell mass in symptomatic anemia; 10 ml/kg raises Hct by 10%.</td>
</tr>
<tr>
<td>RBCs, adenine-saline added</td>
<td>RBC and 100 ml of additive solution (approx. Hct, 60%); WBCs; platelets&lt;sup&gt;a&lt;/sup&gt;; little plasma</td>
<td>330 ml</td>
<td>To increase red cell mass in symptomatic anemia; 10 ml/kg raises Hct by 8%.</td>
</tr>
<tr>
<td>RBCs, leukocytes reduced (prepared by filtration)</td>
<td>&gt;85% original volume of RBCs; &lt;5 × 10&lt;sup&gt;8&lt;/sup&gt; WBCs</td>
<td>&gt;85% of original volume</td>
<td>To increase red cell mass; &lt;5 × 10&lt;sup&gt;8&lt;/sup&gt; WBCs to decrease the likelihood of febrile reactions, immunization to leukocytes (HLA antigens), or CMV transmission.</td>
</tr>
<tr>
<td>RBCs, washed</td>
<td>RBCs (approx. Hct, 75%); reduced WBCs; no plasma</td>
<td>225 ml</td>
<td>To increase red cell mass; reduce risk of allergic reactions to plasma proteins; or reduce free potassium dose.</td>
</tr>
<tr>
<td>RBCs, frozen</td>
<td>RBCs (approx. Hct, 75%);</td>
<td>225 ml</td>
<td>To increase red cell mass; minimize febrile or allergic transfusion reactions; use for prolonged RBC blood storage.</td>
</tr>
<tr>
<td>RBCs, deglycerolized</td>
<td>&lt;5 × 10&lt;sup&gt;8&lt;/sup&gt; WBCs; no platelets; no plasma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Granulocytes, pheresis</td>
<td>Granulocytes (&gt;1.0 × 10&lt;sup&gt;11&lt;/sup&gt;/unit); lymphocytes; platelets (&gt;2.0 × 10&lt;sup&gt;11&lt;/sup&gt;/unit); some RBCs</td>
<td>220 ml</td>
<td>To provide granulocytes for selected patients with sepsis and severe neutropenia (&lt;0.5 × 10&lt;sup&gt;9&lt;/sup&gt;/L).</td>
</tr>
<tr>
<td>Platelet concentrates</td>
<td>Platelets (&gt;5.5 × 10&lt;sup&gt;11&lt;/sup&gt;/unit); RBCs; WBCs; plasma</td>
<td>50 ml</td>
<td>Bleeding due to thrombocytopenia or thrombocytopenia; 1 unit/10 kg raises platelet count by 17–50 × 10&lt;sup&gt;9&lt;/sup&gt;/L.</td>
</tr>
<tr>
<td>Platelets, pheresis</td>
<td>Platelets (&gt;3 × 10&lt;sup&gt;11&lt;/sup&gt;/unit); RBCs; WBCs; plasma</td>
<td>300 ml</td>
<td>Same as platelets; sometimes HLA-matched; benefit is equivalent to 6 platelet concentrates.</td>
</tr>
<tr>
<td>Platelets, leukocytes reduced</td>
<td>Platelets (as above); &lt;5 × 10&lt;sup&gt;8&lt;/sup&gt; WBCs/final dose of pooled or pheresis platelets</td>
<td>300 ml</td>
<td>Same as platelets; &lt;5 × 10&lt;sup&gt;8&lt;/sup&gt; WBCs to decrease the likelihood of febrile reactions, alloimmunization to leukocytes (HLA antigens), or CMV transmission.</td>
</tr>
<tr>
<td>FFP, thawed plasma</td>
<td>FFP: all coagulation factors; thawed plasma: reduced factors V and VII</td>
<td>200 ml</td>
<td>Treatment of some coagulation disorders; 10 ml/kg of FFP raises factor levels by approximately 10%.</td>
</tr>
<tr>
<td>Cryoprecipitated antiplasmin factor</td>
<td>Fibrinogen; factors VIII and XIII; von Willebrand factor</td>
<td>15 ml</td>
<td>Deficiency of fibrinogen, 1 unit/5 kg raises fibrinogen 70 mg/dL; also used for factor XIII replacement; not first-choice therapy for hemophilia A, von Willebrand disease, topical fibrin sealant.</td>
</tr>
</tbody>
</table>
These principles applied in the perioperative period enable treating physicians to have the time and tools to provide patient-centered evidence-based patient blood management in order to minimize allogeneic blood transfusions. (From Goodnough LT, Shander A. Patient blood management. Anesthesiology 2012;116:1367–1376, with permission.)

90-day mortality. This was confirmed by a subsequent randomized, prospective study. Prospective, randomized trials in patients undergoing cardiac surgery and receiving critical care have each demonstrated that such patients can tolerate anemia without transfusion to hemoglobin levels between 7 and 8 g/dl, with equivalent clinical outcomes comparable to patients maintained at hemoglobin levels of greater than 10 g/dl.

A Cochrane meta-analysis of prospective randomized trials comparing “high” versus “low” hemoglobin thresholds on more than 3700 patients found that a hemoglobin of 7 g/dl was sufficient for the majority of patients. AABB clinical practice guidelines suggest that patients should not be transfused with red blood cells, in the absence of symptoms/signs of anemia, unless the Hgb concentration is less than 7 to 8 g/dl, or less than 8 g/dl for patients with symptoms or known to have cardiovascular disease. Comprehensive blood management guidelines from the Societies of Thoracic Surgeons and Cardiovascular Anesthesiologists contain similar recommendations, suggesting that RBC transfusion may be life-saving when hemoglobin is less than 6 and is reasonable in most patients when hemoglobin is less than 7. However, it is unlikely that a hemoglobin value alone should serve as a “transfusion trigger;” patients should be managed, rather than laboratory values.

### Red Cell Transfusion in Specific Settings

#### Massive Hemorrhage

One of the major indications for blood transfusion is the restoration of circulating blood elements after the loss of large amounts of blood (Table 21.2). In general, adults who lose <20% of their blood volume (or approximately 1 L) do well without red cell transfusion, providing that fluid resuscitation is adequate to maintain the circulating blood volume and that further blood loss is avoided. Young healthy patients can sustain losses of up to 30% to 40% of blood volume as long as intravascular blood volume is adequately maintained with intravenous (IV) fluids.

Massive hemorrhage is generally defined as transfusion of more than 10 U of RBC (one complete blood volume replacement) within 24 hours. Massive hemorrhage is a common complication in a number of clinical settings. In traumatic injury, hemorrhage is a major cause of morbidity and is responsible for almost 50% of deaths occurring within 24 hours of injury and up to 80% of intraoperative trauma mortalities. In addition, cardiovascular and hepatobiliary procedures can frequently result in massive bleeding; postpartum hemorrhage events can complicate labor and delivery; and diverticulosis or varices can lead to significant gastrointestinal bleeding.
with use of MT protocols.212–214 Similar to the military data, such studies also support using a more aggressive RBC/plasma ratio, reporting a significant reduction (41% vs 62%) in 30-day mortality as compared with those that received less plasma.225 This was independent of age and Trauma Related Injury Severity Score, which by themselves were independent predictors of mortality.225

Several studies have called into question the benefit of higher plasma ratios.223,226 Nevertheless, the cumulative data appear to support early, proactive support with high ratios of plasma to RBC along with additional support with platelets.218,219 Not all studies showed a mortality benefit, and in the absence of randomized trials, data to convincingly support a particular ratio or formula are needed. However, the existing data suggest that a well-organized MT protocol that is activated in a timely fashion is likely to demonstrate improved patient outcomes and result in less overall blood product usage in large trauma centers.218,219

**Elective Surgery**

In preparation for surgery, preoperative requests for typed and crossmatched blood should be based on the predetermined likelihood of a procedure requiring a blood transfusion.172 Maximum surgical blood order schedules or “standard blood orders” specify the number of units that should be crossmatched for a variety of procedures and include guidelines for pretransfusion assessment.227,228 A pretransfusion request for type and crossmatch should be sent to the blood bank if it is likely (>10% probability) that blood will be required for a specific surgical procedure. The request should be for a type and screen if it is unlikely (<10%) that the patient will require blood. As discussed previously under patient blood management, preemptive evaluation and management of anemia to correct deficits in red cell mass is the single most important determinant of the likelihood of perioperative blood transfusions.172

**Nutritional Deficiencies and Other Anemic States**

RBCs are often transfused in the management of various types of anemia. Published guidelines (see above) advise transfusing on the basis of clinical indications. Physiologic adaptations to anemia, including elevated red cell 2,3-DPG content and increased cardiac output, compensate to preserve oxygen transport and delivery to a significant extent in chronic anemias. Transfusion is rarely indicated in these patients if there is time to correct anemia with alternative therapies.

Patients who are anemic solely because of deficiency of iron, folate, or 
\( B_{12} \) rarely require transfusion. Patients with “life-threatening” anemia (Hgb <6.5 g/dl) by WHO (World Health Organization) and NCI (National Cancer Institute) criteria may require transfusion.229 Elderly patients who present with pernicious or severe iron deficiency anemia may require red cell transfusion, particularly when angina or congestive heart failure has been the cause of the patient seeking medical attention. Iron-deficient patients who are also bleeding actively (e.g., from the gastrointestinal tract) may also require red cell transfusion. In such situations, the goal of transfusion is not to correct the patient’s hemoglobin concentration, but to raise it sufficiently to stabilize the patient until specific therapy can be administered.

**Hemolytic Anemias**

Patients with acute or chronic hemolytic anemias may require red cell transfusion; often, this need arises at the time of a hematologic or aplastic crisis. Such patients are often critically ill, and safe transfusion requires careful clinical attention. In autoimmune hemolytic anemia,290,291 the clinician may be faced with a severely anemic patient for whom crossmatch-compatible blood cannot be obtained. These patients produce an antibody that
reacts with all RBCs including their own, and the transfusion of serologically incompatible red cells may be necessary. At a hemoglobin <6 g/dl, most patients require transfusion. In these cases, withholding transfusion in the absence of “compatible” RBCs places the patient in needless danger. Although “incompatible” cells will have a shorter than normal lifespan, transfusion reactions are infrequent. The risk of complications is increased if the patient has brisk hemolysis and a large volume of blood is infused, or if the patient has an undetected alloantibody in addition to the autoantibody. If time allows, special techniques should be used to evaluate these patients for alloantibodies prior to transfusion (see “Autoagglutination”). Consultation with a transfusion medicine specialist is recommended in these cases.

**Hypoproliferative Anemias**

In aplastic and sideroblastic anemias, myelodysplastic states, and myelofibrosis, patients often depend on regular transfusion of red cells and may die of transfusion-induced iron overload after several years of such support unless precautions are taken to remove iron. The development and use of erythropoiesis stimulating agents have reduced the need for transfusion in many patients with hypoproliferative anemia, such as those with end-stage kidney disease (see Chapter 41) and in patients with chemotherapy-induced anemia.232

**Hereditary Red Cell Disorders**

In children with thalassemia (see Chapter 34), bone marrow hyperplasia with its undesirable effects on the skeleton may be ameliorated, and iron absorption decreased, by regular transfusions to maintain a near-normal hemoglobin concentration.233 Such a program is possible only in conjunction with an aggressive iron chelation program, as the iron load otherwise leads to fatal hemosiderosis. In patients with sickle cell disease and vaso-occlusive crises (see Chapter 33), the adverse microvascular effects of sickle cells can be relieved temporarily by hydration with crystalloid therapy to restore intravascular volume, rather than with RBC transfusions (to avoid chronically unnecessary risks of alloimmunization and iron overload). Red cell exchange may be indicated when impaired oxygenation leads to <95% O₂ saturation, in order to address the generation of sickle cells in acute chest syndromes. A multicenter trial (STOP trial) showed a significant decrease in the incidence of stroke in patients with abnormal transcranial Doppler studies who were treated with simple or exchange transfusions to maintain their hemoglobin S concentrations <30%, compared to patients who remained on standard supportive care with transfusion only when clinically indicated.234

**Pretransfusion Testing of Red Cells**

**Compatibility Testing Process**

The process of selecting red cells for transfusion involves three stages. Blood grouping involves determination of the ABO group and Rh type of both recipient and donor specimens. The recipient’s serum or plasma is screened for the presence of unexpected red cell antibodies. Crossmatching, either serologically or electronically, after selection of a donor unit of the appropriate group and type determines whether the donor cells are compatible with the recipient’s plasma.

Properly selected blood products will be compatible with the recipient, indicating that transfusion should not result in hemolysis of donor red cells. Because only the ABO and Rh(D) red cell antigens are prophyllactically matched in routine transfusion practice, there are always significant antigenic differences between donor and recipient, both for red cells and for the accompanying leukocytes, platelets, and plasma. Repeated exposure to foreign antigens with chronic transfusion or pregnancy may result in antibody formation in the recipient.

There is no room for error in the provision of blood for transfusion. If clerical or laboratory error results in donor and recipient being mismatched for the ABO group, transfusion of even a few milliliters of red cells may lead to a life-threatening transfusion reaction with shock, intravascular coagulation, and acute renal failure. Such reactions are uncommon because of rigid adherence to a routine designed to maximize safety at all levels of the transfusion process; however, with the decrease in the risk of transfusion-transmitted infections, such reactions are becoming one of the leading risks of transfusion.166,235 Careful identification of the patient for whom the blood is ordered, including complete labeling of the specimen at the bedside of that patient, is essential. Careful ABO blood grouping along with comparing results of ABO testing with historical records for each patient adds to the level of safety. Ensuring positive identification of crossmatched units of blood and verifying that the information identifying the unit with the intended recipient is reviewed in the presence of that recipient before the administration of the blood are crucial.2,3

**Blood Grouping**

The presence of ABO antigens is determined by testing the unknown RBCs with anti-A and anti-B sera by one of a variety of methods including slide, tube, gel, or microplate tests.2 Identifying which ABO antigens are on the surface of an individual’s RBCs is called the forward grouping or forward typing. Cells agglutinated only with anti-A serum are group A; those reacting only with anti-B are group B. Those reacting with both antisera are group AB, and red cells that fail to agglutinate with either anti-A or anti-B are group O.

“Reverse grouping” or “reverse typing” should be performed to confirm the reaction obtained by the forward grouping test. This involves testing the reactions of the serum or plasma from the person of unknown type with reagent red cells of known A and B type. Agglutination of the red cells indicates the presence of anti-A or anti-B in the individual’s serum. The conclusions of forward and reverse tests should agree as shown in Table 21.3.

The antisera used in blood group antigen detection can be obtained from donors with naturally occurring high levels of antibodies, from people or animals specifically stimulated to produce antibodies against blood groups, or from monoclonal antibodies of mouse or human origin. The advantages of monoclonal antibodies include their high quality and stability and their ease of production in large quantities. Antisera must be of known specificity and potency, and control testing must be done on a routine basis.2

The Rh type of red cells is determined by examining the cells’ reaction with anti-D serum from commercial sources. Commercial

---

**Table 21.3**

**ABO Grouping**

<table>
<thead>
<tr>
<th>Patient Blood Group</th>
<th>Patient’s Cells with</th>
<th>Patient’s Serum with</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Anti-A</td>
<td>Anti-B</td>
</tr>
<tr>
<td>O</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>A</td>
<td>+</td>
<td>None</td>
</tr>
<tr>
<td>B</td>
<td>None</td>
<td>+</td>
</tr>
<tr>
<td>AB</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>
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Antisera may be modified by the manufacturer with the addition of high concentrations of protein or by chemically altering the immunoglobulin (Ig) G molecules in such a way that they perform as direct agglutinins in the laboratory. This permits rapid, reliable testing to determine the D antigen status of the cells. However, these high-protein reagents may cause false positive reactions because of spontaneous aggregation of some red cells in their presence. If this happens, an Rh-negative patient could be typed as Rh-positive if the recommended Rh control is not tested simultaneously. This problem has led to the development of low-protein, saline-reactive monoclonal reagents. Monoclonal anti-D reagents contain both human IgM and polyclonal IgG antibodies and are currently most widely used. They can also be used in the antiglobulin test for weak D. As with all reagents, the manufacturers’ instructions must be followed.

Red cells reacting weakly with anti-D reagents are called weak D. If donor blood is being tested, the absence of D must be confirmed. If the initial test for D is negative, a second, more sensitive test must be performed using a method that detects weak D. If D is detected by either method, the unit is labeled Rh-positive. In patients, testing for weak D is not required. Patients who are typed as Rh-negative, but who are really weak D-positive, will not be adversely affected by the transfusion of Rh-negative products.

Patients known to be weak D-positive, however, may be given Rh-positive donor blood. Before concluding that a patient is weak D-positive, care must be taken to ensure that the patient has not recently been transfused with Rh-positive red cells or experienced a large fetal–maternal hemorrhage.

Testing for Red Cell Antibodies

Antibodies in potential blood transfusion recipients fall into several categories. The most common blood group antibodies that are clinically significant and may be implicated in hemolytic transfusion reactions or hemolytic disease of the newborn are shown in Table 21.4.

All human plasmas contain naturally occurring antibodies that react with the complementary antigens of the ABH system. These are of great importance in transfusion, as they are complement-fixing IgM antibodies; transfusion of incompatible red cells leads to immediate hemolytic reactions. Many people also have naturally occurring antibodies (usually low-titer IgM antibodies reacting at or below room temperature) that react with some antigens of the Lewis, P, Ii, MN, or other systems; these are rarely active above room temperature and are only occasionally important in transfusion. Finally, people exposed to foreign red cells by prior transfusion or pregnancy may produce IgG antibodies to antigens of certain other systems, primarily Rh (C, c, D, E, e), Kell, Duffy, Kidd, and Ss, but many less common possibilities exist. These red cell antibodies are clinically significant. They do not often lead to intravascular hemolytic reactions, but transfused incompatible red cells may exhibit decreased survival caused by increased clearance in the reticuloendothelial system. Many of these IgG antibodies can also cause hemolytic disease of the fetus and newborn.

There are two major classes of antibodies that react with red cells. Complete or saline antibodies agglutinate red cells suspended in saline solution; these are usually IgM. Antibodies that do not react visibly in saline and are capable of producing agglutination reactions only with special techniques to make their interaction with red cells detectable are called incomplete agglutinins; these are generally IgG antibodies.

The best example of a room temperature saline agglutination test is that used in ABO grouping. Other red cell antibodies that are readily detected in saline suspension are those belonging to

<table>
<thead>
<tr>
<th>Blood Group System</th>
<th>Antibody</th>
<th>Relative Frequency in Antibody Screening</th>
<th>Clinical Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABO</td>
<td>Anti-A</td>
<td>All group B and O</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>Anti-B</td>
<td>All group A and O</td>
<td>Yes</td>
</tr>
<tr>
<td>Rhesus</td>
<td>Anti-D</td>
<td>Common</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>Anti-c</td>
<td>Common</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>Anti-E</td>
<td>Common</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>Anti-C</td>
<td>Common</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>Anti-e</td>
<td>Uncommon</td>
<td>Yes</td>
</tr>
<tr>
<td>Kell</td>
<td>Anti-K</td>
<td>Common</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>Anti-k</td>
<td>Rare</td>
<td>Yes</td>
</tr>
<tr>
<td>Kidd</td>
<td>Anti-Jka</td>
<td>Common</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>Anti-Jkb</td>
<td>Rare</td>
<td>Yes</td>
</tr>
<tr>
<td>Duffy</td>
<td>Anti-Fya</td>
<td>Common</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>Anti-Fyb</td>
<td>Uncommon</td>
<td>Yes</td>
</tr>
<tr>
<td>MNS</td>
<td>Anti-M</td>
<td>Common</td>
<td>Rare</td>
</tr>
<tr>
<td></td>
<td>Anti-N</td>
<td>Rare</td>
<td>Rare</td>
</tr>
<tr>
<td></td>
<td>Anti-S</td>
<td>Uncommon</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>Anti-s</td>
<td>Rare</td>
<td>Yes</td>
</tr>
<tr>
<td>Lewis</td>
<td>Anti-Lea</td>
<td>Common</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>Anti-Leb</td>
<td>Uncommon</td>
<td>No</td>
</tr>
<tr>
<td>P</td>
<td>Anti-P1</td>
<td>Common</td>
<td>No</td>
</tr>
<tr>
<td>li</td>
<td>Anti-I</td>
<td>Uncommon</td>
<td>No</td>
</tr>
</tbody>
</table>
the Lewis, MN, P, and li blood group systems. With the important exception of ABO system antibodies, many of the others detected with this test are of no clinical significance, as they are not reactive at 37°C.

The best examples of incomplete agglutinins, or IgG antibodies, are those that react with antigens of the Rh system. If such antibodies are not detected in the recipient, immediate hemolysis of transfused, incompatible red cells is extremely rare. However, their presence may lead to a significantly decreased survival of transfused cells and the development of an extravascular hemolytic syndrome (delayed hemolytic transfusion reaction [DHTR]).

**Antiglobulin Test**

The antiglobulin (Coombs) test (Figs. 21.3 and 21.4) is based on the reaction between an antihuman globulin (AHG) reagent and antibody- or complement-coated red cells. AHG reagents are commercially available and are prepared either by the injection of an animal with human globulin or through hybridoma technology. AHG reagents may be polyspecific or monospecific. The polyspecific reagents contain antibodies with both antihuman IgG and anticomplement activity. Monospecific AHG reagents, anti-IgG, anti-C3b, and anti-C3d, are used to determine which protein is responsible for a positive direct antiglobulin test.¿

The direct antiglobulin test is performed by washing the patient’s cells with saline, adding polyspecific AHG, and observing for agglutination (Fig. 21.3). Positive reactions (agglutination) suggest the presence of IgG antibodies or complement bound to the red cell.¿ The indirect antiglobulin test is used to determine the presence of red cell antibodies in serum or plasma (Fig. 21.4). Reagent red cells are incubated with the patient’s serum or plasma, washed to remove unbound immunoglobulins, mixed with AHG (usually monospecific anti-IgG), and then centrifuged briefly. The cell button is gently resuspended and examined for agglutination. A positive reaction suggests that IgG antibodies in the patient’s plasma have bound to the reagent cells. A positive indirect antiglobulin test therefore indicates the presence of antibodies capable of reacting with red cells and possibly capable of hemolyzing such cells if they were transfused.

Direct and indirect antiglobulin tests are the simplest approaches to the detection of IgG anti-red cell antibodies. Because many of these serologic reactions are rather weak, the addition of various media has been used to enhance the agglutination reaction. These tests involve procedures that diminish the mutually repulsive electrostatic forces between red cells, permitting visible agglutination by IgG antibodies.¿ Antigens that often require such enhancing tests include those of the Kidd (Jk¿ and Jkª), Rh (D, C, E, c, e), Kell, and Duffy (Fyª and Fyª) systems.

**Media That Enhance Agglutination**

Adding albumin, low-ionic-strength saline (LISS) or polyethylene glycol (PEG) solutions to antibody identification tests can enhance the sensitivity of the test system.¿ These solutions augment the antibody-antigen interaction in a variety of ways, enhancing the detection of weak or otherwise undetectable antibodies. Treating reagent red cells with proteolytic enzymes such as papain or ficin also increases the sensitivity for some antibodies such as those reacting with Rh and Kidd system antigens. These enzyme reagents weaken or destroy other red cell antigens (M,N,Fyª, Fyª, and, in some cases, S, s)—a trait that can be helpful in the identification of multiple red cell antibodies in a single serum sample.¿

**Other Antibody Identification Tests**

Sera containing several antibodies may be analyzed by absorbing with one or more selected red cells. Antibodies so adsorbed may be eluted from the cells, and their specificity may be determined. Alternatively, the specificity of antibodies not absorbed and remaining in the supernatant can be identified. When necessary, the identity of certain antibodies may be confirmed by their inhibition by soluble antigens, such as A, B, and Lewis substances present in the saliva of secretors. Neonatal (cord) red cells exhibit a number of antigens very weakly and may be used to investigate antibody specificity.

**Selection of Red Cells for Transfusion**

A series of serologic tests is used to select donor blood for patients. Although individual transfusion services prefer different specific methods, the general principles of compatibility testing are the same.

A properly labeled, fresh sample of patient blood must be provided. If the patient has been transfused or has been pregnant within the preceding 3 months, the specimen must be obtained within 3 days of the anticipated transfusion.

**Donor**

The ABO group of the donor unit must be confirmed. The donor unit Rh typing must also be repeated if the unit is labeled as Rh-negative. These tests are performed to confirm the blood group and to ensure that the unit has not been mislabeled.

**Recipient**

The recipient’s ABO group and Rh type must be determined. The recipient’s serum is screened for the presence of antibodies that may have been induced by prior pregnancy or transfusion. A set of commercially prepared group O red cells, expressing 18 clinically relevant antigens (D, C, E, c, e, M, N, S, s, P, P, Leª, Leª, K, k, Fyª, Fyª, Jkª, and Jkª), is used in this test in accordance with FDA rules. The use of group O reagent red cells avoids agglutination by anti-A or anti-B. These reagent cells are incubated with the patient’s serum and tested with the indirect antiglobulin test for reactions indicating the presence of antibody in the serum.

If such screening reactions are positive, the antibody specificity can be determined by reaction of the serum with a commercially prepared panel of reagent red cells of known antigenic composition. If an antibody has been found on the screen and the patient’s clinical status allows, it is best to withhold transfusion until identification is complete. The incidence of unexpected RCC antibodies in patients requiring transfusion is low.¿
Type and Screen

If it is unlikely that blood will be required, for example, for a surgical procedure with <10% likelihood of transfusion, a "type and screen" rather than a crossmatch should be requested. In this instance, the blood bank types the patient’s blood and screens for unexpected antibodies; if antibodies are not found, the blood bank ensures that blood of the appropriate group is available for transfusion if necessary. In such an event, an employee call can trigger a rapid crossmatch test and blood will be available with minimal delay. The appropriate use of type and screen improves the efficiency of the blood bank. It assists in inventory control by not segregating blood for patients who are unlikely to require it and is therefore more cost-effective.

Crossmatch

If no antibody has been detected on the screen and there is no record of the previous presence of a clinically significant antibody, only verification of ABO compatibility between the donor unit and recipient is required before transfusion. This can be done either by an immediate spin crossmatch or a computer crossmatch.

The immediate spin crossmatch consists of mixing the patient’s serum with donor saline-suspended red cells at room temperature, spinning the tube, and reading the results immediately. The purpose of this test is to detect ABO incompatibility due to the presence of anti-A, anti-B, or both, in the patient’s serum.

The conditions for computer or “electronic” crossmatch are outlined in the AABB standards. Briefly, the computer system must be validated to prevent release of ABO-incompatible blood. This computer crossmatch can be used only for patients who do not have a record of clinically significant antibodies. The recipient’s ABO blood group must have been determined on at least two separate tests. The system must contain complete information on the donor unit and the recipient, including ABO group and Rh type. Data entered must be verified as correct before the release of blood. The system must contain logic to alert the user to discrepancies for either the donor unit or the recipient, including unit labeling, blood grouping, and ABO incompatibilities.

If a clinically significant red cell antibody has been found when a patient’s plasma or serum is screened for unexpected antibodies, antibody identification should be performed. Once the antibody specificity has been identified, donor units that lack the corresponding antigen should be selected, and a crossmatch using an indirect antiglobulin test should be performed on each unit to ensure compatibility. The physician should also be advised about the nature of the problem, as well as the potential for delays if further units are required.

Once a unit of blood is crossmatched for a patient, there must be positive identification of the patient and the blood product both in the laboratory before release of a blood product to the nursing ward as well as at the patient’s bedside by the transfusionist. Before every transfusion, the requisition, the label on the blood product, and the patient’s identification must be checked. These aspects of patient and blood product identification are critical safety steps and must be documented.

Uncrossmatched Blood for Emergency Transfusion

For patients in hemorrhagic shock, it is necessary to transfuse blood immediately, and no blood bank testing should be attempted before emergency transfusion. The risk of transfusing group O “uncrossmatched” red cells is extremely low and is certainly much lower than the risk of the patient’s death if blood transfusion is delayed. If a patient is to be given uncrossmatched blood, a specimen of the patient’s blood should be obtained prior to transfusion so that typing and screening can be performed while the transfusion is proceeding.

Once the patient’s blood group has been determined, ABO group-compatible uncrossmatched blood may be used. Until the patient’s Rh type is determined, uncrossmatched blood should be Rh(D)-negative when used in women of childbearing age, in whom sensitization to D would be undesirable. As Rh-negative blood is often in limited supply, Rh-positive blood is often used for emergency transfusion of older females and of males of unknown blood group. In such cases, sensitization may occur, but the risk of an immediate hemolytic reaction is low.

Despite the lack of a crossmatch, transfusion of group-specific blood under emergency situations is safe. The incidence of red cell alloantibodies in healthy people is low, and most such antibodies do not cause dangerous acute intravascular hemolytic transfusion reactions. However, the decision to use uncrossmatched blood is the responsibility of the attending physician, who must weigh the risks against the expected benefits and document in the patient’s record the need for the uncrossmatched blood.

Table 21.5 outlines the selection of blood and plasma by ABO type. If the blood group is known, group-compatible red cells and plasma can be selected. If the group is not known, group O

<table>
<thead>
<tr>
<th>Component</th>
<th>Recipient ABO Type</th>
<th>Preferred</th>
<th>Alternate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Red blood cells</td>
<td>O</td>
<td>O</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>A</td>
<td>A</td>
<td>O</td>
</tr>
<tr>
<td></td>
<td>B</td>
<td>B</td>
<td>O</td>
</tr>
<tr>
<td></td>
<td>AB</td>
<td>AB</td>
<td>A, B, O</td>
</tr>
<tr>
<td>Fresh frozen</td>
<td>O</td>
<td>O</td>
<td>A, B, AB</td>
</tr>
<tr>
<td>plasma</td>
<td>A</td>
<td>A</td>
<td>AB</td>
</tr>
<tr>
<td></td>
<td>B</td>
<td>B</td>
<td>AB</td>
</tr>
<tr>
<td></td>
<td>AB</td>
<td>AB</td>
<td>None</td>
</tr>
</tbody>
</table>

Red cells should be used; if plasma is required, group AB plasma should be used because it contains no anti-A or anti-B.

Crossmatching Problems
Standard serologic techniques often depend on agglutination as an end point. There are several agglutinating phenomena that can interfere with the correct interpretation of these serologic tests and may delay antibody identification and crossmatching. 

Pseudoagglutination refers to red cell clumping (rouleaux formation) that typically occurs in the presence of dysproteinemias, or after the administration of dextran or hydroxystaryl starch. Dilution in saline abolishes the reaction. Autoagglutination refers to red cell agglutination by the patient’s own serum or plasma and often indicates the presence of a cold agglutinin. Washing patient red cells with warm saline can often remove enough of the antibodies so testing can be completed. Polyagglutination is the phenomenon in which a patient’s red cells are agglutinated by most or all group-compatible sera. During bacterial or viral infections, enzymes of the infecting organism can cause alteration of antigenic structures on the red cell membrane, exposing previously hidden antigens such as T, or more rarely, Tn. Most adult sera contain naturally acquired antibodies capable of reacting with these determinants. The situation may be elucidated by testing the patient’s red cells with cord serum, which lacks the antibodies necessary for this reaction, and by examining for reactions with plant lectins that have specific activity with the antigens involved in polyagglutination.

Red Cell Autoantibodies
A positive indirect antiglobulin test against all screening and donor red cells often indicates the presence of an IgG, warm-reacting autoantibody. The patient’s direct antiglobulin test is also positive. Such autoantibodies may preclude the identification of any serologically compatible donor units. If red cells are transfused, it is essential that ABO compatibility be ensured. The patient’s serum should be screened for alloantibodies that might be masked by the autoantibody. Such screening requires the removal of the autoantibody from the patient’s serum, so that any alloantibodies present can be identified. If the patient has not been transfused within the last 3 to 4 months, this can be done by absorbing autoantibody from the serum with autologous red cells, from which already attached antibody has been removed by enzyme or chemical treatment. Alternatively, autoantibody may be removed by absorption with a panel of cells selected to lack the antigens to which the patient may become alloimmunized. The autoantibody-depleted serum can then be examined for the presence of residual alloantibodies, and a serologic crossmatch can be done. If only the autoantibody is present, transfusion of red cells is generally well tolerated.

Alloantibody to High-incidence Antigens
Occasionally, a patient may have a red cell antibody that does not react with the patient’s own cells but reacts with all donor red cells. Identification of these antibodies is particularly challenging, requiring rare cells that lack common red cell antigens. Assistance of specialized laboratories may be needed both to identify the antibody to a high-incidence antigen as well as to locate compatible blood. In some of these cases, it is not clear whether the antibody is likely to cause significant hemolysis. The utilization of DNA-based methodologies to identify donors with rare blood types is a useful tool in these challenging situations.

Drugs
Some drugs may stimulate an autoantibody in the patient that reacts with all reagent cells tested as well as with donor red cell units crossmatched. Drugs implicated include α-methyldopa, levodopa, fludarabine, and procainamide. In some cases, the in vitro findings may be identical to those found in autoimmune hemolytic anemias. The presence of these antibodies may or may not be clinically significant but may result in a delay if a transfusion is required. In most cases, however, drug-induced antibodies are associated with a positive direct antiglobulin test that is not part of the standard pretransfusion or crossmatch testing, and the indirect antiglobulin test is negative. The mechanisms of drug-induced hemolytic anemias are discussed in Chapter 29.

Red Cell Genotyping
The use of DNA-based methods for red cell antigen identification can assist in securing the optimal blood products for transfusion. The molecular bases for many of the major blood group antigens have been identified and DNA-based methods for their detection developed. Because these methods do not directly detect the presence of red cell antigens, challenges with widespread application still exist. When used with standard serologic testing, however, such methods are useful in identifying donors for patients with multiple red cell antibodies or blood donors with rare antigen types. Additionally, these methods are helpful in determining a patient’s red cell antigen makeup when chronically or recently transfused or when access to a blood specimen increases patient risk (e.g., fetus).

Special Considerations in Neonatal Transfusion

Pretransfusion Testing
The so-called naturally occurring IgM ABO antibodies do not begin to appear until approximately 3 to 6 months of age. However, IgG antibodies of maternal origin, including maternal anti-A or anti-B, may be passively transferred to the fetus. Thus, pretransfusion testing in the newborn consists of ABO and Rh typing of the infant’s cells and an antibody screen for passively transferred maternal IgG antibodies, including anti-A or anti-B. If the initial antibody screen is negative, the infant may be transfused with products compatible with the patient’s ABO/Rh type, and no further compatibility testing is required for the first 4 months of life. If a clinically significant antibody of maternal origin is detected, units that are antigen-negative or crossmatch-compatible must be issued until the antibody is no longer detectable in the infant’s serum.

Selection of Products for Neonatal Transfusion
Preterm infants may require multiple transfusions to replace blood drawn for laboratory tests. It has become common practice to limit donor exposure by reserving one unit or half unit for a single preterm infant. Serial aliquots may be obtained using a sterile connection device up to the outdate of the unit. When used with standard serologic testing, however, DNA-based methods for their detection developed. Because these methods do not directly detect the presence of red cell antigens, challenges with widespread application still exist. When used with standard serologic testing, however, such methods are useful in identifying donors for patients with multiple red cell antibodies or blood donors with rare antigen types. Additionally, these methods are helpful in determining a patient’s red cell antigen makeup when chronically or recently transfused or when access to a blood specimen increases patient risk (e.g., fetus).

Exchange Transfusion
The most common indication for exchange transfusion is hydrops fetalis resulting from hyperbilirubinemia that has not responded adequately to
Administration of Platelets

Platelet concentrates may be provided by the blood bank in their individual plastic bags or pooled before transfusion. Apheresis platelets do not require any preparation. Once the blood bag is opened by puncturing one of the sealed ports, the platelets must be administered within 4 hours. Platelets must be administered through a filter approved for platelet use, either a standard 170-μm filter or a leukoreduction platelet filter.

Dosage and Expected Response

The usual dose of platelets is one unit for each 10 kg body weight, or approximately six units (or one apheresis platelet) for a typical adult dose. The in vivo recovery of transfused platelets should be assessed by a platelet count obtained 10 minutes to 1 hour posttransfusion.

As noted earlier, even under ideal circumstances, only two thirds of transfused platelets are expected to be found in the circulation of the recipient. One can estimate the maximum expected increase in circulating platelet count after transfusion of one apheresis platelet product containing the minimum of 3 x 10^11 platelets into a 70-kg adult with a blood volume of 5 L as follows: Maximum increase in count = \( \frac{3}{5} \times 3 \times 10^{11} \) platelets distributed in 5 L blood volume = \( 40 \times 10^{10}/L \).

In practice, the observed posttransfusion platelet recovery in patients is often much lower than ideal. Hematologists typically achieve an increment of approximately \( 20 \times 10^{10}/L \), about 50% of ideal, after infusion of \( 3 \times 10^{11} \) platelets. A recovery as low as 30% of the ideal is generally considered "acceptable." This would correspond to an increase in platelet count of approximately \( 13 \times 10^{10}/L \) after transfusion of one apheresis platelet product to a 70-kg adult. The expected and "acceptable" increases in platelet count would be proportionately lower in a larger adult and higher with transfusion of a larger dose of platelets.

Many investigators have assessed the acceptability of a posttransfusion platelet increment by calculating a corrected count increment (CCI). With the CCI, the measured increment in circulating platelet count is corrected for the patient's size and for the dose of platelets given as follows: CCI = (posttransfusion count – pretransfusion count) × body surface area (m²)/number of platelets administered (10^11).

The maximum achievable CCI is approximately \( 25 \times 10^{10}/L \). The typical CCI in patients is approximately one half of this, and the lowest "acceptable" CCI is considered to be approximately \( 7.5 \times 10^{9}/L \). Patients with in vivo recoveries or CCIs lower than acceptable values should be evaluated for causes of platelet refractoriness such as an enlarged spleen or alloimmunization (as discussed in the section, "Platelet Refractoriness and Alloimmunization").

In healthy adults, the half-life of transfused platelets is 3 to 5 days. In thrombocytopenic patients, however, platelet survival is reduced. A fixed rate of platelet consumption of \( 7.1 \times 10^{9}/L/\text{day} \) has been measured in otherwise stable patients with severe thrombocytopenia. It is assumed that this platelet consumption is associated with maintenance of vascular integrity. The rate of consumption may be higher in critically ill patients.

Given the limited absolute increase in platelet count achieved with the standard dose of platelets and the presence of ongoing platelet consumption, many patients return to their baseline platelet count within 1 to 2 days of platelet transfusion. In stable patients, the transfusion-free interval may be increased by administering larger doses of platelets with each transfusion. However, this strategy can result in an increase in the total number of platelets transfused.

Indications for Platelet Transfusion

The risks of posttraumatic and spontaneous bleeding increase as the platelet count falls. In general, assuming that platelet function

PLATELET TRANSFUSION

Platelet transfusion may be life-saving when hemorrhage is caused by thrombocytopenia. Modern treatment for hematologic malignancies would not be possible without the ability to prevent or treat thrombocytopenic bleeding. Similarly, many surgical procedures would not be feasible without platelet transfusions. Whether this therapeutic modality is effective depends on recipient factors, such as the presence of sepsis, azotemia, drugs, and platelet antibodies, and on the ability of the blood bank to provide functional platelets in sufficient numbers.

For the patient's benefit, the blood product with the patient has been verified in the presence of the patient. The identity and documentation that the information identifying the patient should be added to or infused through the same tubing as the blood product. Compatible plasma may be added. No other solution and no medication should be kept in the blood bank until needed for transfusion.

The first step before the administration of blood or of a blood product is to obtain consent for the transfusion from the patient. Every hospital should set its own policy. A note in the chart indicating that the risks of transfusion as well as the indications and alternatives have been discussed with the patient and that the patient has accepted this form of therapy may be adequate, depending on applicable laws and regulations. There must be a written order for the administration of the product.

All blood products should be given through an appropriate blood administration set containing a filter; careful aseptic technique should be practiced at all times. There must be confirmation and documentation that the information identifying the blood product with the patient has been verified in the presence of the patient.

Vital signs should be documented before and after transfusion and as clinically required. For the first 15 minutes after the infusion has begun, the patient should be kept under close observation to detect any signs of a serious transfusion reaction. If none is observed, the infusion rate may be increased. One unit of red cells is often given in 1 to 4 hours, depending on the amount to be transfused and on the patient's cardiovascular status. Infusion of a unit for longer than 4 hours is not recommended, as there is a risk of bacterial proliferation because the opened unit is at room temperature. Normal (0.9%) saline, 5% albumin, or ABO-compatible plasma may be added. No other solution and no medication should be added to or infused through the same tubing as a blood product unless there is documentation of compatibility or FDA approval. Dextrose causes red cells to agglutinate or hemolyze; hypotonic saline causes hemolysis. Ringer's lactate or other solutions containing calcium must never be added to a blood product because the calcium present leads to coagulation.

When the transfusion has been completed, the transfusion tag or record should become part of the patient's chart.

The transfusion has been completed, the transfusion tag or record should be kept in the blood bank until needed for transfusion.

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is normal, there is minimal risk of spontaneous bleeding due to thrombocytopenia at platelet counts >50 × 10^9/L, and this level is usually sufficient to permit surgical procedures. As the count falls below this level, there is an increasing risk of microvascular bleeding, characterized by petechiae, ecchymoses, oozing at venipuncture and incision sites, epistaxis, menorrhagia, gastrointestinal bleeding, or intracranial hemorrhage.

The precise degree of bleeding risk at any given platelet count is difficult to determine, as many other clinical variables have important effects. These include the cause of thrombocytopenia; the duration of thrombocytopenia; the nature of concurrent disease processes including sepsis, uremia, vasculitis, or malignant processes invading blood vessels or other organs; the coexistence of coagulopathies, such as liver disease, vitamin K deficiency, intravascular coagulation, or heparin treatment; and the presence of drugs such as ASA or semisynthetic penicillins that interfere with platelet function.

In general, the risk of significant spontaneous hemorrhage increases gradually as the platelet count drops to <50 × 10^9/L and is high at counts <5 × 10^9/L. The Joint Commission has developed Performance Indicators for prophylactic platelet transfusions. Additionally, a Performance Indicator for prophylactic platelet transfusions has been developed by The Joint Commission for patients with malignant hematologic diseases or those who undergo stem cell transplantation, in which a platelet count threshold of 10,000/mm^3 is appropriate for prophylactic platelet transfusions.

Current guidelines from the European Union and United States recommend a transfusion trigger of 10 × 10^9/L for platelets transfused prophyllactically. These guidelines are based on outcomes from four randomized clinical trials that compared prophylactic triggers of 10 × 10^9/L versus 20 × 10^9/L in patients with acute leukemia and in autologous and allogeneic hematopoietic stem cell transplant recipients. Two additional prospective studies also demonstrated safety with the lower threshold of 10 × 10^9/L for prophylactic platelet transfusions.

The impact of these thresholds on numbers of platelet and blood transfusions is variable, however; one study demonstrated a 36% and 16% reduction in platelet and blood transfusions, respectively, while another showed no differences.

A recent trial demonstrated that “low dose” prophylactic platelet transfusions are equally effective as those with “standard” or “high” dose. For therapeutic platelet transfusions, algorithms for platelet transfusions based on point-of-care testing have demonstrated promise in patients who have platelet-derived bleeding such as in cardiothoracic surgery and in trauma. Additional evidence-based studies in platelet transfusion are needed.

### Prophylactic Platelet Transfusion

Prophylactic platelet transfusion in the management of acute leukemia prevents major bleeding episodes, except perhaps during the terminal phase of the patient’s illness. However, no difference in mortality has been demonstrated between patients transfused prophylactically and those transfused only when bleeding occurred. Despite lack of such proof, it is common practice to attempt to prevent bleeding problems by administering prophylactic transfusions to thrombocytopenic patients.

The indications for prophylactic transfusion remain controversial. Until recently, it was common practice to transfuse platelets when the count was <20 × 10^9/L. A number of studies have demonstrated that reducing the trigger for prophylactic platelet transfusion from 20 × 10^9/L to 10 × 10^9/L resulted in decreased platelet transfusion without an increased frequency of significant hemorrhage. In these studies, however, the trigger for transfusion was liberalized in the presence of clinical factors suspected to increase the risk of hemorrhage, such as fever, an increased WBC count, coagulopathy, bleeding, or invasive procedures. When significant hemorrhagic events occurred, they were often in patients with morning platelet counts >20 × 10^9/L. Infection, vascular lesions, or prolonged duration of thrombocytopenia may contribute to the risk of significant hemorrhage. Thus, it appears that a prophylactic transfusion trigger of 10 × 10^9/L is as safe as one of 20 × 10^9/L in most patients with acute leukemia or after myeloablative hematopoietic cell transplant.

However, an assessment of individual clinical risk factors is appropriate.

A strategy of therapeutic-only platelet transfusions in patients after autologous peripheral blood stem cell transplantation was found to reduce platelet transfusions by one half, despite 27% of transfusions given in breach of protocol guidelines, with no difference in number of red blood cell transfusions required. Important questions remain regarding whether prophylactic...
platelet transfusions are effective in reducing the risk of bleeding in clinically stable patients. A trial of prophylactic platelet study (TOPPS) versus therapeutic platelet transfusions in thrombocytopenic patients with malignancy, is currently underway in the UK.\(^{278}\)

Prophylactic platelet transfusion is usually recommended before major surgical procedures in patients with platelet count <50 \(\times\) 10\(^9\)/L.\(^{258,261,279\)} The safety of performing surgical procedures at counts below this level has not been formally evaluated. It has been demonstrated that bone marrow aspirations and biopsies, bronchoscopies, and lumbar punctures may be safely performed in patients with platelet counts of <20 to 25 \(\times\) 10\(^9\)/L.\(^{261\)} However, the minimum safe platelet level for specific invasive procedures remains to be defined.

Prophylactic transfusion of platelets is generally not recommended in patients with platelet consumption disorders, such as idiopathic thrombocytopenic purpura (ITP) and thrombotic thrombocytopenic purpura (TTP). In ITP, there is reduced recovery and survival of transfused platelets; transfusion usually does not result in a measurable increase in platelet count. There is some evidence that platelet transfusion may be harmful in patients with TTP.\(^{250,251}\) However, platelet transfusion may be used to treat life-threatening bleeding in patients with these disorders.\(^{262}\)

**Therapeutic Platelet Transfusion**

Rapid massive bleeding is unlikely to be due solely to thrombocytopenia and suggests the presence of a vascular injury. Rapid massive bleeding in the postoperative setting is usually surgical in nature and, therefore, not correctable by platelet transfusion. However, bypass-induced platelet dysfunction may contribute to bleeding after cardiac surgery;\(^{262\)} platelet transfusion may improve hemostasis in such situations.

Platelet transfusion is most useful in thrombocytopenic patients with microvascular bleeding (e.g., oozing or mucous membrane or gastrointestinal bleeding). Transfusion to achieve a platelet count of 50 \(\times\) 10\(^9\)/L is generally recommended for bleeding patients. However, hemostasis may be achieved through repeated platelet transfusion even in the absence of a demonstrable rise in platelet count. Transfusion is indicated in bleeding patients with platelet dysfunction, regardless of the platelet count.

Dilutional thrombocytopenia may occur after massive transfusion of red cells and plasma volume expanders. In the absence of platelet consumption, a platelet count of 50 \(\times\) 10\(^9\)/L is generally recommended for bleeding patients. However, hemostasis may be achieved through repeated platelet transfusion even in the absence of a demonstrable rise in platelet count. Transfusion is indicated in bleeding patients with platelet dysfunction, regardless of the platelet count.

**Immune Platelet Refractoriness and Alloimmunization**

Refactoriness to platelet transfusions is a clinical state that can be defined as an unacceptable recovery of transfused platelets on two or more occasions. As noted previously, a CCI of <5 to 7.5 \(\times\) 10\(^9\)/L at 10 minutes to 1 hour after the transfusion is a commonly used definition of an unacceptable response or, as a general rule of thumb, an absolute increment of <13 \(\times\) 10\(^9\)/L after transfusion of six units of platelets to a 70-kg adult. Clinical factors reported to be associated with refractoriness to platelet transfusions are listed in Table 21.6.\(^{93,254,263,285–287}\)

**Immune Causes of Refractoriness**

The major immune cause of refractoriness is the presence of anti-HLA antibodies. These antibodies are stimulated by pregnancy or by transfusion of WBC-containing blood products. Platelets bear HLA class I antigens on their surface. Anti-HLA antibodies are produced by 30% to 50% of recipients of WBC-containing blood products (Table 21.7).\(^{124\)} They are found in up to 30% of untransfused patients.

**Table 21.6**

<table>
<thead>
<tr>
<th>Factors Reported to Be Associated with Platelet Refractoriness</th>
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<tbody>
<tr>
<td><strong>Immune Factors</strong></td>
</tr>
<tr>
<td>Alloantibodies</td>
</tr>
<tr>
<td>Anti-HLA</td>
</tr>
<tr>
<td>Anti-platelet glycoprotein</td>
</tr>
<tr>
<td>ABO</td>
</tr>
<tr>
<td>Anti-HLA</td>
</tr>
<tr>
<td>Autoantibodies</td>
</tr>
<tr>
<td>Idiopathic thrombocytopenic purpura</td>
</tr>
<tr>
<td>Drug-related</td>
</tr>
<tr>
<td><strong>Nonimmune Factors</strong></td>
</tr>
<tr>
<td>Splenomegaly</td>
</tr>
<tr>
<td>Fever, infection</td>
</tr>
<tr>
<td>Disseminated intravascular coagulation</td>
</tr>
<tr>
<td>Immune complexes</td>
</tr>
<tr>
<td>Bone marrow transplantation</td>
</tr>
<tr>
<td>Amphotericin</td>
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</tbody>
</table>

**Table 21.7**

<table>
<thead>
<tr>
<th>Efficacy of Leukocyte-Reduced Products in Preventing Transfusion-Induced HLA Alloimmunization</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Type of Blood Products Received</strong></td>
</tr>
<tr>
<td>Author</td>
</tr>
<tr>
<td>Elghouzzi</td>
</tr>
<tr>
<td>Schiffer</td>
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<tr>
<td>Andreu</td>
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<tr>
<td>Sniecinski</td>
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<td>Rebulla</td>
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<td>Van Marwijk</td>
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<td>Oksanen</td>
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<td>Handa</td>
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<tr>
<td>Lane</td>
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<tr>
<td>Williamson</td>
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<td>TRAP</td>
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</tbody>
</table>

Note: This is a summary of prospective controlled trials in hematology and oncology patients. Each numerator indicates the number of patients developing HLA antibodies; the denominator indicates the number of patients transfused with that type of blood product. The number in parentheses represents the calculated proportion of patients making antibodies. Modified from Dzik WH. Leukoreduced blood components: laboratory and clinical aspects. In: Simon TL, Dzik WH, Snyder EL, et al., eds. Rossi’s principles of transfusion medicine, 3rd ed. Philadelphia, PA: Lippincott Williams & Wilkins, 2002:270–287.
women with a history of pregnancy. After exposure to blood products, up to two thirds of women with a history of pregnancy produce HLA antibodies. Transfusion of platelets that are serologically incompatible with a pre-existing HLA antibody typically results in no increase in platelet counts.

The incidence of clinically significant alloantibodies to platelet-specific glycoproteins in transfusion recipients is unclear. Antibodies to platelet glycoproteins have been detected almost exclusively in patients who also have broadly reactive anti-HLA antibodies. Using the sensitive MAIPA (monoclonal antibody immobilization of platelet antigen) assays, investigators have reported detection of antibodies to platelet glycoproteins in as many as 25% of HLA-alloimmunized transfusion recipients.

A significant proportion of the antibodies detected have ill-defined specificity, and the contribution of such antibodies to platelet refractoriness is unclear. The presence of platelet-specific antibodies in patients who are broadly sensitized to HLA presents an enormous transfusion support challenge. Although many blood centers maintain HLA-typed donor registries, at present, very few of these donors are typed for platelet antigens. The solid-phase red cell adherence or recently developed MAIPA-based platelet cross-matching assays could theoretically be used to test HLA-selected products for compatibility with a patient’s antiplatelet antibodies, although it has not yet been established whether these assays have adequate sensitivity and specificity for this application.

As discussed earlier, high-tiered ABO antibodies have been implicated in platelet refractoriness. Many investigators recommend a trial of ABO-compatible products in refractory patients, although studies have not demonstrated a high likelihood of improvement.

Antiplatelet autoantibodies are usually associated with absolute refractoriness to platelet transfusion. However, in the event of life-threatening bleeding, patients with ITP may benefit clinically from repeated infusions of platelets even in the absence of a demonstrable rise in platelet count. Antiﬁbrinolytics or recombinant factor VIIa may also be helpful in this setting, as discussed later (see “Role of Pharmacologic Agents in Managing Thrombocytopenic Patients”).

Nonimmune Causes of Refractoriness

Of the nonimmune factors implicated in refractoriness, splenomegaly is the most potent. Transfused platelets pool in the enlarged spleen; increasing the dose of platelets does not necessarily improve the posttransfusion increment. Each of the other nonimmune factors listed in Table 21.6 has been reported to be associated with refractoriness, although the importance of each factor has not been demonstrated consistently.

Prevention of HLA Alloimmunization

Although platelets express HLA class I molecules on their surface, purified platelets do not appear to induce primary immunization to HLA antigens. It appears that the presence of WBCs is necessary, presumably because of their dual expression of both HLA class I and class II antigens. Multiple studies have demonstrated that the prophylactic use of leukoreduced blood products significantly decreases the incidence of HLA immunization in transfusion recipients (Table 21.7). Use of leukoreduced blood products is recommended for patients who are likely to require intensive platelet transfusion support, because the development of anti-HLA antibodies would complicate such support.

Purified platelets can stimulate a secondary immune response to HLA. Patients with prior pregnancy are highly likely to produce HLA antibodies after transfusion. HLA alloimmunization has been observed in up to two thirds of such patients. The use of leukoreduced products appears to be of limited benefit in such patients. HLA antibodies are produced by 33% to 44% of patients with a history of pregnancy despite the use of leukoreduced products.

As an alternative to removing WBCs from blood products, in vitro studies indicate that ultraviolet (UV) irradiation of WBCs abrogates their ability to present HLA antigens in mixed lymphocyte culture. UV irradiation of blood products is as effective as leukocyte reduction in preventing primary HLA alloimmunization. UV irradiation of platelet products requires special blood containers and equipment and is not currently available in the United States.

Early studies suggested that HLA alloimmunization in platelet transfusion recipients could be reduced by minimizing donor exposure through the use of pheresis platelets rather than pooled platelet concentrates. However, it has been shown that if all products are leukoreduced, there is no incremental benefit to the use of pheresis products.

Diagnosis and Management of Alloimmunization

Historically, anti-HLA antibodies have been detected by lymphocytotoxicity assays. Newer methods of testing for HLA antibodies include enzyme or flow-based immunoassays in which HLA glycoproteins are immobilized on a plastic plate or beads. A commercially available solid-phase red cell adherence assay permits screening for serologic reactivity against platelets selected from inventory.

Early studies demonstrated that thrombocytopenic patients with lymphocytotoxic antibodies could be successfully supported with platelets obtained from donors who were HLA-identical to the patient, or donors who were partially HLA-matched and whose lymphocytes were serologically compatible with the patient’s antibody. These observations led to the practice of providing apheresis platelets from “HLA-matched” donors for patients with lymphocytotoxic antibodies. Depending on the availability of family members, the rarity of the patient’s HLA type, and the size of the HLA-typed donor registry, it may be difficult or impossible to locate platelet donors who are HLA-identical to the patient.

Therefore, many platelets provided as HLA-matched bear one or more antigens that are foreign to the recipient. Serologic crossmatching of mismatched products can be used to identify those that are more likely to result in a good posttransfusion increment.

In most HLA-alloimmunized patients, the specificity of the antibody can be defined. Patients can be successfully supported with products that lack the HLA antigen(s) to which the antibodies are directed. If the platelet inventory is HLA-typed, products lacking the offending antigen(s) can usually be found in inventory; thus, many patients can be supported with products on the shelf, without the need for special donor recruitment or serologic crossmatching.

Alternatively, serologic crossmatching of HLA-untyped products may be used to support patients whose antibodies are not broadly reactive. For many alloimmunized patients, it is possible to identify serologically compatible platelets among HLA-untyped products in the blood center inventory using the solid-phase red cell adherence crossmatching assay. However, compatible products are unlikely to be found in inventory for patients who have broadly reactive antibodies; such patients require specific recruitment of HLA-selected donors.

In summary, HLA-alloimmunized patients may be supported (a) by using products from donors who are HLA-identical to the patient or who lack HLA antibodies foreign to the recipient; (b) by using products that are partially HLA-matched and serologically compatible; (c) by identifying the specificity of the patient’s HLA antibody and avoiding products that bear the offending antigen(s); or (d) by serologic crossmatching of products in inventory. These methods are often limited by the inadequate availability of donors. The last method is not applicable to patients with broadly reactive
antibodies, who comprise approximately 10% to 15% of alloimmunized patients.\textsuperscript{307,311}

It should be noted that HLA antibodies may appear or disappear over the course of a patient’s treatment.\textsuperscript{93,297} It is important to monitor patients’ responses to platelet transfusion and to re-evaluate them serologically if they do not respond to products that were previously acceptable.

**Platelet Transfusions for Refractory Patients**

Strategies for the optimal use of platelets are undergoing evolution.\textsuperscript{276} A published guideline suggests withholding prophylactic transfusion for nonbleeding patients who do not achieve acceptable posttransfusion increments in platelet counts.\textsuperscript{256} However, many clinicians arbitrarily transfuse one dose of platelets daily, based on the assumption that some platelets are necessary to maintain vascular integrity.\textsuperscript{255} For bleeding patients, many practitioners recommend infusion of larger or more frequent doses of platelets.\textsuperscript{254,312}

**Role of Pharmacologic Agents in Managing Thrombocytopenic Patients**

Attempts to improve responses with intravenous immunoglobulin (IVIg) therapy in patients refractory to platelets have not convincingly demonstrated benefit; some found improved 1 hour but not 24 hour posttransfusion increments.\textsuperscript{313} Fibrinolytic inhibitors were shown to be of value in avoiding platelet transfusions in aplastic patients.\textsuperscript{314} by helping stabilize any clots that are being formed.\textsuperscript{315} Anecdotal reports\textsuperscript{316} have suggested that recombinant factor VIIa (rFVIIa) may stop bleeding, particularly in patients with refractory, severe thrombocytopenia.\textsuperscript{317,318} However, a randomized trial failed to demonstrate any difference between the placebo group and the three rFVIIa cohorts combined, in the primary endpoint of bleeding score at 38 hours.\textsuperscript{319} Raising red cell mass by blood transfusion or treatment with erythropoiesis stimulating agents (ESA) has been shown to improve coagulopathy related to anemia\textsuperscript{320} or uremia,\textsuperscript{321} but evidence for clinical efficacy is needed. Thrombopoiesis-stimulating agents have been shown to be efficacious in improving platelet counts in patients with immune thrombocytopenias.\textsuperscript{322,323} Platelets contain significant amounts of micro RNAs that may provide proteins that affect hemostasis and inflammation.\textsuperscript{324,325} Finally, development of fibrinogen-coated, ADP-encapsulated liposomes may offer a promising platelet substitute.\textsuperscript{326}

**Selection of Platelet Products**

**ABO Group**

The clinical importance of ABO compatibility in platelet transfusion is controversial. Platelets bear both intrinsic\textsuperscript{227} and adsorbed\textsuperscript{228} antigens of the ABH system. Transfusion of ABO-incompatible platelets may be associated with decreased posttransfusion platelet recovery and normal survival.\textsuperscript{299,300} The reduction in recovery is variable and may be related to the isohemagglutinin titer of the recipient. Rarely, a high titer of anti-A or anti-B may cause frank refractoriness to ABO-incompatible platelets.\textsuperscript{333-335}

Platelet products contain a significant amount of donor plasma. Rarely, high-titered donor isoagglutinins in platelet products may cause intravascular hemolysis of recipient red cells.\textsuperscript{336} Especially platelets from group O donors.\textsuperscript{337,338} Some investigators have suggested that patients who receive platelets mismatched for ABO develop refractoriness at a higher rate than patients who receive ABO-compatible products.\textsuperscript{335,339,340} However, these studies were small, did not control for the presence of HLA antibodies, and differed in their observations as to whether it was cell or plasma compatibility that was important. Most important, patients who developed refractoriness to ABO-incompatible products did not show better responses when given ABO-identical products, suggesting that ABO may not have been the cause of refractoriness.\textsuperscript{338,340} In practice, it is difficult to ensure availability of ABO-identical platelet products, and many centers simply limit the volume of incompatible plasma transfused.

**Rh Type**

Platelets do not carry Rh antigens, and the donor’s Rh type is important only because the red cells present in the platelet concentrate may immunize Rh-negative recipients. Although early studies found that as many as 19% of D-negative recipients of platelets from D-positive donors developed anti-D, several recent studies in hematology/oncology patients found that immunization did not occur.\textsuperscript{341,342} It is possible that the difference in observations is related both to an increase in intensity of chemotherapy as well as to a substantial improvement in the purity of platelet products. The red cell content of most apheresis platelets currently is below the dose thought to be immunizing. For most platelet recipients, anti-D prophylaxis would be of little benefit.\textsuperscript{343} For pediatric patients and females with future childbearing potential, however, it may be reasonable to consider administration of intravenous anti-D Ig to prevent D immunization.\textsuperscript{344-345}

**PLASMA TRANSFUSION**

**Use of Platelet Components**

FFP or FP24 are utilized in patients who are bleeding or who are having an invasive procedure and who are deficient in multiple coagulation factors or in a single factor for which there is no specific factor concentrate available. They are also used for replacement of clotting factors during massive transfusion, for reversal of warfarin (if immediate reversal is necessary), and as the replacement fluid for plasma exchange procedures in patients with TTP.\textsuperscript{3,346} They should not be used as volume expanders or for therapeutic plasma exchange for other disorders, because alternative fluids with lower risks of infectious diseases, allergic reactions, and TRALI are available for these purposes (e.g., crystalloid, albumin, starch). The typical dose of plasma is 10 to 20 ml/kg.\textsuperscript{3}

Patients may not tolerate infusion of larger volumes. The expected rise in coagulation factor activity is approximately 10% for each 10 cc/kg of plasma infused.\textsuperscript{347}

**Efficacy of Plasma Transfusions**

In a recent evidence-based review, the Transfusion Practices Committee of the AABB recommended plasma therapy for only a few clinical indications, based on the available evidence in the literature (which was assessed to be of “weak quality”): trauma patients with substantial hemorrhage, patients undergoing complex cardiovascular surgery, and patients with intracranial hemorrhage requiring emergency reversal of warfarin-associated coagulopathy.\textsuperscript{348} Patients with mild prolongations of the INR (less than 1.7) are not at risk of bleeding and do not need plasma therapy for minor procedures.\textsuperscript{349} so that for the majority of clinical settings there is ample evidence that plasma transfusions are inappropriate. However, logistical/technical barriers that prevent effective and timely plasma therapy (possibly resulting in plasma therapies that are “too little, too late”) have probably contributed to the paucity of evidence demonstrating any benefit for plasma therapy.\textsuperscript{177}

One of the largest prospective studies of plasma transfusions and their effect on INR and bleeding included both medical and surgical patients with pretransfusion INR of between 1.1 and 1.85.\textsuperscript{350} The authors reported that less than 1% of patients
had normalization of their INR and only 15% had at least 50% correction. The median dose of plasma was 2 units (only 5 to 7 ml/kg), and there was no correlation between plasma dose and change in INR. This study had many of the limitations common to other reports370 in this clinical arena: lack of control groups, only modest prolongation in coagulation tests, poorly-defined clinical endpoints (e.g., change in hemoglobin or need for transfusion), and/or an inadequate dose of plasma therapy.

The paucity of evidence for the benefit of plasma transfusion therapy has been accompanied by growing evidence that risks of plasma have been underrecognized; in a prospective study, 6% of transfused patients developed transfusion-associated cardiac overload,332 which is much higher than previously-reported rates in retrospective studies.333-335 Transfusion-related acute lung injury is a significant cause of morbidity/mortality from blood transfusions, whose incidence has declined subsequently with use of plasma from male donors or female donors who have no history of pregnancy.336

GRANULOCYTE TRANSFUSIONS

Severe bacterial and fungal infections in the setting of prolonged chemotherapy-associated neutropenia are common causes of morbidity and mortality in the treatment of malignancy. Risk of serious bacterial infection appears as the neutrophil count falls below 1.0 × 10^9/L and increases rapidly below 0.5 × 10^9/L. Fungal infections occur with much higher frequency as the neutrophil count falls below 0.2 × 10^9/L.337 Other risk factors include the duration of neutropenia and the rate of fall of the neutrophil count.338 The use of growth factors (e.g., granulocyte colony-stimulating factor [G-CSF]) has reduced the severity and duration of neutropenia, but many patients still have long periods of poor granulocyte production, lasting 2 to 3 weeks or longer.339-341 Although the idea of enhancing host defenses with granulocyte infusions dates back 60 years, difficulty obtaining adequate granulocyte yields as well as safety concerns stifled the initial interest generated after early clinical successes in the 1970s.342,343 Modern apheresis techniques, growth factors which increased yields, and positive results from clinical trials led to renewed interest in applying granulocyte therapy to a wider range of patients.344-346

Clinical Indications and Efficacy

Currently, there is no definitive evidence from controlled trials to support or refute the use of granulocyte transfusion therapy in neutropenic patients.346,347-349 Currently a large randomized control trial is being undertaken in an attempt to clarify this situation; nonetheless, prior clinical granulocyte transfusion trials in the setting of neutropenia give insight into populations that may benefit from this therapy. A review of 32 papers349 revealed that most studies have been uncontrolled, involved small heterogeneous populations of patients, and had different treatment approaches. Approximately 62% of the 206 patients with bacterial sepsis were reported to have benefited from granulocyte transfusion; conversely, 71% of 63 patients with invasive fungal infection did not respond to the infusions. Seven controlled trials were completed between 1972 and 1982. Three showed a positive effect, two showed benefit in specific patient populations, and two demonstrated no benefit. Some studies were likely limited by the cytapheresis techniques used and the low cell yields obtained, as most donors were pretreated with corticosteroids only. Further analysis confirmed the importance of higher neutrophil doses as well as leukocyte compatibility in the three positive trials. More recent trials350-352 provide additional evidence supporting the use of granulocyte transfusions in critically ill neutropenic patients with bacterial as well as candida sepsis. Based on this information, granulocyte therapy may warrant consideration in severely neutropenic patients with bacterial infections unresponsive to typical antimicrobial therapy.

The applicability of granulocyte infusions in the setting of invasive fungal infections remains unclear. No study has shown clear efficacy in patients with active aspergillosis, although often the neutrophil dose was not known or was suboptimal. Limited clinical and animal model data give some indication of usefulness in the setting of candidal and noninvasive fungal infections.370,372,373 As the overall data are limited, a brief trial of granulocyte infusions may be warranted in patients with self-limited neutropenia and documented fungal infection who are refractory to standard antifungal therapy.

The effect of the prophylactic use of granulocyte transfusions to diminish the risk of serious infections in severely neutropenic patients during therapy of hematologic malignancies and after bone marrow transplantation has been investigated in a number of controlled trials.365,374 Although prophylactic granulocyte transfusion may decrease the risk of septicemia, the increased incidence of adverse effects observed with this therapy may outweigh the beneficial effects.375-381 Until there are more published randomized, controlled clinical trials, the use of prophylactic granulocyte transfusions should be carefully considered and viewed as experimental.

Granulocyte transfusions may also be indicated in infected patients with severe neutrophil dysfunction (e.g., chronic granulomatous disease and leukocyte adhesion deficiency) who are not responding to appropriate antimicrobial therapy. Although controlled trials have not been performed, transfused granulocytes do migrate within recipients and appear to be of therapeutic benefit.382-384 Because of the adverse effects associated with the transfusion of granulocytes, they should be used judiciously in the patient with severe documented infections, as the infusions may result in alloimmunization of the recipient and render him or her unresponsive to granulocyte transfusion therapy at a later date.

Neonatal bacterial sepsis continues to be a major cause of morbidity and mortality. The neutrophil function in neonates is impaired, with diminished chemotaxis and abnormal adhesion properties. Infection may result in neutropenia and depletion of the neutrophil storage pool. Granulocytes have been used to treat neonatal sepsis with varying results.367 The efficacy of this approach has been evaluated in six controlled trials with four studies demonstrating a survival benefit. Overall, data analysis does not show clear benefit when other available therapies are considered.362,367 When compared with standard therapy of intravenous Ig, neonates with group B Streptococcus may experience increased survival after receiving granulocyte support.385 Although conflicting data exist, centers that experience a high mortality rate in septic infants with neutropenia and ongoing neutrophil storage pool depletion may consider a trial of granulocyte therapy. The recommended dose is 1 × 10^9 granulocytes/kg of body weight.365

Donor Preparation/Selection

High granulocyte yields were initially obtained using preparations from donors with chronic myelogenous leukemia.386 Subsequently, methods were developed to collect sufficient granulocytes from normal donors. Apheresis became the standard method for collecting granulocyte concentrates.358,359,387,388 The quantity and quality of granulocytes obtained depend on the apheresis collection technique as well as the level of donor neutrophils. Infusion of hydroxyethyl starch or dextran to improve the sedimentation of donor red cells during centrifugation improves the efficiency of apheresis, but the granulocyte yield remains low.389 Data suggest that a daily granulocyte dose of about 10^10 cells would be needed to achieve benefit.389 Oral corticosteroids produce a transient donor neutrophilia, but the collection yield remains in
the range of 2 to 3 × 10^{10}. Studies have shown the ability of G-CSF to increase the dose/collection. Donors treated with G-CSF with or without corticosteroids produce yields ranging from 2.4 to 9.9 × 10^{10} granulocytes. Although adverse effects occur in 30% to 69% of donors, most consist of mild to moderate degrees of bone pain, headache, myalgias, and fatigue. Data from the bone marrow transplant literature support the short-term safety of G-CSF use in healthy donors, although rare serious adverse events have been reported. Long-term follow-up data are limited and deserve further attention. G-CSF administration to healthy donors is generally performed under institutional review board-reviewed protocols. Based on available evidence, donor pretreatment with a single dose of G-CSF (300 to 600 μg subcutaneously) with dexamethasone (8 mg orally) 12 hours before collection gives reliable yields in a well-tolerated and cost-effective manner. Although repeated daily G-CSF stimulation and granulocyte collection have been reported, standard practice is to perform a second collection no sooner than 7 days after the initial cytapheresis procedure.

Prospective granulocyte donors should meet all FDA and AABB standards for donation. Because granulocyte products must usually be transfused before completion of donor infectious disease testing, donors who have been tested recently are strongly preferred. Donors should also be free of disorders that might be exacerbated by dexamethasone (e.g., diabetes) or G-CSF (e.g., arthritis, vasculitis, splenomegaly, gout, thrombocytopenia). Donor/recipient pairs should be ABO-compatible because of the risk when seropositive donors are used for immunocompromised patients; therefore, CMV-negative patients should be transfused before completion of donor infection testing. Developing a CMV-negative donor pool for immunocompromised patients is strongly preferred. Donors should also be free of disorders that might be exacerbated by dexamethasone (e.g., diabetes) or G-CSF (e.g., arthritis, vasculitis, splenomegaly, gout, thrombocytopenia). Donor/recipient pairs should be ABO-compatible because of the risk when seropositive donors are used for immunocompromised patients; therefore, CMV-negative patients should receive CMV-negative products.

Patients requiring granulocyte transfusions may have become alloimmunized to HLA, and/or RBC antigens during the course of prior transfusion support or pregnancy. Studies suggest decreased recovery and survival as well as failure of granulocytes to localize at the site of inflammation in patients who have lymphocytotoxic or granulocyte-specific antibodies. Recipients can be screened for the presence of HLA antibodies particularly if clinical suspicion for alloimmunization is high. In alloimmunized patients, HLA-compatible random donors or family members can be used; random donors may be preferred over family members if related allogeneic transplantation is anticipated as part of the treatment for the underlying disease. If laboratory tests for alloimmunization are not readily available, the likelihood of sensitization may be estimated by reviewing the patient’s record for a history of platelet refractoriness or febrile transfusion reactions.

Granulocyte Collection/Storage

Once an appropriate donor has been selected and prepared, granulocytes are typically collected by leukapheresis during which 7 to 10 L of blood is processed over 3 to 4 hours. Hydroxyethyl starch is often used to reduce RBC contamination by sedimentation. According to AABB standards, at least 1 × 10^{10} granulocytes/apheresis are collected. Current techniques achieve mean yields of 2 to 3 × 10^{10} leukapheresis in 200 to 400 ml of plasma, with 10 to 30 ml of RBCs, and 1 to 6 × 10^{11} platelets. For pediatric recipients, whole blood buffy coats from donors stimulated with G-CSF may present an alternative to apheresis. Although granulocytes can be stored for up to 24 hours at room temperature, transfusion within 8 hours of collection is recommended. Biochemical assessments of the effects of storage on subsequent function (e.g., nicotinamide adenine dinucleotide phosphate oxidase activity, adhesion protein expression, respiratory burst activity, and bactericidal activity) reveal that effective storage may be possible for up to 48 hours at 10°C.

Administration of Granulocytes

Granulocytes should be administered on a daily basis until the patient’s endogenous neutrophil count rises to 0.5 × 10^{9}/L or until the infection clears. Granulocyte concentrates should be given through a standard filter set to ensure that aggregates are not administered. The concentrate should be given slowly (over 1 to 2 hours) with the patient under constant observation, including the use of pulse oximetry. Transfusion reactions occur in 10% to 50% of patients but are usually mild, consisting of fever and chills. Premedication with antihistamines, acetaminophen, or steroids is common practice before infusion. More severe reactions occur in 1% to 5% of patients and tend to be pulmonary in nature. A serious potential interaction between granulocyte transfusions and amphotericin B has been reported, but this association has not been substantiated by others. Nevertheless, many physicians administer granulocytes and amphotericin at least 8 hours apart to limit the potential for increased pulmonary toxicity. If there are any signs or symptoms of respiratory distress, the transfusion should be discontinued immediately, the recipient should be examined for antibodies that react with neutrophils. Granulocyte products contain lymphocytes and are capable of causing transfusion-associated GVHD (TA-GVHD). Thus all granulocyte products should be irradiated with 1500 to 3000 cGy to prevent transfusion-related GVHD without significantly impairing granulocyte function. Pre- and posttransfusion neutrophil counts should be determined to guide therapy. With large doses (>8 × 10^{10}), neutrophil increments may exceed 2 × 10^{9}/L immediately after infusion and may last for 24 to 48 hours.

ADVERSE EFFECTS OF BLOOD TRANSFUSION

The potential complications of blood transfusion therapy are many, but most present problems only in patients requiring repeated or large numbers of transfusions. The risks associated with the transfusion of any specific unit of blood are low. However, the risks must be weighed against the benefits at the time each transfusion is ordered.

Transfusion complications can be classified as immunologic and nonimmunologic (Table 21.8). Many of the immune reactions are caused by the stimulation of antibody production by foreign alloantigens present on transfused red cells, leukocytes, platelets, or plasma proteins. Such alloimmunization may lead to immunologically mediated reactions when transfusions carrying these antigens are administered in the future. These include hemolytic reactions caused by red cell incompatibility; febrile or pulmonary reactions caused by leukocytes and platelet antigens; allergic or anaphylactic reactions caused by antibodies reacting with soluble antigens, usually plasma proteins, in the transfused material; and GVHD caused by engraftment of transfused lymphocytes in immunosuppressed recipients.

The nonimmune reactions are caused by the physical or chemical properties of the transfused blood products, as well as contaminating infectious agents. Nonimmune reactions include circulatory overload and certain adverse effects encountered specifically when large numbers of transfusions are given.

Immunologic Transfusion Reactions

Alloimmunization to Transfused Antigens

Alloantibodies Reacting with Red Cell Antigens

Although the antigenic composition of transfused red cells always differs from that of the recipient, only a minority of
multitransfused recipients develop red cell alloantibodies. The risk of red cell alloimmunization has been estimated at 1.0% to 1.4% per unit transfused; in multitransfused patients, the incidence of such antibodies ranges from 5% to 30%.\footnote{404,405} Multiple red cell antibodies may be encountered. Antibodies to Rh system antigens and to Kell (K) are most often detected. Antibodies to antigens of the Duffy (Fy) and Kidd (Jk) systems also occur, but transfusion-induced antibodies to other red cell antigens are less commonly found.

The production of such antibodies is a property of both the recipient’s immune response and the immunogenicity of the different red cell antigens. The incidence of antibodies does not appear to be related to the patient’s diagnosis. For example, patients with hemoglobinopathies, thalassemia, and leukemia and those undergoing surgery requiring multiple transfusions produce antibodies with approximately the same frequency.\footnote{404,405} The reported incidence of RBC alloimmunization for patients with thalassemias is 5% to 10%, versus 20% to 30% for those with sickle cell anemia. The increased incidence of alloimmunization in sickle cell patients has been attributed to the difference in race between the blood donor pool and the patient population.\footnote{407} As a result, there is a greater likelihood of minor-antigen incompatibility between donor and recipient. The differing immunogenicity of various red cell antigens also plays a role. For patients with sickle cell anemia, red cells phenotypically matched for Rh and Kell antigens are recommended. This measure was shown to reduce the alloimmunization rate in this population from 3% to 0.3% per unit transfused.\footnote{408}

### Alloantibodies Reacting with Leukocyte Antigens

Alloimmunization to HLA and other leukocyte-associated antigens has been discussed earlier with respect to problems encountered in granulocyte and platelet transfusion. These antibodies occur mainly in multiparous women\footnote{209,409} and multitransfused patients. In patients receiving nonleukoreduced transfusion support for aplastic anemia or acute leukemia, 20% to 70% become immunized to HLA antigens.\footnote{410} Interestingly, HLA alloimmunization is significantly increased in male patients with pre-existing RBC antibodies compared to multiply transfused male patients without such antibodies.\footnote{411} As discussed in the section “Platelet Transfusion” and shown in Table 21.7, the prophylactic use of leukocyte-reduced blood products significantly reduces the incidence of HLA alloimmunization in patients with no prior exposure to these antigens.

### Alloantibodies Reacting with Plasma Proteins

Although antibodies to soluble plasma proteins such as lipoproteins and to Gm and Inv determinants on IgG are often detectable in multitransfused patients, transfusion reactions have rarely been attributed to such antibodies.\footnote{412–414} Some anaphylactic reactions are attributed to anti-IgA antibodies,\footnote{415,416,417} especially in patients who are IgA-deficient, although the presence of antibodies that react with IgA is not always clearly correlated with the occurrence of this type of transfusion reaction.\footnote{418}

### Hemolytic Transfusion Reactions

The development of antibodies capable of reacting with red cell antigens may lead to red cell destruction, usually involving transfused rather than recipient cells. The clinical significance of such reactions ranges from life-threatening to trivial. Whether hemolysis occurs immediately within the circulation, more slowly within the reticuloendothelial system, or not at all depends on the antigen and antibody involved.\footnote{419–421,422}

The incidence of such reactions is variably reported. Several studies from the Mayo Clinic document a hemolytic reaction rate, both immediate and delayed, of between 1 in 6,200 and 1 in 1,400 red cell transfusions. In these reports, reactions caused by 400,401 antigen and antibody involvement without such antibodies.

#### Immediate (Intravascular) Hemolytic Transfusion Reactions

Immediate hemolytic transfusion reactions (IHTRs) are most typically associated with ABO incompatibility, because anti-A and anti-B antibodies are predominantly IgM and are capable of binding complement and causing immediate destruction of red cells.
An IHTR caused by ABO incompatibility is rare and is usually related to human error. Other red cell antigens such as Jkα, K, and Fy4 (which may bind complement) may also lead to such reactions.

Infrequently, hemolytic transfusion reactions may be caused by destruction of recipient red cells after the transfusion of plasma-containing antibodies.427,428 For example, anti-A1 occurring naturally in group A donors of subgroup A2, has been reported to cause hemolytic transfusion reactions.429 More recently, hemolytic transfusion reactions have been reported in association with apheresis platelets containing abnormally high titer (>1:250) anti-A or anti-B antibodies in the plasma. Plasma volume reduction is recommended for such products if the plasma is incompatible with the recipient.430 Hemolytic reactions caused by the transfusion of plasma containing other antibodies are extremely rare, as blood donors are screened for red cell antibodies other than ABO.

**Signs and Symptoms.** IHTRs occur soon after the incompatible transfusion has begun. Occasionally, they are mild; more typically, there is a sudden change clinically. Fever with or without chills is one of the most common manifestations of such reactions. Other signs and symptoms include anxiety, chest or back pain, flushing, dyspnea, tachycardia, and hypotension. If the patient is under general anesthesia, these symptoms may not be recognized; only severe hypotension and evidence of oozing or hemoglobinuria serve as clues to the presence of a hemolytic reaction.

IHTRs may be life-threatening, and complications may include acute renal failure, shock, and intravascular coagulation. It has been estimated that a fatal immediate hemolytic reaction occurs in approximately 1/600,000 red cell transfusions 427. The mortality of a severe IHTR increases with the amount of blood transfused, with a 44% mortality rate in patients receiving more than 1 L of incompatible blood.

**Pathophysiology.** The primary event in IHTRs is the interaction between the antibody and the red cell membrane, resulting in the development of immune complexes, activation of complement leading to the release of C3a and C5a with anaphylactoid activity, and the coagulation mechanism via cytokines and factor XII (leading to both consumptive coagulopathy and generation of bradykinin). Vasomotor mediators implicated in the transfusion reaction include histamine, serotonin, and cytokines. Shock results from release of such vasoactive substances.421,422

The renal failure that may occur in this setting is of complex and poorly understood etiology but appears to be primarily ischemic, caused by a combination of hypotension, vasoconstriction (via nitric oxide inactivation by hemoglobin), and intravascular coagulation. The free hemoglobin circulating in such patients was once thought to be the major cause of renal failure by precipitating in and obstructing the renal tubules, but there is adequate evidence to discount this hypothesis. Infusion of incompatible red cell stroma, free of hemoglobin, is sufficient to produce acute renal failure.420

**Management.** On any suspicion of a hemolytic transfusion reaction, the transfusion must be discontinued immediately, as the severity of the reaction is related to the volume of red cells infused. A recheck of the patient’s identity with the information on the discontinued blood unit is necessary to rule out bedside identification errors. The reaction must be reported to the blood bank without delay; a posttransfusion blood sample and the discontinued bag of blood should be sent to the blood bank for investigation of the cause of the reaction. Hydration must be begun immediately to prevent renal failure. An infusion of normal saline is given to maintain the blood pressure and increase the urine flow rate to 100 ml/h. Diuretics may be needed to maintain urine output. If oliguric renal failure develops, fluid challenges must be restricted. Once renal failure is established, the usual supportive measures, including fluid restriction, management of electrolyte balance, and dialysis, are required.

Additional interventions may be needed depending on the severity of the reaction. Some recommend early heparinization at moderate dose as management of coagulopathy if no specific contraindication exists; its use remains controversial. The patient may require support of the defective hemostatic mechanisms with platelets and cryoprecipitate or plasma. In massive intravascular hemolytic transfusion reactions, exchange transfusion has been performed.431

**Investigation of Immediate Transfusion Reactions.** The following steps must be carried out in the investigation of patients with immediate transfusion reactions. The patient’s identity must be confirmed, and all the records on the patient and the donor blood label must be checked for clerical errors. A new, properly labeled sample of blood must be drawn from the patient and sent to the blood bank with the discontinued unit of blood. The posttransfusion sample must be visually checked for hemolysis. In intravascular reactions, free plasma hemoglobin can be detected most quickly by centrifuging a tube of blood anticoagulated with ethylenediamine-tetraacetic acid (EDTA) or heparin; pink to red plasma indicates intravascular hemolysis—that is, evidence of red cell destruction. There must be an investigation for possible alloantibodies. A direct antiglobulin test must be performed on the specimen submitted at the time of the reaction. If the test is positive, the pretransfusion sample should be retested, because the patient may have had a positive direct antiglobulin test before transfusion.

Red cell typing should be repeated on all specimens. If the posttransfusion ABO and Rh types do not agree with pretransfusion results, there has been an error in patient identification or typing. Antibody detection tests should be repeated on the pre- and post-reaction samples. The direct antiglobulin test on the post-reaction specimen may reveal sensitization of red cells in the patient only if the antibody or complement-coated transfused incompatible cells have not been immediately destroyed. A serologic crossmatch should be positive, although the antibody may not be readily demonstrable in serum at the time the reaction is suspected clinically. In a minority of patients in whom there is a high clinical suspicion of a hemolytic transfusion reaction, no immunologic abnormality may be identified. In some, repeated examination for antibodies over a prolonged period of time may eventually reveal the cause; in others, results may be persistently negative. In such patients,51Cr red cell survival testing may be of value in documenting hemolysis caused by incompatibility.432-435

Patients with major hemolytic transfusion reactions should be assessed for the possible presence of intravascular coagulation, and their renal function should be monitored closely. Urinary hemosiderin or free hemoglobin in the urine may also be detected; wine-colored urine is typical of intravascular hemolysis. The laboratory can confirm the identity of the pigment. Demonstration of methemalbuminemia, reduced serum haptoglobin, or hyperbilirubinemia may provide supportive evidence.

**Prevention.** Most IHTRs are preventable. The most likely cause is human error, such as mislabeling of the patient sample, drawing the sample from the wrong patient, transcription errors, and improper identification of the antibody or complement-coated transfused incompatible cells. Mechanisms to ensure positive identification of the patient (recipient), the blood sample, and the transfusion component must be in place to prevent IHTRs.5

**Delayed Hemolytic Transfusion Reactions.** DHTRs generally are much milder than those occurring immediately, and red cell destruction is predominantly extravascular.419,423,436,437 The transfused red cells are destroyed beginning 2 to 10 days after a transfusion. Investigation may reveal the presence of a red cell antibody not detected in the pretransfusion blood sample. The direct antiglobulin test is often positive, but the reaction is transient and may be missed if it is performed too late. The test reverts to negative as the incompatible red cells are removed from the circulation.
DHTRs almost always represent secondary, or anamnestic, antibody responses. On first exposure to an immunogenic red cell antigen, a primary antibody response generally is delayed in onset and slow to reach its peak. For example, anti-D appears a minimum of 4 to 8 weeks after transfusion and may not develop for up to 5 months, after most or all the donor red cells have been removed by the aging process. The antibody level gradually declines, and antibody screening and crossmatch tests may be negative. After a subsequent transfusion, the previously sensitized recipient manifests a much more brisk immune response, with high concentrations of IgG antibody developing within days. Donor cells remaining in the circulation may become coated with antibody and removed by the reticuloendothelial system. Often, there are no symptoms, with a new red cell antibody and positive direct antiglobulin test detected incidentally.

Symptoms, with a new red cell antibody and positive direct antiglobulin test detected incidentally, may include fever, falling hematocrit, jaundice, and, infrequently, hemoglobinemia and hemoglobinuria. Rarely, the reactions may be dramatic; renal failure is uncommon, but fatalities have been reported. The antibodies responsible for DHTRs are well defined. Antibodies to Kidd (Jk) antigens and to the major offenders, with anti-Kell and anti-Duffy (Fy) implicated in most other delayed reactions. Anti-Kidd antibodies are particularly troublesome because the plasma concentration of these antibodies declines more rapidly than others, so pretransfusion tests are more commonly negative in patients who are in fact sensitized.

In delayed hemolytic reactions, destruction of the sensitized red cells is predominantly extravascular; that is, the IgG-coated red cells are removed by the reticuloendothelial system. Often, there are no symptoms, with a new red cell antibody and positive direct antiglobulin test detected incidentally. If present, symptoms and signs may include fever, falling hematocrit, jaundice, and, infrequently, hemoglobinemia and hemoglobinuria. Rarely, the reactions may be dramatic; renal failure is uncommon, but fatalities have been reported. The antibodies responsible for DHTRs are well defined. Antibodies to Kidd (Jk) antigens and to the major offenders, with anti-Kell and anti-Duffy (Fy) implicated in most other delayed reactions. Anti-Kidd antibodies are particularly troublesome because the plasma concentration of these antibodies declines more rapidly than others, so pretransfusion tests are more commonly negative in patients who are in fact sensitized.

Investigation of Delayed Hemolytic Transfusion Reaction. If a DHTR is suspected, a fresh blood sample should be obtained from the patient. This sample should be screened for the presence of previously undetectable red cell antibodies. A direct antiglobulin test should be done. If it is positive, the antibodies should be eluted from the red cells and identified. If the transfused cells have already been destroyed, the direct antiglobulin test will not be positive, but an antibody should be detectable in the patient’s serum. The physician must be advised and the patient given a card indicating the presence of the antibody. The blood bank must retain a permanent record of clinically significant antibodies because the antibody may again become undetectable.

Management. In most instances, no specific therapy is necessary. The few patients who experience severe reactions should be treated with adequate hydration. If further transfusions are indicated, crossmatch-compatible blood negative for the offending antigen(s) should be administered. The physician and patient should be informed about the antibody so that transfusions may be administered safely in the future.

Pseudohemolytic Transfusion Reactions

In patients manifesting a clinical syndrome consistent with intravascular hemolysis, but in whom no blood group incompatibility can be identified, other explanations should be considered. Conditions that mimic hemolytic transfusion reactions are called pseudo hemolytic transfusion reactions. These include bacterial contamination with organisms such as Yersinia enterocolitica, resorption of large hematomas, and hemolysis caused by drug reactions or vascular prostheses. Pretransfusion hemolysis of donor blood caused by mechanical trauma, freezing, heat, or hypotonic solutions, should always be considered a potential cause of such a reaction.

Fenite Nonhemolytic Transfusion Reactions

FNHTRs have been reported in a variable proportion of patients receiving transfusions, ranging between 0.5% and 3.0%; they are more common in multiply transfused patients. The typical reaction consists of a chill followed by fever of 1°C or greater, usually during or within a few hours of the transfusion. Headache, nausea, and vomiting may occur. Occasionally, the reaction may be severe but usually these reactions are mild. Whatever their degree, febrile transfusion reactions usually run their course within a few hours. Some causes of FNHTRs are as follows.

Alleloimmunization to antigens on leukocytes and platelets is one of the most common causes of nonhemolytic febrile reactions. Early studies detected the presence of leukoagglutinins in such patients. HLA antibodies are most commonly found, followed by platelet-specific antibodies; granulocyte-specific antibodies are detected in only a minority of patients.

Another cause of FNHTRs is the transfusion of cytokines that have developed during product storage, especially in nonleukoreduced whole blood–derived platelet concentrates stored at room temperature. During storage, leukocytes in platelet concentrates release cytokines that appear to be responsible for the febrile reaction. The causative role of accumulated cytokines is supported by the observation that leukoreduction filtration after storage does not eliminate many of the FNHTRs to platelet concentrates. The incidence of FNHTRs to nonleukoreduced platelet concentrates increases with the age of the platelet concentrate and the leukocyte concentration in the product. The reactions appear to be mediated by the supernatant of the platelet products. The concentration of cytokines in platelet concentrates and incidence of FNHTRs can be decreased by leukoreducing the products soon after collection. Apheresis platelets are leukoreduced by the collection technology and have reduced cytokine levels.

The possibility of bacterial contamination of the product must be considered as a possible cause of FNHTR. Symptoms caused by transfusion of bacteria or their toxins can be mild or may be fatal. Platelet components are involved more often because they are stored at room temperature. However, certain organisms such as Yersinia enterocolitica proliferate in red cells at storage temperatures of 1°C to 6°C. Bacterial contamination is often not considered as a cause of a febrile reaction; it may be more prevalent than reported because of underinvestigation.

Management of Febrile Reactions

The approach to management of febrile transfusion reactions must be based on an understanding of all the possible causes. Although many such reactions are caused by WBC alloimmunization or cytokines, fever may also be an indication of an unsuspected hemolytic transfusion reaction or contamination of the donor blood by bacteria or endotoxin. For these reasons, every transfusion complicated by a febrile transfusion reaction should be discontinued until the patient has been carefully assessed by a physician and the blood bank alerted. Although controversial, the physician, depending on the clinical condition of the patient and the institution’s policies regarding such steps, may elect to restart the transfusion if a hemolytic or bacterially contaminated transfusion has been ruled out.

The possibility of a hemolytic reaction should be considered when fever occurs. If suspected, the donor unit, along with a patient blood specimen, should be returned to the blood bank for investigation. Other tests for hemolysis should be done as discussed previously, if clinically indicated. The donor unit and patient blood should be cultured if there is any suspicion of bacterial contamination.

The symptoms of a febrile transfusion reaction may often be ameliorated with an antipyretic such as acetaminophen or hydrocortisone in patients who develop severe reactions. Meperidine may be used to decrease or stop severe shaking chills. Antihistamines are indicated only if the patient also has allergic symptoms such as hives.

Prevention of Febrile Transfusion Reactions

Febrile transfusion reactions to red cells occur most commonly in patients who have been sensitized to WBC antigens by previous
transfusions or pregnancies. In such patients, the risk of a febrile transfusion reaction varies with the leukocyte content of the donor unit. Use of leukoreduced red cells may decrease the incidence of FNHTRs. Every patient who experiences a reaction does not routinely need specific preventive measures, because only a minority will have a second reaction.

When whole blood–derived platelets are given, febrile reactions are common. Removal of leukocytes from these components at the time of transfusion often fails to prevent FNHTR because of the high level of cytokines in these products. Reduction of the level of cytokines by using platelet concentrates stored for a shorter time, prestorage leukoreduction of the platelet concentrates, plasma reduction, or use of apheresis platelets reduces the incidence of FNHTR to platelet products. If reactions persist, premedication with antipyretics or corticosteroids may be required. Because granulocyte concentrates cannot be modified by leukoreduction, premedication should be considered in patients who receive these products.

Transfusion-related Acute Lung Injury

Transfusion-related acute lung injury (TRALI) most commonly presents as severe respiratory distress of sudden onset, caused by a syndrome of noncardiogenic pulmonary edema resembling the adult respiratory distress syndrome. Chills, fever, hypotension, and cyanosis, as well as the usual manifestations of pulmonary edema, may be seen. TRALI is reported by the FDA as the number-one cause of transfusion-associated fatality. The incidence of TRALI varies greatly, from 1 in 5,000 to 1 in 557,000 depending on the blood component involved. It is hypothesized that TRALI reactions may be the result of two cumulative events: the first event is linked to the patient (i.e., underlying sepsis, hematologic disease, and/or postsurgical status), and the second event is related to the transfusion of potential granulocyte primers such as inflammatory cytokines, active lipids, and/or alloantibodies. The diagnosis of a TRALI reaction is based on the onset of acute lung injury (ALI) within 6 hours of transfusion. ALI is characterized by an acute onset of hypoxemia (oxygen saturation <90% by pulse oximetry for a patient breathing room air or a PaO2/FiO2 ≤ 300 mmHg), bilateral infiltrates on frontal chest radiograph, and no evidence of circulatory overload. Based on studies of adult respiratory distress syndrome, which has similar pulmonary manifestations, it has been suggested that agglutination of granulocytes and complement activation occur in the pulmonary vascular bed, leading to capillary endothelial damage with consequent fluid leak into the alveoli.

Management involves supportive measures for the pulmonary edema and hypoxia, including ventilatory support if required. Hemodynamic monitoring may be required to determine whether fluid overload is a factor; if not, diuretics are of no proven value. The AABB requires evaluation of donors implicated in TRALI. Donors whose plasma is implicated in such reactions should be examined for the presence of granulocyte-specific and HLA antibodies that react with recipient leukocytes. It is recommended to avoid further transfusion of plasma-containing products from implicated donors found to have anti-HLA or anti-granulocyte antibodies. In 2006, the AABB recommended that blood banks minimize the production of high-plasma-content components (such as plasma products andpheresis platelets) from donors at risk for alloimmunization (e.g., women with a history of pregnancy). This change has resulted in a decrease of reported TRALI cases. Allergic Reactions

Allergic reactions are common in transfusion recipients, with an estimated incidence of 1% to 3%, but their actual incidence may be higher because they are often not reported. They range from urticarial lesions (hives), other skin rashes, bronchospasm, and angioedema to anaphylactic shock. Minor reactions are dose-related, with an incidence related to the volume of plasma transfused. Whole blood and plasma are more likely than concentrated red cells to cause such reactions; washed red cells or albumin are rarely implicated. Minor urticarial reactions are the only transfusion reactions that do not necessitate immediate discontinuation of the transfusion. Fortunately, the incidence of severe anaphylactic transfusion reactions is very low, as such reactions can be life-threatening.

Most allergic reactions are thought to be mediated by recipient IgE to proteins or other soluble substances in donor plasma. The interaction between the antigen and IgE stimulates the release of histamine from mast cells and basophils. Most patients do not have repeated allergic reactions, but those with a history of atopy are at higher risk for additional reactions. For patients with repeated allergic reactions, premedication with an H1-blocking antihistamine is usually sufficient for prevention. If maximal premedication fails to control the allergic response, reducing the plasma content of the transfused blood product is another option. This can be accomplished by centrifuging the product and removing almost all the plasma or by red cell washing.

In patients with severe anaphylactoid or anaphylactic reactions, antibodies reacting with IgA in donor plasma should be considered. The incidence of genetically determined IgA deficiency in the otherwise normal population is high, ranging from 1 in 400 to 1 in 500. Without necessarily having prior transfusion exposure, approximately 20% to 25% of such patients produce antibodies to IgA, generally class-specific (i.e., reacting with all IgA molecules). Such patients should be transfused, when necessary, with washed red cells or with IgA-deficient blood products. In addition, many patients with normal IgA levels have antibodies that react with some, but not all, IgA molecules; the incidence of such limited-specificity antibodies has been reported at 2% of normal adults, but the incidence may be as high as 21% in multiply transfused patients. The concentration of such limited-specificity antibodies generally is low, and the resulting reactions are usually milder, but the possibility of a major reaction exists.

Posttransfusion Purpura

Posttransfusion purpura is the development of life-threatening thrombocytopenia 5 to 10 days after transfusion. This rare complication is caused by the development of alloantibodies directed against platelet-specific antigens; anti–HPA-1a is often implicated, although antibodies with other specificities have also been reported (see Chapter 47). Posttransfusion purpura is thought to occur as a result of a secondary immunologic response to the platelet-specific antigen, most patients having been sensitized by prior pregnancy or transfusion. The mechanism of destruction of the patient’s own platelets is uncertain. Management includes high-dose IVIG or corticosteroids or plasma exchange.

Posttransfusion thrombocytopenia may also be associated with the passive administration of a platelet-specific antibody. Both anti–HPA-1a and anti–HPA-5a have been implicated; these cases can be defined as passive posttransfusion purpura, and the resulting thrombocytopenia occurs within hours of the transfusion. It is important to identify the donors of these blood products to prevent further infusion of plasma-containing products from such donors.

Transfusion-related Immunomodulation

Allogeneic blood transfusion results in the transfer of not only RBCs, but also significant amounts of potential immune effector cells, their products (e.g., cytokines), and various substances that may be seen by the host immune system as foreign antigens.
A large body of literature exists that substantiates the modulation of host immune systems by transfused allogeneic cells and substances, raising the possibility of the development of clinical syndromes generally referred to as transfusion-related immunomodulation (TRIM).479 Beneficial transfusion-related immunomodulatory effects have been reported in renal transplant patients, women with recurrent spontaneous abortions, and patients with Wegener’s disease.

A large number of clinical studies have been performed specifically addressing two potential harmful TRIM-associated effects: cancer recurrence and postoperative bacterial infections. The aim of the studies has been to document TRIM and to ascertain the potential benefit of leukoreduction or use of autologous blood.481-489 Despite some reported observations of a transfusion-associated increased risk of cancer recurrence or postoperative infections, many studies include potential confounders or sources of bias. Meta-analyses have concluded that a deleterious clinical effect of transfusion immunomodulation remains controversial.490,491,492

Transfusion-associated Graft-versus-Host Disease

Most cellular blood products, including red cell, platelet, and granulocyte products, contain viable, immunocompetent T lymphocytes.493 When transfused into immunocompetent recipients, these donor lymphocytes may proliferate in the patient and lead to the clinical syndrome of transfusion-associated graft-versus-host disease. TA-GVHD has also been reported in immunocompetent patients, especially those who receive transfusions from family members or from random donors who share HLA antigens, as is the case when the donor is homozygous for a shared HLA haplotype.496,497 In these cases, the recipient does not recognize the donor cells as foreign, allowing the transfused lymphocytes to proliferate and cause TA-GVHD. A higher incidence has been reported in countries such as Japan, whose populations are genetically similar.

Transfusion of leukocyte or platelet concentrates or fresh blood has been responsible for most cases of posttransfusion GVHD. Frozen-thawed plasma products (FFP, cryoprecipitate) have not been definitively associated with TA-GVHD. TA-GVHD occurs earlier than that seen after bone marrow transplantation, usually within 1 to 2 weeks, but is otherwise similar.498 Fever is the most common symptom, followed by a typical erythematous, maculopapular skin rash that begins centrally and spreads peripherally to the hands and feet. Abnormalities of hepatic function, nausea, and bloody diarrhea often occur as the process progresses. Leukopenia followed by pancytopenia due to marrow failure is quite common in TA-GVHD and is seen most often 2 to 3 weeks after the onset of symptoms. The diagnosis is based on the clinical picture and can be confirmed histologically with a skin biopsy. Laboratory confirmation that the GVHD is transfusion-induced can be obtained by demonstrating the presence of donor lymphocytes in the patient. This can be done by HLA typing of patient and donor cells by DNA methods for class I and II antigens, by cytogenetic analysis, or by analysis of DNA microsatellite polymorphisms or variable-number tandem repeats.493 Severe systemic infections are the most common cause of death, which often occurs within 3 to 4 weeks from the time of the implicated transfusion. Despite aggressive treatment, the fatality rate in TA-GVHD is significantly higher than that associated with bone marrow transplantation and has been reported to be >90%.498 Corticosteroids, antithymocyte globulin, cyclosporine, and growth factors have all been used with minimal success in the treatment of TA-GVHD. Although a few reports of spontaneous resolution have been reported, current treatment approaches have used combinations of immunosuppressant medications with lymphocyte-directed antibody therapy (anti-CD3, anti-interleukin-2 receptor, antithymocyte globulin). Because of the lack of effective treatment regimens, TA-GVHD should be prevented by pretransfusion irradiation of all blood products administered to patients at risk. Irradiation inhibits proliferation of donor lymphocytes with little significant adverse effect on red cell, platelet, or granulocyte function. Changes in the red cell membrane do occur that result in an increased loss of potassium from the cell, limiting the storage time of irradiated red cells to 28 days. This may be important in neonates, as the dose of free potassium may be high in a relatively large-volume transfusion, necessitating the use of freshly irradiated or washed RBCs. The recommended dose for the irradiation of blood and blood products is 2,500 cGy at the center of the irradiation field, with a minimum dose of 1,500 cGy at any point in the field.5,131

Based primarily on case reports and reviews, a number of immunosuppressed and immunocompetent patient groups can be stratified according to risk for developing TA-GVHD (Table 21.9).

Nonimmunologic Adverse Effects of Blood Transfusion

Transfusion-associated Circulatory Overload

Transfusion of red cell preparations or plasma products may result in transfusion-associated circulatory overload (TACO). In chronically anemic patients, the plasma volume expands so that the blood volume is normal. Virtually the entire volume of the blood product infused remains in the circulation; in elderly patients with limited cardiac reserve or in severely anemic patients in congestive heart failure, transfusion may lead to fatal pulmonary edema. Diuretic therapy and other measures to manage heart failure may be of some benefit; partial exchange transfusion may be indicated. Prevention of these reactions is most important. Transfusions should be administered slowly, at a rate of 1 to 2 ml of blood/kg of body weight per hour, with the

<table>
<thead>
<tr>
<th>TABLE 21.9</th>
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<tr>
<td><strong>PATIENTS AT INCREASED RISK FOR TRANSFUSION-ASSOCIATED GRAFT-VERSUS-HOST DISEASE</strong></td>
</tr>
<tr>
<td><strong>High Risk</strong></td>
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<tr>
<td>Bone marrow transplant (allogeneic and autologous)</td>
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<tr>
<td>Intrauterine transfusions</td>
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<tr>
<td>Granulocyte or HLA-matched platelet transfusions</td>
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<tr>
<td>Transfusions from blood relatives</td>
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<tr>
<td>Congenital immunodeficiencies</td>
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<tr>
<td>Hodgkin disease</td>
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<tr>
<td><strong>Moderate Risk</strong></td>
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<tr>
<td>Hematologic malignancy (acute myelogenous leukemia/acute lymphocytic leukemia/non-Hodgkin lymphoma)</td>
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<tr>
<td>Patients treated with purine-analog drugs (e.g., chronic lymphocytic leukemia)</td>
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<tr>
<td>Malignancies treated with intensive chemo-/radiotherapy (e.g., neuroblastoma, sarcoma)</td>
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<tr>
<td>Solid organ transplant recipients</td>
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<tr>
<td>Preterm infants</td>
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<tr>
<td>Newborns receiving exchange transfusion</td>
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<tr>
<td><strong>Low/Theoretical Risk</strong></td>
</tr>
<tr>
<td>Human immunodeficiency virus/acquired immunodeficiency syndrome</td>
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<td>Healthy term newborns</td>
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</tbody>
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patient under close observation. Splitting red cell components or volume-reducing apheresis platelets can be helpful in managing the most difficult cases.

**Massive Transfusion**

**Metabolic Transfusion**

Stored blood differs in its composition from that circulating in the body. If large amounts of stored blood are infused rapidly, one may observe adverse effects related to such differences. The elevated K⁺ content of stored red cells rarely leads to hyperkalemia, but it is a risk in the presence of renal failure, shock, with acidosis, or hemolysis. Plasma contains a significant amount of citrate as anticoagulant; recipients with normal circulatory status promptly metabolize this in the liver, but during plasma exchange or in patients in shock or severe liver failure, citrate excess may lead to hypocalcemia. Hypocalcemic reactions caused by citrate may be treated by intravenous calcium infusion.\(^{499}\)

**Hypothermia**

Hypothermia may occur if a large volume of cold blood is infused rapidly. Hypothermia is one of the most common complications of massive transfusion and contributes to the associated coagulopathy. Neonates and the elderly are particularly sensitive to this reaction. Hypothermia affects the way the liver metabolizes citrate, resulting in an increased risk of hypocalcemia. Rapid infusions of citrated blood products in such patients, especially through central venous lines, may lead to arrhythmias. Hypothermia interferes with platelet function and clotting, both of which are improved when the patient is warmed.\(^{499}\)

One way of approaching this problem is with the use of warmed intravenous fluids or blood. Blood-warming devices are available that can adequately warm the blood administered, even during a rapid and massive transfusion. All patients who are receiving large amounts of red cells and plasma should have those products administered through blood-warming devices. Blood warmers must be checked regularly to ensure that they maintain their temperature. If the blood is overheated, hypocalcemia and the associated complications of transfusing hemolyzed blood may result.

Any one of these potential problems alone is rarely significant. However, in the critically ill patient who requires massive transfusion, acidosis, hypoxemia, hypothermia, hypocalcemia, and hypo- or hyperkalemia often coexist, with a consequent risk of cardiac arrhythmias. Neonates receiving exchange transfusions are particularly susceptible to such physical and metabolic effects.\(^{132,500}\)

**Dilutional Coagulopathy**

Massive transfusion of one to two blood volumes in patients results, first, in abnormalities of the prothrombin time (PT) and of the activated partial thromboplastin time (APTPT); and second, in thrombocytopenia.\(^{501}\) Massively transfused patients are often affected by sepsis, shock, and intravascular coagulation, which may aggravate the dilutional hemostatic defects.

In practice, most patients tolerate otherwise uncomplicated dilutional coagulopathy well. Factor VIII activity may rise as a response to stress; factor V falls, but rarely to dangerous levels. Moderately severe thrombocytopenia, accompanied in some cases by a significant degree of platelet dysfunction, may be a more significant problem. Transfusion therapy of such patients is best guided by laboratory measurements, but clinical assessment is most important because conventional coagulation tests take time to obtain. As discussed earlier in this chapter, for patients undergoing rapid massive transfusion, the first line of treatment (with regard to hemostatic blood products) should include plasma to correct the levels of coagulation factors, followed by platelet products.\(^{205,206,208,222,224}\)

**Age of Transfused Blood**

In 2008, a study suggested a relationship between the length of blood product storage and the in-hospital mortality of transfused cardiac surgery patients.\(^{63}\) The study was retrospective in nature and elicited much discussion and further investigation. Meta-analyses of studies looking at the effect of age of transfused blood on patient outcomes failed to clarify an association.\(^{502,503,504}\)

Prospective studies are now ongoing.\(^{505–507}\)

The changes that stored red blood cells undergo while awaiting transfusion are referred to as the “storage lesion.” In short, these changes are a decrease in both 2,3-diphosphoglycerate, ATP, and an increase in extracellular potassium. Red cell membrane changes result in decreased flexibility of the cell, hemolysis, and formation of microparticles. Whether the red cell storage lesion is responsible for deleterious clinical effects awaits further investigation.

**Miscellaneous**

Air embolism is a potential hazard when perioperative infusion devices are used.\(^{508}\) Fat embolism may occur in the rare situation in which blood products are transfused via the bone marrow. The plastic materials used to ensure the flexibility of some blood storage bags can leach into the product and, although no adverse effects have been demonstrated to date,\(^{509}\) attempts are being made to identify alternatives.

**Iron Overload: Transfusion Hemosiderosis**

Iron overload is a major problem in patients who require long-term red cell transfusion support for chronic anemias due to bone marrow failure.\(^{510,511}\) Each unit of red cells contains approximately 0.25 g of iron. After a large number of red cell transfusions, in the absence of blood loss, the recipient develops the stigmata of transfusion siderosis: impaired growth, failure of sexual maturation, myocardial and hepatic dysfunction, hyperpigmentation, and, often, diabetes. Patients such as those with thalassemia who are at risk of this complication should receive prophylactic aggressive iron chelation therapy.

**INFECTIOUS COMPLICATIONS OF BLOOD TRANSFUSION**

**Overview of Blood Donor Screening for Infectious Diseases**

In the 1960s, transfusion-associated hepatitis (TAH) occurred in more than 30% of multiply transfused patients. The development and implementation of a screening test for HBsAg and the switch to an all-volunteer blood supply resulted in a dramatic reduction in the incidence of both B and non-A, non-B (NANB) TAH (Fig. 21.7).\(^{312}\) However, a significant risk of NANB hepatitis persisted.

In the early 1980s, the blood banking industry was further challenged with the appearance of AIDS. In the early and mid-1980s, before the identification of the causative agents of AIDS or NANB hepatitis, the idea of using surrogate tests to identify donations at increased risk of transmitting one of these infections was introduced. Candidate tests included those that would detect the consequences of an infection (e.g., elevated alanine aminotransferase [ALT] in the case of NANB hepatitis or inverted helper-to-suppressor T-cell ratio in the case of AIDS) or those likely to be positive in individuals who engaged in high-risk sexual activity or needle sharing (e.g., antibody to the hepatitis B core antigen [anti-HBc]).\(^{513–516}\)

Before the availability of a specific test for HIV, some blood suppliers implemented HBc antibody testing or donor
T-cell testing in an attempt to reduce the risk of transmitting AIDS through blood transfusion.

After the development and implementation of a test for HIV antibody in 1985, it became clear that there is a delay between the onset of infection and the development of detectable antibody. A blood donation made during this "window period" could pass infectious disease screening tests but transmit infection. The FDA required blood centers to inform prospective donors about the window period and to question them directly about specific risk behaviors. Gradually, improvements in the sensitivity of the HIV antibody test led to shortening the HIV window period from 45 days to about 22 days.

During the mid-1980s, surrogate tests for NANB hepatitis and risk activity (ALT and HBc antibody) became required in the United States. A donor screening test for the retrovirus HTLV-I was implemented in 1988. The first donor screening test for antibody to hepatitis C became available in 1990, and an improved test became available in 1992. In 1996, a donor screening test for HIV-1 p24 antigen was implemented because available information suggested that this test could shorten the HIV window period by an additional 6 days. By this time, the risks of transfusion-transmitted HIV and hepatitis were too low to measure prospectively and could only be estimated with the aid of mathematical modeling (Fig. 21.8).

Despite the extremely low risk of transfusion-transmitted HIV and hepatitis, there continued to be immense public pressure to further improve transfusion safety. In 1999, nucleic acid testing (NAT) for HIV and HCV RNA was added to blood donor screening via clinical trials. Initially available NAT methods were labor-intensive and could not be applied to rapid screening of large numbers of blood donations. NAT screening was rendered feasible by performing the assays on "minipools" of donor specimens (initially pooling 16 to 24 samples together for testing, more recently 6 to 16 samples). Clinical trials of minipool NAT for HIV and HCV RNA confirmed that this testing detects infection earlier than antigen or antibody assays.

NAT testing for HIV and HCV RNA is now a FDA requirement. With implementation of licensed NAT for HIV, the FDA permitted discontinuation of the HIV p24 antigen test.

NAT assays continue to be improved and new assays developed. Donor NAT assays for HIV and HCV RNA are now fully
automated and have been multiplexed to include HBV DNA detection. Testing for West Nile virus RNA was initiated in 2003 using investigational assays; this testing is now required by FDA.

Additional donor serologic screening tests have also been developed or are in development. A donor screening assay for antibodies to T. cruzi became available in 2007; FDA now requires every donor to be tested once for this infection (see below). Tests for Babesia infection are in development.

### Residual Risks of Infection

Table 21.10 lists the tests currently performed on volunteer blood donations in the United States. It is thought that the residual risk of transmitting HIV and hepatitis by transfusion is related mainly to window period donations. The probability that a donation was made during the window period can be calculated from the observed incidence of new infections in blood donors and the length of the window period.\(^\text{19,521,524}\)

The implementation of nucleic acid testing for HIV and HCV has permitted direct detection of donors with newly-acquired infections (i.e., donors who are NAT-positive, antibody negative). New HIV and HCV infections in repeat blood donors are very rare. However, studies indicate that first-time donors are two to three times more likely than repeat blood donors to have newly-acquired infection.\(^\text{19,521,524}\)

Thus, current estimates of transfusion risk include an adjustment for a 2- to 3-fold higher probability that a first-time donor is in the window period compared to a repeat donor.\(^\text{523,524-526}\)

Table 21.11 shows the current risk estimates for transfusion-transmitted HIV, HCV, and HBV based on the length of the window period and the estimated frequency of window period donations.

Because the current risks of transmitting HIV and HCV are low, the absolute benefit gained from further incremental improvements in blood donor testing for these infections would be very small. The implementation of individual-unit NAT for HIV and HCV, mainly to window period donations. The probability that a donation was made during the window period can be calculated from the observed incidence of new infections in blood donors and the length of the window period.\(^\text{19,521,524}\)

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Because the current risks of transmitting HIV and HCV are low, the absolute benefit gained from further incremental improvements in blood donor testing for these infections would be very small. The implementation of individual-unit NAT for HIV and HCV, for example, would be associated with extremely high cost with very little incremental improvement in blood safety in the US.\(^\text{527,528}\)

Similarly, the value of processes to chemically inactivate residual pathogens in blood products has been questioned in view of the low residual risks of HIV and HCV. These treatments, however, might represent a reasonable approach toward reducing the risk of transmitting infectious agents for which there are currently no donor screening tests.\(^\text{529,530}\)

Some pathogen reduction treatments for platelets and fresh plasma are in use outside the US, but as of April 2012 these were not approved for use in the US. Commercial plasma derivatives are, however, subjected to a solvent/detergent treatment that inactivates lipid-enveloped viruses such as HIV, HCV, and HBV. Solvent/detergent treatment cannot be applied to cellular blood components.

### Transfusion-associated Hepatitis

Before the development of serologic tests capable of determining the cause of TAH, all TAH was thought to be due to hepatitis B (the “serum hepatitis” agent). After the HBsAg test became available, however, it was discovered that hepatitis B accounted for only about 25% to 30% of TAH cases.\(^\text{531,532}\)

Subsequent studies excluded hepatitis A virus (HAV), CMV, and the Epstein-Barr virus (EBV) as common causes of TAH. The designation NANB hepatitis was created to describe the majority of TAH cases.\(^\text{533}\)

In 1988, the major causative agent of NABN hepatitis was identified as HCV.\(^\text{534,535}\) Widespread testing of all blood donations for this virus was implemented in 1990. An improved test for hepatitis C became available in 1992. Since then, TAH has become rare.

### Hepatitis B

The discovery of HBsAg and application of this test to blood donor screening led to a dramatic reduction in transmission of HBV by transfusion (Fig. 21.7).\(^\text{536}\)

Screening of all blood products for HBsAg began in 1970 in the United States with low-sensitivity tests and was made mandatory in 1972. The high-sensitivity HBsAg test in current use becomes positive an average of 38 days after the onset of infectivity.\(^\text{537}\)

This test detects most but not all donors who are infectious for hepatitis B. Three types of individuals with hepatitis B infection may be missed by the current HBsAg test: (1) individuals with early infection whose HBsAg has not yet become detectable; (2) individuals who were previously vaccinated against HBV and have anti-HBs but who acquire HBV infection after subsequent exposure (so-called “vaccine breakthrough” infections);...
and (3) individuals with chronic infection whose HBsAg has fallen below the limits of detection (“occult HBV infection”). Units from individuals with chronic occult HBV (category 3 above) are currently excluded from the US blood supply by donor testing for anti-HBc. In the US, anti-HBc–positive donations are permitted into pooled plasma derivatives, however, because HBV infectivity is eradicated from these products by the pathogen inactivation processes to which the products are subjected. Based on currently mandated donor screening tests (i.e., HBsAg and anti-HBc), the current estimated risk of HBV transmission by individual blood components in the United States is 1 in 280,000 units.\(^{526}\) (Table 21.11).

As of April 2012, HBV DNA testing of blood donors was not required in the US. However, most US blood donors were, in fact, being tested for HBV DNA because probes for this target were included in the donor screening NAT assays used for HIV and HCV RNA detection. In November 2011 the US FDA issued a draft guidance document indicating its intention to make HBV DNA screening a requirement.\(^{538}\) HBV DNA tests detect some, but not all, of the HBV-infected donors missed by HBsAg testing.\(^{539}\) HBV DNA screening of blood donors has more value in HBV endemic countries where donors are not screened for anti-HBc.\(^{540}\)

**Hepatitis C**

Donor screening for HCV includes NAT for HCV RNA as well as HCV antibody testing. It is estimated that the donor RNA test detects infection an average of 7.4 days after exposure. Based on window period/incidence modeling, the risk of HCV transmission by transfusion of fresh blood products is now estimated to be approximately 1 in 1,149,000 (Table 21.11).\(^{525}\)

**Hepatitis A Virus**

Transfusion-related transmission of HAV by fresh blood products is rare.\(^{541,542}\) However, transmission of HAV has been associated with pooled plasma products.\(^{543}\) Because HAV is not lipid-enveloped, infectivity is not eliminated by solvent/detergent treatment. Therefore, immunization to HAV is recommended for patients who are expected to receive pooled plasma products, such as those with clotting disorders.\(^{545}\) The FDA does not require donor screening for this agent. Some plasma-derivative manufacturers, however, test plasma pools for HAV nucleic acid in an effort to reduce the risk of transmitting this agent.

**Human Immunodeficiency Virus Type 1 and Type 2**

Current donor screening for HIV includes nucleic acid testing for HIV-1 RNA and testing for antibodies to HIV-1 and HIV-2. The window period for HIV, based on time to detection of RNA via minipool nucleic acid screening, is currently estimated at 9 days.\(^{525}\) The current estimated risk of HIV transmission by transfusion is approximately 1:1,467,000 units (Table 21.11). Donor questioning regarding HIV risk behavior and the temporary exclusion of individuals at increased risk of being in the HIV window period are critical and essential elements of this safety level.\(^{544}\)

Whether certain deferral periods could be shortened without compromising blood transfusion safety has been the topic of intense public discussion.\(^{545}\)

**Other Infections**

Essentially any infection that can circulate in the blood of an apparently healthy blood donor can be transmitted by transfusion. Recently, the AABB’s Transfusion-Transmitted Diseases (TTD) Committee evaluated a number of potentially transmissible infections, their risks of causing severe disease, and the need for intervention strategies.\(^{546}\) This analysis is available online and is updated periodically. Some of the agents that have been the focus of recent interventions or public debate are discussed below.

**Infections Transmitted by Arthropods**

Over the past decade, much attention has been focused on infectious agents that can be transmitted to donors by insects and further transmitted to patients via transfusion.\(^{546}\) This category of pathogens includes West Nile virus, *Trypanosoma cruzi*, babesia, malaria, and dengue fever.

**West Nile Virus**

West Nile virus was first detected in the United States in 1999, and has since spread through the North American continent in annual epidemics. Birds are the natural reservoir of the virus, which is spread to humans by mosquitoes.\(^{547}\) Eighty percent of infected individuals are asymptomatic, 20% have a relatively nonspecific febrile illness, and <1% develop neuroinvasive disease (meningitis, encephalitis, or flaccid paralysis), which can lead to chronic disability or death.

WNV was first demonstrated to be transmissible by transfusion in 2002, when infection in 23 recipients was linked to blood components later found to contain WNV RNA but no WNV antibody.\(^{548}\) In 2003, minipool NAT screening of blood donations for West Nile virus RNA was implemented throughout the United States using investigational assays. WNV NAT assays are now FDA-approved and required. Transmissions despite minipool donor testing led to the discovery that 20% to 30% of donors with WNV infection may be missed by minipool testing because of low levels of circulating virus.\(^{549,550}\) Therefore, at times of high WNV activity, donor WNV RNA screening must performed on individual donations.\(^{551}\)

**Malaria**

Malaria is a common infection globally. However, transfusion-transmitted malaria is rare in the United States, with only zero to three cases per year occurring during the last decade.\(^{552}\) This degree of safety is remarkable considering that there is no donor screening test for malaria in the United States. Screening is accomplished entirely by donor questioning. According to current FDA guidelines, individuals are deferred from donation for 1 year after travel to a malarious area and for 3 years after living in a malarious area. Almost 3% of otherwise eligible donors are excluded on the basis of this questioning. Of the donors implicated in the recent cases of transfusion-transmitted malaria in the United States, approximately 60% (including the majority of *Plasmodium falciparum* infections) should have been excluded by donor deferral criteria. The remaining cases are largely related to chronic asymptomatic infections in donors who are beyond the deferral period.\(^{552}\)

**Babesiosis**

Babesiosis is caused by a protozoan parasite that infects human RBCs. It is transmitted by the *Ixodes* tick, the same vector that transmits the causative agents of Lyme disease and human granulocytic anaplasmosis. US cases of babesiosis were first identified in the northeast United States but have now also been identified in Minnesota, Wisconsin, and California.\(^{553}\)

Incubation ranges from 1 to 6 weeks or longer. Symptoms range from none to mild flu-like symptoms to a malaria-type illness with hemolytic anemia. Asymptomatic individuals may remain infective for months or years.\(^{546}\) More than 150 cases of transfusion-transmitted babesiosis have been identified, including fatal cases. Asplenic, immunocompromised, and elderly patients appear to at increased risk for severe infection. It is suspected
that transfusion-transmitted babesiosis is vastly underrecognized. The need for an intervention to reduce transfusion-transmitted babesiosis in the US has been acknowledged at the national level. Antibody screening of donors or pathogen reduction could theoretically reduce transmission, but there is currently no intervention approved for use.

Lyme disease is caused by the spirochete Borrelia burgdorferi and is transmitted by the same tick vector that transmits babesiosis. The organism has been found to survive the storage conditions of RBC and platelet components. Nevertheless, there have been no documented cases of transfusion-transmitted Lyme disease. 

Trypanosoma cruzi

Trypanosoma cruzi, the protozoan parasite that causes Chagas disease, is endemic in portions of Mexico, Central America, and South America. It is transmitted to humans by the reduvid bug. Acute infection is usually self-limited, although rarely it may involve myocarditis or meningoencephalitis and may be fatal, particularly in immunocompromised patients. In most cases, however, the acute infection goes undiagnosed, and the infection becomes chronic. After decades, 20% to 30% of chronically infected individuals develop cardiac or intestinal dysfunction that can be fatal. The transmission of T. cruzi by transfusion is well documented in endemic areas. A blood donor screening assay for T. cruzi antibody became available in the US in 2007. The vast majority of the infected donors detected have been immigrants from endemic areas; US-acquired T. cruzi appears to be rare. Therefore, the FDA has endorsed a strategy of testing each US donor only once for this infection. 

Dengue Virus

Studies in dengue-endemic regions outside the continental US have documented a high prevalence of blood donors with asymptomatic viremia during dengue outbreaks. Concern about this virus in the US has increased recently with recognition of infections in the southern part of the country. Although there does not currently appear to be a need for blood donor screening for this virus within the continental US, activity of this virus will need to be monitored. 

Transmissible Spongiform Encephalopathies: Creutzfeldt-Jakob Disease and Variant Creutzfeldt-Jakob Disease

Both classical Creutzfeldt-Jakob disease (CJD) and variant Creutzfeldt-Jakob disease (vCJD) are rapidly progressive fatal infections of the nervous system caused by prions. Individuals at increased risk for classical CJD are currently excluded from blood donation in the United States, despite evidence that this disease is not transmissible by transfusion. In contrast, variant CJD (vCJD) does appear to be transmissible by transfusion. Human vCJD is caused by the same prion that causes bovine spongiform encephalopathy (BSE), or “mad cow disease.” As of April 2012, four cases of apparent transfusion-transmitted vCJD had been identified in the UK, where a BSE epidemic occurred between 1980 and 1996. In addition, one case of vCJD had been identified postmortem in a hemophilia patient in the UK who died of other causes. Worldwide, steps have been taken in an effort to minimize the risk of vCJD transmission by blood products in the absence of a donor screening test for the infection. In the United States, individuals are currently excluded from donating blood if they lived in the UK for 3 months or more between 1980 and 1996, if they lived in Europe for 5 years or more since 1980, or if they received a transfusion in the UK or France since 1980. Filters that may absorb prions are in development, and attempts to develop blood donor screening tests are also underway. Because prions lack lipid coats and nucleic acid, the causative agent of vCJD would not be inactivated by any of the pathogen inactivation processes currently in use or under development.

Bacterial Contamination

Bacteria are present in approximately 1/3,000 cellular blood components. Potential sources of bacteria include asymptomatic bacteremia in the donor and bacteria from the donor’s skin. Bacterial contaminants multiply fairly readily in platelet components, which are stored at room temperature, but less readily in red cell products, which are refrigerated. Recognition of morbidity and mortality from transfusion of bacterially contaminated platelets prompted the AABB to implement, in 2004, a requirement for bacterial testing of platelet components. AABB now also requires diversion of the first several milliliters of donor blood into a sample pouch to reduce contamination of platelet units by skin contaminants. The quantity of bacteria in blood components just after collection is too low to detect by any diagnostic assay. The platelet bacterial screening process used by most US blood centers involves a 36 to 48 hour quarantine of the platelet components. First, there is a 24-hour hold after collection to allow potentially contaminating bacteria to multiply to detectable levels. Then, a sample is taken from each product and inoculated into a blood culture bottle. If the culture is negative after 12 to 24 hours, the product is made available for use, but the culture is continued for the shelf life of the unit. About 1 in 5,000 apheresis platelets are found by this screening to be bacterially contaminated. This screening process is imperfect, however, and still fails to detect some bacterially contaminated platelets. Recently, a strip immunoassay which could be used by hospitals to retest platelets was reported to find bacteria in approximately 1 in 3000 platelet platelets that had been negative on their culture screen. This immunoassay or alternative tests are associated with false positives and logistical challenges, however, and still fail to detect some contaminated products. Given the imperfections of current platelet screens, and the lack of any bacterial screen for red cell products, bacterial contamination must remain in the differential diagnosis when transfusion recipients become febrile or hypotensive following transfusions. The pathogen inactivation systems in development for cellular blood components all appear likely to inhibit the growth of bacteria.

Cytomegalovirus

CMV is a DNA virus in the herpesvirus family. Like other herpesviruses, it remains latent after acute infection, with the potential for reactivation. In immunologically normal adults, CMV disease manifestations range from none to a mononucleosis-like syndrome. In immunosuppressed or immunodeficient patients, however, both primary and reactivation disease may be associated with overwhelming manifestations including thrombocytopenia, hemolytic anemia, pneumonitis, colitis, hepatitis, meningoencephalitis, and death. Effective antiviral treatment is available. The incidence of severe disease can be reduced by prophylactic treatment of high-risk patients with antiviral drugs or by careful monitoring of such patients and initiation of therapy with the first evidence of infection. CMV is transmitted only through cellular blood components. The incidence of transmission of CMV by transfusion appears to be low (<1%) in immunologically normal recipients. Immunodeficient patients, however, are at increased risk of acquiring CMV from transfusion. CMV transmission to these patients can be greatly reduced by restricting their cellular
components to products obtained from CMV-seronegative donors or by use of leukoreduced blood components.\textsuperscript{563} Most studies have detected no transmission of CMV by leukoreduced blood components. Some transmissions were detected, however, in a large randomized study that evaluated the incidence of CMV infection and CMV disease in 502 bone marrow transplant recipients randomized to receive either leukoreduced (i.e., leukofiltered) or CMV antibody-negative blood components.\textsuperscript{566} CMV infection was observed in 1.3\% of recipients of seronegative components and in 2.4\% of recipients of leukoreduced components, a difference that was not statistically significant. However, in the leukoreduced arm, all CMV-infected patients developed disease, and five out of six died; in the serologically screened arm, there were no cases of CMV-related disease or death. A meta-analysis estimated that the risk of transfusion-transmitted CMV is approximately 1.5\% with use of CMV antibody-screened components, compared to 2.5\% with leukoreduced, antibody-unscreened components.\textsuperscript{566} Most of the cellular components in the US are leukoreduced. Whether it is clinically beneficial to perform CMV antibody screening in addition to leukoreduction remains controversial.\textsuperscript{563}

It is generally recommended that cellular products with a reduced risk of transmitting CMV (leukoreduced or CMV antibody negative) be used for patients at increased risk of severe primary CMV disease, including unborn babies (i.e., intrauterine transfusion), low-birth-weight infants of seronegative mothers, seronegative recipients of seronegative solid organ or HPC transplants, and seronegative patients with severe cellular immunodeficiency (e.g., HIV-infected patients). Products with reduced CMV risk are often provided also for seronegative patients who are likely to require transplantation in the future, in order to reduce their future risk of CMV-reactivation disease.\textsuperscript{563}

There is no clinical benefit of providing products of reduced CMV risk to patients who are already seropositive. Although second-strain infections may occur, these have not been shown to be clinically important given the high risk of reactivation disease these patients face. In CMV-positive recipients of allogeneic hematopoietic progenitor cell transplants, the use of CMV-positive stem cell donors has no detectable adverse effect on patient outcomes.\textsuperscript{563} Therefore, it seems that CMV-seropositive blood components would also be acceptable in this setting.

Seronegative recipients of seropositive organ and stem cell transplants are at high risk of CMV disease\textsuperscript{568} and are likely to be monitored closely, treated prophylactically, or both. It is unclear whether providing blood products with reduced CMV risk to such patients is of clinical benefit.

Pathogen Reduction Technologies

Donor screening and testing cannot completely eliminate the possibility of transfusion-transmitted infection or blood product contamination. The ideal pathogen reduction technology (PRT) would effectively inactivate residual pathogens without adversely affecting the function, toxicity, or immunogenicity of the blood component. Most commercial plasma derivatives are treated with heat and/or organic solvents and detergents (SD). SD treatment inactivates lipid-coated agents. Cellular blood components, however, cannot withstand this treatment. Most of the PRTs in development for cellular products consist of blood product additives that bind to and damage DNA and thereby prevent residual pathogens from proliferating in the blood component or in the recipient. These treatments would theoretically also prevent transfusion-related GVHD because the DNA of WBCs in the blood product would also be affected. The efficacy of PRT agents is dependent on their ability to penetrate cellular membranes or viral envelopes and reach the target nucleic acid. Because of concern that DNA-altering agents could cause long-term toxicity in transfusion recipients, many of the PRT systems include processes that remove the DNA-binding agent or inactivate it. PRTs in distribution outside the US and in development have been recently reviewed.\textsuperscript{530,562} Examples are listed in Table 21.12.

PRTs can reduce the residual risk related to window period transmissions of HIV, HCV, and HBV, but these risks are small. The primary benefit of PRTs is to reduce transmission of agents for which there are currently no tests.\textsuperscript{529} These treatments are costly. The incremental costs of PRT can be offset if they are approved by regulators as eliminating the need for irradiation, CMV antibody screening, and bacterial testing.\textsuperscript{529} Elimination of platelet bacterial testing would also expedite release of these products.

Several PRT systems for plasma are in use outside the US. One (S/D plasma) is a commercial product manufactured from pools of donor plasma. A pooled product has both theoretical advantages and disadvantages. For example, pooling dilutes antibodies from individual donors and thereby theoretically reduces the risk of antibody-mediated transfusion complications such as TRALI. However, pooling could increase a recipient’s risk of exposure to an emerging pathogen that is not removed or inactivated by the manufacturing process. PRTs that involve treatment of individual plasma units are more logistically challenging. All of the plasma PRTs listed in Table 21.12 have been determined to satisfy the Council of Europe plasma quality standards.

As of April 2012, the amotosalen/UV and riboflavin/UV PRTs for platelet products were in distribution in some countries outside of the US. Both of these treatments appear to be associated with some loss of platelet product potency.\textsuperscript{101,102} The clinical importance of the potency changes relative to the theoretical benefit of PRT is unclear.

**TABLE 21.12**

<table>
<thead>
<tr>
<th>Component</th>
<th>Technology</th>
<th>Manufacturer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma: commercially prepared pools</td>
<td>Solvent/detergent treatment</td>
<td>Octapharma</td>
</tr>
<tr>
<td>Plasma: individual units</td>
<td>Amotosalen (psoralen) + UV light</td>
<td>Cerus</td>
</tr>
<tr>
<td></td>
<td>Riboflavin (vitamin B2) + UV light</td>
<td>Terumo BCT</td>
</tr>
<tr>
<td></td>
<td>Methylene blue + light</td>
<td>MacoPharma</td>
</tr>
<tr>
<td>Platelets</td>
<td>Amotosalen (psoralen) + UV light</td>
<td>Cerus</td>
</tr>
<tr>
<td></td>
<td>Riboflavin (vitamin B2) + UV light</td>
<td>Terumo BCT</td>
</tr>
<tr>
<td></td>
<td>UV light</td>
<td>MacoPharma</td>
</tr>
<tr>
<td>Red Blood Cells</td>
<td>Fragile nucleic acid crosslinker</td>
<td>Cerus</td>
</tr>
<tr>
<td>Whole Blood</td>
<td>Riboflavin (vitamin B2) + UV light</td>
<td>Terumo BCT</td>
</tr>
</tbody>
</table>

UV, ultraviolet.

management of patients with hemoglobinopathies, leukostasis, or thrombocytosis, respectively.

Guidelines for clinical practice have been developed by the American Society for Apheresis (ASFA) and are regularly updated every 3 to 7 years with a systematic review of the medical literature. The current guidelines published in 2010 review the therapeutic apheresis procedures most commonly performed (i.e., therapeutic plasma exchange (TPE), red blood cell exchange, erythrocytapheresis, thrombocytapheresis, leukocytapheresis, extracorporeal photopheresis (ECP), immunoadsorption (IA), selective removal methods, adsorptive cytophoresis, and membrane differential filtration. Additionally, the guidelines contain 59 specific disease fact sheets listing the type of apheresis procedure to be performed and the rationale for it, the recommended blood volume to be exchanged, and the duration of the treatment.

The disorders for which therapeutic apheresis has been used are divided into four categories: category I, for which apheresis is the accepted first line of therapy; Category II, for which apheresis is considered a second-line therapy, after a patient has failed or is unable to undergo the first-line therapy; category III, for which the optimum role of apheresis therapy is not established and decision making should be individualized; and category IV disorders, in which published evidence demonstrates or suggests apheresis to be ineffective or harmful.

Some of the indications for therapeutic plasma exchange are listed in Table 21.13.

**Therapeutic Plasma Exchange**

**Indications**

The therapeutic goal of therapeutic plasma exchange (TPE) is to remove plasma components such as monoclonal proteins and cryoglobulins, immune complexes, lipoproteins, or toxins responsible for physical or metabolic problems. These may include removal of autoantibodies, as in myasthenia gravis and Goodpasture syndrome, or alloantibodies, as in posttransfusion purpura or patients with Factor VIII inhibitors. The existence and pathogenic role of antibodies or immune complexes are presumed in several situations.

**TABLE 21.13**

<table>
<thead>
<tr>
<th>Accepted as Therapy (Category I)</th>
<th>Accepted as Supportive Therapy (Category II)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thrombotic thrombocytic purpura</td>
<td>Cold agglutinin hemolytic anemia</td>
</tr>
<tr>
<td>Posttransfusion purpura</td>
<td>ABO-incompatible marrow transplant</td>
</tr>
<tr>
<td>Guillain-Barré syndrome</td>
<td>Cryoglobulinemia</td>
</tr>
<tr>
<td>Myasthenia gravis</td>
<td>Lambert-Eaton myasthenic syndrome</td>
</tr>
<tr>
<td>Chronic inflammatory demyelinating polyneuropathy</td>
<td>Rapidly progressive glomerulonephritis</td>
</tr>
<tr>
<td>Goodpasture syndrome</td>
<td>Autoimmune thrombocytopenia</td>
</tr>
<tr>
<td>Refsum disease</td>
<td>Myeloma and Waldenstrom macroglobulinemia, and other paraproteinemias with renal failure or hyperviscosity</td>
</tr>
</tbody>
</table>

**Technical Considerations**

The amount of plasma to be removed from the patient is determined by the physician, depending on the clinical situation. A patient’s plasma volume may be estimated at 40 ml/kg, determined from a nomogram based on the patient’s sex, height, weight, and hematocrit; or estimated according to the weight and hematocrit by the following formula:

\[
\text{Circulating blood volume} = \text{patient weight (kg)} \times 70 \text{ ml/kg.}
\]

Circulating plasma volume = circulating blood volume \times 1.0 − hematocrit (expressed as a decimal).

TPE is typically performed with 1.0 to 1.5 plasma volume exchanges or approximately 3,000 to 4,500 ml. If <1,000 ml is removed from an adult, it may be possible to replace the loss with crystalloid alone; if a more extensive plasma exchange is performed, use of a colloid is necessary. Albumin (5%) is the replacement fluid most commonly used in the United States. FFP or FP24 is indicated in certain instances, such as TTP or as a component of the replacement fluid in the setting of a coagulopathy.

After exchange of one plasma volume, approximately 62% of the original plasma has been removed. The efficiency of plasma exchange decreases with further exchange (Table 21.14).

In practice, measurement of plasma protein concentrations after exchange has confirmed the approximate validity of these estimates. However, efficacy varies with the plasma factor to be removed. IgM and fibrinogen, which are largely confined to the intravascular space, are removed most efficiently; the optimal exchange regimens for different diseases are unknown.

**Therapeutic Cytapheresis**

Therapeutic leukapheresis is used in the treatment of patients with leukostasis as a result of extremely high circulating concentrations of immature cells. At blast counts >100 × 10^9/L, there is an increasing risk of cerebral and pulmonary leukostasis, resulting

**TABLE 21.14**

<table>
<thead>
<tr>
<th>Number of Plasma Volumes Exchanged</th>
<th>Percent (%) of Original Plasma Remaining</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5</td>
<td>60</td>
</tr>
<tr>
<td>1.0</td>
<td>38</td>
</tr>
<tr>
<td>1.5</td>
<td>22</td>
</tr>
<tr>
<td>2.0</td>
<td>15</td>
</tr>
</tbody>
</table>
in impaired capillary blood flow resulting from obstruction of small vessels. This situation may be encountered in the acute leukemias but rarely in chronic lymphocytic leukemia or chronic myelogenous leukemia. Therapeutic leukapheresis decreases the circulating blast count more rapidly than chemotherapy alone; chemotherapy must be instituted promptly once the patient is stabilized, to prevent rebound leukocytosis. The only exception is in pregnancy, in which leukapheresis may be indicated until after the delivery of the fetus, thereby protecting the fetus from the teratogenic effects of chemotherapy.

Therapeutic leukapheresis has also been used in the treatment of patients with other leukemic diseases, such as chronic lymphocytic leukemia that is resistant to drugs, Sézary syndrome, and hairy cell leukemia, and as maintenance therapy in chronic myelogenous leukemia. However, it has not found a distinct role in such conditions with high platelet counts, usually >1.0 to 1.5 x 10^11/L, in whom the high count is directly responsible for serious thrombotic or hemorrhagic disease, or in whom other urgent clinical situations necessitate immediate lowering of the platelet count. Therapeutic plateletppheresis must be followed by cytotoxic therapy to prevent rebound after the procedure, or its effect is very short-lived.

Erythrocytapheresis (red cell exchange) is used in sickle cell disease to replace sickled cells with normal erythrocytes and thereby prevent thromboses and improve capillary circulation. Selective pheresis is performed very rarely and is not considered to be first-line therapy. It is indicated in patients with very high platelet counts, usually >1.0 to 1.5 x 10^11/L, in whom the high count is directly responsible for serious thrombotic or hemorrhagic disease, or in whom other urgent clinical situations necessitate immediate lowering of the platelet count. Therapeutic plateletppheresis must be followed by cytotoxic therapy to prevent rebound after the procedure, or its effect is very short-lived.

**Therapeutic Absorption of Plasma Constituents**

Apheresis technology may be used to selectively remove constituents of plasma implicated in disease processes. In these procedures, a patient’s plasma is withdrawn and separated by apheresis technology, passed over a selective absorption column, and reinfused into the patient. This technique has been used to selectively remove IgG (staphyloccocal protein A columns) or low-density-lipoprotein (LDL) cholesterol. Selective apheresis may specifically treat diseases such as LDL-hypercholesterolemia. Patients with LDL-hypercholesterolemia are at risk of developing severe coronary artery disease despite a low-fat diet and cholesterol-lowering agents. Selective LDL apheresis involves separation of the patient’s plasma, followed by selective removal of apoB-containing atherogenic lipoproteins, preserving the cardioprotective HDL cholesterol, after which the cleansed plasma is recombined with the cellular portion of the blood and returned to the patient. This procedure was shown to be safe and efficacious in controlling patients with familial hypercholesterolemia.

**Adverse Effects**

Adverse reactions to therapeutic apheresis are common but usually mild. In a 1-year period in Canada, there were side effects in 12% of more than 5,235 procedures in 627 patients. They included vasovagal reactions, fluid imbalance with hypovolemia or overload, fever, chills, and hypocalcemic rebound after plasma exchange has been suggested but has not been observed clinically. Perhaps because many patients so treated are also receiving immunosuppressive agents for the underlying diseases. Infections related to indwelling venous lines are not uncommon. Deaths have been reported with therapeutic apheresis. It is important that patients be carefully assessed and the indications reviewed before implementing this form of therapy.

**SUMMARY**

Blood transfusion is an essential component of therapy for a wide variety of disorders. The menu of blood components and the technologies for collecting, processing, and screening blood are constantly changing. Collaboration between transfusion medicine professionals and patient care teams ensures the most appropriate application of blood transfusion therapies.

**Acknowledgments**

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The full reference list for this chapter can be found in the online version.

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