

Blood Component Therapy

Ross Fasano, MD^{a,c}, Naomi L.C. Luban, MD^{b,c,*}

^a*Children's National Medical Center, Department of Hematology/Oncology,
111 Michigan Avenue NW, Washington, DC 20010, USA*

^b*Children's National Medical Center, Department of Laboratory Medicine,
111 Michigan Avenue, NW, Washington, DC 20010, USA*

^c*The George Washington University Medical Center, Washington, DC, USA*

Blood component transfusion is an integral part of the treatment of many infants and children cared for by general pediatricians, surgeons, intensivists, and hematologists/oncologists. Technologic advances in blood collection, separation, anticoagulation, and preservation have resulted in component preparation of red blood cells (RBCs), platelets, white blood cells (WBCs), and plasma, which are superior to whole blood (WB) used in the past. Recent advances in donor selection, infectious disease testing, use of leukoreduction filters, and gamma irradiation also deem today's products safer than the past. Physicians prescribing blood components not only should have a basic understanding of the indications (and contraindications) for their use but also should be cognizant of the methods of preparation, the proper storage conditions, and the requirements for further modification of blood products to prevent potential adverse effects.

Blood component preparation and modification

Blood components are prepared from blood collected by WB or apheresis donations. Transfusion of WB is uncommon in modern medicine. Uses for WB or reconstituted WB units include blood priming for extracorporeal circuits (ie, therapeutic apheresis in small patients, cardiovascular bypass, extracorporeal membrane oxygenation, and continuous hemoperfusion), neonatal exchange transfusions, and patients who have active bleeding and massive volume loss. Given that platelet function is poor after 24 hours

* Corresponding author. Children's National Medical Center, Department of Laboratory Medicine, 111 Michigan Avenue, NW, Washington, DC 20010.

E-mail address: nluban@cnmc.org (N.L.C. Luban).

of storage and that coagulation factors (especially V and VIII) decrease throughout storage, most blood centers rarely collect WB for allogeneic use. In situations when RBC and coagulation factor replacement are needed, components can be given in the form of “reconstituted” WB (RBC unit and a plasma unit in one bag).

Component preparation from whole blood donation

One unit of WB contains approximately 450 mL of blood collected from a healthy adult donor into a sterile plastic bag containing 63 mL of anticoagulant/preservative (AP) solution. Because RBCs, platelets, and plasma have different specific gravities, they can be separated from each other via centrifugation. In North America, this is done most commonly initially by performing a soft spin, which separates the heavier RBCs from platelet-rich plasma. The RBCs then are collected into a sterile satellite bag containing an anticoagulant solution. For separation of platelets from plasma, a hard spin then is performed. One unit of platelet concentrate (PC), which contains a minimum of 5.5×10^{10} platelets in approximately 50 mL of remaining plasma, is the result. The resulting PC can be stored as multiples of single units or pooled with other donor PCs. The typical volume of a unit of plasma collected from WB is approximately 250 mL. In order for the plasma to be labeled as fresh frozen plasma (FFP), the unit must be separated from the other blood components and stored at -18°C within 8 hours of collection.

Component preparation by apheresis

An alternative to WB collection and separation of blood components is to collect a specific component via apheresis. This entails a process where an automated apheresis instrument draws blood into an external circuit, separates the components by centrifugation or filtration, collects the desired component, and returns the remaining blood components to the donor. Although traditionally this has been used for platelet, plasma, and granulocyte collection, newer methods support RBC collection. These methods provide larger quantities of the desired component than WB collection methods. For example, a single apheresis platelet unit contains approximately the same number of platelets as a pool of six to eight random donor platelet units collected from WB (3×10^{11} platelets/U for single donor apheresis platelets versus 5.5×10^{10} platelets/U for single donor WB collected platelets). “Double” collections also are possible for platelets and RBCs. Because platelet and red cell apheresis products expose recipients to fewer donors, there also is a theoretic advantage of decreasing the risk for alloimmunization and transfusion-transmitted diseases in chronically transfused patients. Regarding donors, because RBC loss is minimal during platelet apheresis, donation can be performed more often than with WB collection.

Anticoagulant/preservative solutions

When RBCs are stored for transfusion, several prerequisites must be met: the product must be sterile, the cellular components must remain viable during storage, their in vivo survival after storage must be greater than 75% 24 hours after transfusion, and hemolysis should be less than 1%. RBC viability and functional activity require that RBCs be preserved in solutions that support their metabolic demands. All anticoagulant solutions contain citrate, phosphate, and dextrose (CPD). These constituents function as an anticoagulant, a buffer, and a source of metabolic energy for the RBCs, respectively. Recent advances in the development of AP solutions largely are the result of the addition of nutrients that stabilize the RBC membrane and maintain 2,3-diphosphoglycerate and ATP within the erythrocyte. Mannitol is used in some AP solutions because it stabilizes RBC membranes, and adenine enters RBCs and is incorporated within the nucleotide pools resulting in higher levels of ATP within the RBC products. The use of AP solutions has increased the shelf life of RBCs from 21 days for CPD to 35 days for citrate-phosphate-dextrose-adenine (CPDA)-1 and to 42 days for the newer AP solutions (Adsol, Optisol, and Nutricell).

The concentrations of the additives of products licensed for use in the United States are safe for most children and neonates receiving simple transfusions; however, extremely ill premature neonates requiring massive transfusion (ie, exchange transfusion, extracorporeal membrane oxygenation, or cardiopulmonary bypass), or those who have significant renal or hepatic insufficiency may be at risk for metabolic abnormalities [1–3]. The amounts of adenine and mannitol in small volume transfusions (15 mL/kg RBCs) to neonates using anticoagulant/preservative solution #1 (AS-1) equates to less than one tenth the toxic dose [4]. There are no clinical data, however, on metabolic abnormalities in massive transfusion for neonates. Therefore, some experts recommend avoiding use of RBCs stored in extended-storage media (Adsol, Optisol, or Nutricell) until such data are published. Several options for reducing the AP exist, including inverted storage, centrifugation, or even washing of the RBC product.

Leukocyte reduction of blood components

The American Association of Blood Banks (AABB) states that in order for a blood product to be labeled “leukoreduced,” it must contain fewer than 5×10^6 total WBCs per unit [5]. Current third-generation leukocyte reduction filters consistently provide a 3 to 4 log or 99.9% reduction of WBC content to fewer than 5×10^6 WBCs and, with some filters, fewer than 1×10^6 per product. This leukocyte reduction step is performed best prestorage per manufacturer’s requirements with good quality control techniques.

Febrile nonhemolytic transfusion reactions (FNHTRs) typically are caused by reactions to donor WBCs or to cytokines present in the product.

Leukocyte reduction reduces the incidence of FNHTRs, especially when prestorage leukoreduction is used, because lower levels of cytokines are present in prestorage leukocyte-reduced products [6–8]. Alloimmunization to foreign HLA class I antigens is a significant concern for patients who may require repeated platelet transfusions. Because platelets also express HLA class I antigens, patients sensitized to such antigens can become refractory to platelet transfusions. Leukocyte reduction also is proved to reduce the incidence of HLA alloimmunization [9].

Leukocyte reduction also is used to reduce transmission of cytomegalovirus (CMV) in high-risk patient populations. Recipient groups at increased risk for post-transfusion CMV-related morbidity and mortality include [10]

- Premature, seronegative neonates less than 1250 g who require blood component support
- Recipients of hematopoietic stem cell and solid-organ transplants
- Fetuses who receive intrauterine transfusions
- Other individuals who are severely immunocompromised

Although the use of CMV-seronegative blood is considered the gold standard, such products often are difficult to obtain depending on donor demographics in a specific area. Because CMV is harbored within WBCs, manipulation of leukocyte number and viability should reduce transmission of CMV. Irradiation of blood products (discussed later) is not shown to prevent post-transfusion CMV infection; however, leukocyte reduction ($<5 \times 10^6$ WBCs/U) is effective in preventing CMV infection in adults who have hematopoietic malignancies, neonates, and patients post stem cell transplant. Whether or not leukocyte reduction is as efficacious as CMV-seronegative blood is debated widely. In a landmark study, Bowden and colleagues [11] found equivalent rates of post-transfusion CMV infection in an allogeneic hematopoietic stem cell population (1.4% for seronegative versus 2.4% for leukocyte reduction). Although this study's conclusions are debated widely, no formal consensus on the debate of equivalency has been formulated. A subsequent study by Nichols and colleagues [12] demonstrated that although leukocyte-reduced platelet products were deemed similar to CMV-seronegative products regarding transfusion transmission of CMV, leukocyte-depleted RBCs were not. The investigators warned against the practice of abandoning “dual inventory” blood products for CMV-seronegative and -seropositive units. Nonetheless, variable practices exist depending on donor demographics and the number of high-risk patients treated at a given center [10,13]. Many institutions use algorithms based on (pretransplant) serostatus of recipients, serostatus of hematopoietic stem cell donors, and donor demographics within the area. It is unlikely that further randomized controlled trials will be performed to assess comparability of CMV-seronegative versus leukoreduced products.

Gamma irradiation of blood components

Transfusion-associated graft-versus-host disease (TA-GVHD) occurs when an immunosuppressed or immunodeficient patient receives cellular blood products that possess immunologically competent lymphocytes. The transfused donor lymphocytes are able to proliferate and engraft in the immunologically incompetent recipient because they are unable to detect and reject foreign cells. The degree of similarity between HLA antigens also increases the ability of donor lymphocytes to engraft with the recipient. This explains why TA-GVHD can occur in situations of directed donation from family members. In the event where a donor is homozygous and a recipient is heterozygous for a particular HLA antigen, the donor lymphocytes may escape immune surveillance and thus are able to engraft in the immunocompetent host, resulting in TA-GVHD. This situation also may occur in populations with limited HLA variability, such as in Japan, necessitating universal gamma irradiation of all cellular components in specific situations.

Clinical symptoms of TA-GVHD include fever, an erythematous rash that may progress to bullae and desquamation, anorexia, and diarrhea, which develop within 3 to 30 days of receiving cellular blood components. Because the hematopoietic progenitor cells (HPCs) in particular are affected, severe cytopenia usually is present. Mild hepatitis to fulminant liver failure may occur. Mortality for TA-GVHD is 90% in the pediatric population. Patients at high risk for TA-GVHD include [14]

- Patients who have congenital immunodeficiencies of cellular immunity
- Those receiving intrauterine transfusion followed by neonatal exchange transfusion
- Bone marrow transplant recipients
- Recipients of HLA-matched cellular components or blood components from blood-related donors
- Patients who have hematologic malignancies and cancer patients undergoing intense chemotherapy or immunomodulatory therapy (ie, fludarabine and other purine analogs)

Neonates, especially those who are extremely premature, are considered by many to be at high risk for TA-GVHD. Whereas some neonatal centers irradiate all cellular blood products for infants less than 4 months of age, others irradiate only blood products given to preterm infants born weighing less than or equal to 1.2 kg [15]. Given the lack of clinical studies on the incidence of TA-GVHD in the neonatal population, however, and the concern for failing to recognize infants who have an undiagnosed congenital immunodeficiency, there exists no standard of care regarding irradiation of blood products for otherwise non-high-risk infants born with a weight greater than 1200 g.

TA-GVHD can be prevented by gamma irradiation of cellular blood components at 2500 cGy [16]. Because in vivo recovery of irradiated

RBCs is decreased compared with nonirradiated RBCs, at 42 days of storage, the Food and Drug Administration recommends a 28-day expiration for irradiated RBCs [17]. Potassium and free hemoglobin (Hb) are increased after irradiation and storage of RBCs. Therefore, it is preferable to irradiate in a time frame close to administration rather than prolonged refrigerator storage products, especially for neonates, who may not be able to tolerate a large potassium load. Irradiation of platelets does not affect function, and although superoxide production and phagocytic function is shown to be decreased in granulocytes irradiated at 2500 cGy, most authorities recommend irradiating granulocytes before administering.

Red blood cell products

RBCs are prepared by removal of 200 to 250 mL of plasma from 1 unit of WB. RBCs collected in CPDA-1 have a volume of approximately 250 mL and a hematocrit of 70% to 80%. When RBCs are supplemented with additional preservative solutions (ie, Adsol, Nutricell, or Optisol) the volume is increased to approximately 350 mL and the hematocrit is reduced to 50% to 60%. These RBC components have approximately 50 mL of plasma and the advantage of longer storage shelf life (42 days versus 35 days) and lower viscosity; therefore, they flow more rapidly than the traditional CPD and CPDA components. Notice must be taken by today's practitioners of the lower hematocrit of the current AP-based RBC products when calculating Hb increments post transfusion. For example, using the formula: Volume of RBCs to be transfused = $TBV \times ([\text{desired Hb}] - [\text{actual Hb}]) / [\text{Hb}]$ of RBC unit, where *TBV* (total blood volume) is 70 to 75 mL/kg by 3 months of age.

Although approximately 10 mL/kg increases the Hb concentration by 3 g/dL for individuals receiving RBCs in CPDA (hematocrit 69%), approximately 12.5 to 15 mL/kg is necessary to attain the same Hb concentration increment for individuals receiving RBCs in AS-1 (hematocrit 54%).

In addition to leukocyte reduction and gamma irradiation, RBC products can be washed using sterile saline to rinse away the remaining plasma proteins within an RBC unit or frozen using high glycerol concentrations for long-term storage of RBC units with unique phenotypes. RBC washing removes plasma proteins, microaggregates, and cytokines and is indicated for severe, recurrent allergic reactions to blood components despite premedication with antihistamines, because these reactions usually are the result of reactions from foreign plasma proteins. Patients who have IgA deficiency and anti-IgA are at risk for anaphylaxis from donor IgA within the plasma and may benefit from washed RBCs [18]. RBC washing should not be considered a substitute for leukoreduction because the washing process removes by only 1 log versus the 3 to 4 log depletion attained by

third-generation leukoreduction filters. Given that the average total WBC content in a standard RBC unit is 2 to 5×10^9 , washed RBCs contain an average of 5×10^8 WBC/U versus 5×10^6 WBCs/U via leukoreduction. Washed RBC units also are used for some neonates receiving large volume transfusions (> 20 mL/kg) with RBCs that are older than 14 days or that have been irradiated before storage. The washing process removes approximately 20% of the RBCs for a final volume of 180 to 200 mL and hematocrit of 70% to 80%. The washing process itself causes electrolyte leakage from RBCs, especially when washing an already irradiated RBC unit, so the unit should be transfused as soon as possible after being washed [19]. Regardless of irradiation, the RBC product needs to be transfused within 24 hours of being washed, because the washing process itself creates an open system.

In cases when a RBC unit is found to have a unique phenotype, it may be frozen and cryopreserved by the use of glycerol. Once frozen, these units have a shelf life of 10 years at less than or equal to -65°C . When needed, the unit is deglycerolized, which entails defrosting and washing. This entire process reduces the WBC/U by 100-fold (2 log). As with washed RBC units, defrosted-deglycerolized RBCs must be transfused within 24 hours of preparation. These RBC units are suspended in approximately 250 mL of saline with a hematocrit of 55% to 70% (Table 1).

Special considerations and indications for red blood cell transfusion

Although published clinical guidelines for RBC transfusions exist in the pediatric literature, they often are based on expert panel consensus rather than scientific data because of a relative void of randomized controlled trials on RBC transfusion thresholds for children and neonates. In cases of acute hemorrhage, RBC transfusion should be administered if the amount of bleeding exceeds 15% of TBV [20]. In acutely bleeding patients, the measured Hb concentration does not reflect an accurate assessment of the RBC mass. Therefore, careful assessment of the amount of blood loss and signs of circulatory decompensation are imperative. In contrast to acute hemorrhage, patients who have hemolysis usually are normovolemic, and the measured Hb concentration is a more accurate gauge of the level of anemia. The indication for RBC transfusion in this setting depends on Hb concentration, the rate of decrease of the Hb, the underlying etiology for hemolysis, and whether or not alternative management options (eg, steroids or intravenous immunoglobulin G for autoimmune hemolytic anemia) are exhausted. The use of crossmatch compatible RBCs always is preferred, but on rare occasions, crossmatch “least incompatible” blood must be considered because of the presence of warm-reactive autoantibodies or multiple alloantibodies [21]. Consultation with a transfusion medicine physician in these cases is paramount. In life-threatening autoimmune hemolytic anemia, transfusion of crossmatch incompatible blood often is necessary. If children

Table 1
Blood component characteristics

Component	Storage	Volume	Expiration	Dose
RBC (CPDA-1)	1°C–6°C	250 mL	35 days	10–20 mL/kg
RBC (AP)	1°C–6°C	300–350 mL	42 days	10–20 mL/kg
RBC (washed)	1°C–6°C	180–200 mL	24 hours	10–20 mL/kg
RBC (deglycerolized)	Frozen: < –65°C Deglycerolized: 1°C–6°C	250 mL	Frozen: 10 years Deglycerolized: 24 hours	10–20 mL/kg
PC	20°C–24°C with agitation	50–75 mL	5 days	1–2 U/10 kg ^a
Apheresis platelets	20°C–24°C with agitation	200–400 mL	5 days	1–2 U/10 kg ^a
FFP	Frozen: < –18°C Thawed: 1°C–6°C	200–500 mL	Frozen: 1 year Thawed: 24 hours	10–20 mL/kg
Fresh plasma	Frozen: < –18°C Thawed: 1°C–6°C	200–500 mL	Frozen: 1 year Thawed: 24 hours	10–20 mL/kg
Cryoprecipitate	Frozen: < –18°C Thawed: 20°C–24°C	10–15 mL	Frozen: 1 year Thawed: 6 hours ^b	1 U/5 kg
Granulocyte concentrate	20°C–24°C (no agitation)	200–300 mL	24 hours	1–2 × 10 ⁹ PMNs/kg/d ^c

^a Neonates: 10–15 mL/kg.

^b 4 hours if pooled.

^c 4 to 8 × 10¹⁰ PMNs per day for older children/adults.

Data from Luban NL. Basics of transfusion medicine. In: Furman B, Zimmerman JJ, editors. Pediatric critical care. 3rd edition. Philadelphia: Mosby; 2006. p. 1185–98.

have signs of cardiac failure, partial exchange transfusion should be considered to avoid circulatory overload.

Congenital hemoglobinopathies

Individuals who have sickle hemoglobinopathies (HbSS, HbSC, and HbS/ β -thalassemia) are unique in that the reason for RBC transfusion not always is to increase the oxygen-carrying capacity and delivery; it also decreases the percentage of Hb S relative to Hb A. Raising the total Hb concentration while lowering the Hb S percentage to 30% is effective in the management of acute cerebrovascular accident (CVA), acute chest syndrome, splenic sequestration, and recurrent priapism. In a large multicenter trial, Vichinsky and colleagues [22] showed that preoperative transfusion to a total Hb concentration of 10 g/dL was equivalent to more aggressive preoperative exchange transfusion with a goal of reducing the Hb S to 30% of total Hb. Because transfusion-related complications were twice as common in the preoperative exchange group, simple transfusion to a total Hb of 10 g/dL is considered by some to be appropriate management to prevent significant morbidity and mortality in patients who have preoperative sickle-cell disease (SCD). A retrospective cohort study of children who had SCD showed that in the absence of concurrent medical events associated with first CVA, recurrent CVA within 5 years was 22% for those not on a chronic transfusion versus 1.9% for those who received regularly scheduled blood transfusions after first CVA [23]. The Stroke Prevention Trial in Sickle Cell Anemia (STOP) showed that children who had SCD and abnormal transcranial Doppler (blood flow greater than 200 cm per second in internal carotid or middle cerebral artery) are at increased risk for initial CVA and that initiation of chronic transfusions in these high-risk patients significantly decreases the risk (14.9% versus 1.6%) [24]. In the STOP II follow-up study, discontinuation of transfusion for the prevention of stroke in children who had SCD resulted in a high rate of reversion to abnormal blood flow velocities on Doppler studies and CVA [25]. Although there is a paucity of clinical studies, chronic transfusions may be indicated in patients who have SCD who have experienced recurrent episodes of severe acute chest syndrome or severe splenic sequestration.

Children who have thalassemia major require chronic transfusions to alleviate anemia and to suppress extramedullary erythropoiesis, which leads to poor growth and bony abnormalities. The common practice involves RBC transfusions every 3 to 4 weeks with the goal to keep the pretransfusion Hb concentration at 9 to 10 g/dL [18,21]. Although all children receiving chronic transfusions are at significant risk for developing iron overload, patients who have thalassemia are at even greater risk because of increased intestinal iron absorption.

Alloimmunization

RBC alloimmunization is estimated to occur in 18% to 47% of pediatric patients who have SCD versus 5% to 11% of chronically transfused thalassemia patients and 0.2% to 2.6% of the general population [26]. It is believed that alloimmunization rates are higher in patients who have SCD because of the disparity between RBC antigens and possibly also an altered immunologic response to foreign antigens. Almost two thirds of clinically significant antibodies are directed toward the rhesus (Rh) and Kell blood group antigens. Methods to reduce the risk for alloimmunization in high-risk populations vary; however, phenotypically matching for Rh (D, C, E, c, and e) and Kell (K and k) decreases the incidence of alloantibodies per unit transfused and the incidence of hemolytic reactions in chronically transfused SCD patients [27]. Extended RBC antigen phenotyping (ABO, Rh, Kell, Kidd, Duffy, Lewis, and MNS blood group systems) for all patients who have SCD should be performed before initiating transfusion therapy, and more extensive red cell antigen matching may be used for those patients who develop multiple alloantibodies. Other strategies include methods to increase African American donor recruitment so as to racially match blood for patients who have SCD. This strategy capitalizes on the different RBC antigen frequencies that exist in those of European and those of African origin [28]. Recent technologic advances in blood group antigen genotyping using molecular methods may enhance the ability to match red cell antigens in this high-risk patient population.

Neonates

Transfusion indications for neonates, especially premature neonates, are controversial because there are few randomized controlled studies. Current guidelines take into account the level of anemia in lieu of the overall cardiorespiratory support, which is required by neonates (Table 2) [20,29]. Recently, two studies addressed liberal versus restrictive guidelines for RBC transfusions in preterm infants [30,31]. Although they are different in design and outcome, neither study establishes unequivocally an appropriate Hb target. Although the multi-institutional Canadian Premature Infants in Need of Transfusion study [30] demonstrated no advantage for liberal transfusion, Bell and coworkers' study [31] suggested that restrictive transfusion is more likely to result in neurologic events and apneic episodes.

Transfusion of neonates is complicated by neonatal blood containing variable amounts of maternal immunoglobulins in the serum, which may be directed against A, B, or both antigens, depending on the maternal blood group and type and the amount of maternal antibody transferred via the placenta. For this reason, some blood banks choose to transfuse group O RBCs to all neonates whereas others use group-specific blood if a neonate's serum is free of maternal antibodies directed toward the neonate's RBC ABO antigens. In cases when reconstituted WB is needed for exchange transfusion or cardiopulmonary bypass, a neonate may be given plasma

Table 2

Red blood cell transfusion guidelines for patients less than 4 months of age

United States guidelines [20]	
Clinical status	Hemoglobin concentration
Severe pulmonary or cyanotic heart disease/congestive heart failure	< 15 g/dL
CPAP/MV with mean airway pressure > 6–8 cm H ₂ O ^a	< 12 g/dL
FiO ₂ > 35% via oxygen hood	
CPAP/MV with mean airway pressure < 6 cm H ₂ O	< 10 g/dL
FiO ₂ < 35% via oxygen hood	
On nasal canula	
Significant apnea/bradycardia, tachypnea, tachycardia ^b	
Low weight gain (< 10 g/d over 4 days)	
Low reticulocyte count and symptoms of anemia ^c	< 7 g/dL
British guidelines [29]	
Clinical status	Hemoglobin concentration
Anemia in first 24 hours of life	< 12 g/dL
Neonate receiving intensive care	< 12 g/dL
Chronic oxygen dependency	< 11 g/dL
Late anemia, stable patient	< 7 g/dL
Acute blood loss	10% TBV
Cumulative blood loss in 1 week, neonate requiring intensive care	10% TBV

Abbreviations: FiO₂, fraction of inspired oxygen; TBV, total blood volume.

^a Continuous positive airway pressure/mechanical ventilation.

^b Heart rate greater than 180 beats per minute and respiratory rate greater than 80 breaths per minute over 24 hours.

^c Poor feeding, tachycardia, tachypnea.

Data from Robitaille N, Hume HA. Blood components and fractional plasma products: preparations, indications, and administration. In: Arceci RJ, Hann IM, Smith OP, editors. *Pediatric hematology*. 3rd edition. New York: Wiley Blackwell; 2006. p. 693–708.

that is ABO compatible with the neonate's RBCs but receive RBCs that are compatible with maternal serum. To limit donor exposure in these situations, some blood centers advocate using low-titer group O WB. Because of the immaturity of neonates' immune system, antibody screens and serologic crossmatch do not need to be repeated until 4 months of age [18,20,21].

Because premature neonates have small blood volumes and often require multiple RBC transfusions throughout their hospitalizations, many pediatric transfusion services have adopted a system in which aliquots from one RBC unit are reserved for and dispensed to one or more neonates for each RBC transfusion. This practice theoretically reduces donor exposure to neonates and reduces the amount of wastage. This is accomplished by use of sterile connecting devices to assure that the original RBC unit remains in a closed system.

Platelets

Platelets may be prepared by one of two methods: WB collection and separation via centrifugation or apheresis. Platelets prepared by centrifugation

of individual units of WB often are referred to as random-donor platelets. Each PC usually contains approximately 7.5×10^{10} platelets but must contain at least 5.5×10^{10} platelets in 50 to 70 mL of plasma. Apheresis platelets (often called single-donor platelets) are collected from a donor by selectively removing platelets in a volume of approximately 200 to 400 mL of plasma whereas the rest of the blood components are returned to the donor during the cytopheresis procedure. This technique allows collection of platelets with a minimum of 3×10^{11} platelets per 250-mL bag (see Table 1). This limits the amount of donor exposure per platelet transfusion because this technique collects the equivalent of a pool of six to eight random donor platelets. Regardless of the method of collection, all platelet units must be stored at 20°C to 24°C under constant agitation because storage at cold temperatures is detrimental to platelet function. As a result of these warmer storage temperatures, the shelf life of platelet products is only 5 days because of the risk for bacterial contamination. In compliance with AABB standards, all blood banks and transfusion services must have methods in place to limit and detect bacterial contamination [5].

Platelets express intrinsic ABO antigens but not Rh antigens. Whenever possible, ABO-compatible platelets should be administered, especially for small children and neonates, because of reports of intravascular hemolysis after transfusion of ABO-incompatible platelets. If ABO-incompatible platelets are to be transfused, selection of low isoagglutinin (anti-A, anti-B) titer units or volume reduction should be considered. With volume reduction, however, approximately 20% of platelets are lost in the final product. Patients who are RhD negative (especially women) should be transfused “Rh-negative” platelets because RBCs are present in small amounts (apheresis platelets 0.001 mL per unit versus 0.3 mL in WB-derived platelets) [32]. The minimal volume reported to cause Rh alloimmunization in D-volunteer subjects is 0.03 mL as a result of the manufacturing process [33]. In cases when Rh-negative platelets are unavailable, Rh immune globulin may be administered within 72 hours of transfusion at a dose of 120 IU/mL of RBCs intramuscularly (90 IU/mL of RBCs intravenously). Although the exact immunizing dose in pediatric patients is unknown, certain patient groups, such as pediatric oncology patients, require further study to confirm their limited ability to mount an anti-D response [34].

Platelet transfusion is indicated for the treatment of qualitative and quantitative platelet abnormalities. Clinical factors considered when assessing the need for a platelet transfusion include the primary diagnosis; the bone marrow function and its ability to compensate or recover; the presence of fever, sepsis, or splenomegaly, which increases platelet consumption; and the presence of uremia or medications that may alter platelet function. Until recently, physicians transfused patients platelets for platelet counts under 20,000/ μ L. Several large prospective studies, however, mainly of acute leukemia, showed no difference in bleeding risk between transfusion thresholds of 10,000/ μ L and 20,000/ μ L. Most recommend, therefore, that for

prophylaxis, platelets should be maintained greater than 10,000/ μ L for adults and children who do not have additional bleeding risk factors [35–37]. Platelet counts greater than 20,000/ μ L are indicated for invasive procedures and greater than 50,000/ μ L for major surgeries or invasive procedures with significant bleeding risk. For central nervous system bleeding or planned central nervous system surgery, the platelet count should be maintained greater than 100,000/ μ L [20]. Because of the risk for intraventricular hemorrhage in sick neonates, many physicians traditionally have adopted a fairly aggressive platelet threshold for transfusion. Although there is little data on the appropriate threshold for platelet transfusion in (preterm) neonates, Murray and colleagues [38], in their retrospective study of 53 neonates (44 preterm) who had severe thrombocytopenia, concluded that a threshold of 30,000/ μ L without other risk factors or previous intraventricular hemorrhagic is safe for the majority of patients in neonatal ICUs.

Platelet refractoriness

A calculated platelet dose of 5 to 10 mL/kg for neonates and 0.1 to 0.2 U/kg for children over 10 kg should result in a platelet increment of 50,000/ μ L to 100,000/ μ L if no predisposing risk factors for refractoriness exist. Few data exist as to the difference in platelet increment that result from the use of apheresis versus PCs. An attenuated result can be the result, however, of a host of causes, which can be immune related or nonimmune related. Nonimmune causes include splenomegaly, fever, sepsis, disseminated intravascular coagulation (DIC), bleeding, antibiotic therapy (eg, vancomycin), and use of immunosuppressive agents. Immune causes include autoantibodies, such as immune thrombocytopenic purpura, or alloantibodies to HLA class I antigens or uncommonly to platelet-specific antigens (eg, HPA-1a). Evaluation of platelet refractoriness entails evaluation of the platelet increment (PI) at 1 hour and 24 hours post transfusion and calculation of the calculated count increment (CCI). The CCI can be calculated as follows: $CCI = (PI \times BSA)/\text{number of platelets transfused (in units of } 10^{11})$, where BSA is body surface area.

Two consecutive transfusions with a CCI less than 7500/ μ L are evidence of the refractory state. Although immune-mediated refractoriness has minimal increment at 1 hour and 24 hours post transfusion, nonimmune-mediated refractoriness traditionally has an adequate initial increment at 1 hour but with poor platelet increment at 24 hours post transfusion. No special platelet product can improve platelet increments in cases of nonimmune refractoriness. Patients who have immune refractoriness after ABO-identical platelets should be screened for the presence of HLA antibodies and, if positive, their specificity determined.

Support of patients who have platelet refractoriness from HLA antibodies generally involves the use of HLA-matched platelets, crossmatched platelets, or platelets selected that lack the specific antigen to which the

patients have antibodies. HLA-matched apheresis platelets are graded on a scale of A (most identical) to D (least identical). This must be considered when judging responses to HLA-matched pheresis platelets, because “HLA-matched” platelets rarely are identical [39]. Crossmatching apheresis platelet samples with an immunized patient’s serum can detect compatible platelet products without requiring an HLA phenotype or antibody identification; however, a compatible crossmatch is predictive of successful platelet increments in only 50% to 60% of transfusions [40]. Because the shelf life of platelets is only 5 days, crossmatching must be performed frequently for alloimmunized patients requiring chronic support. HLA-matched and cross-matched platelets are hindered by the fact that finding exact matches using these methods is challenging, even in large blood centers with a wealth of donors. Selection of antigen-negative platelets, as first described by Petz and colleagues [41], is analogous to selection of red cell products for those who are alloimmunized to red cell antigens. Patients’ sera are combined with panels of lymphocytes of known HLA phenotype and observed for cytotoxicity. Phenotyped apheresis platelets that lack the antigens to which antibody is present are considered compatible for transfusion to alloimmunized patients. This approach expands the number of compatible platelet products and seems as efficacious as crossmatching [39,42]. Regardless of the method used, excellent communication between clinicians and transfusion medicine specialists is critical for success in managing alloimmunized patients.

Plasma products

Fresh frozen plasma

Plasma is prepared by WB separation by centrifugation or by apheresis. When prepared by the former method, one unit contains a volume of 200 to 250 mL, whereas when prepared by the latter method, a volume up to 500 mL can be collected from one donor. To be labeled as FFP, the plasma product needs to be stored at -18°C or colder within 8 hours of collection. FFP can be stored at this temperature for up to 1 year. Another plasma product, frozen plasma (FP), is plasma frozen within 24 hours of collection. Although FP has less factor V (FV) and factor VIII (heat labile factors) activity, it is considered clinically similar to FFP and used interchangeably [18]. Because FFP undergoes a freezing process in the absence of a cryoprotectant, the majority of WBCs are killed or nonfunctional. Therefore, leukoreduction and irradiation are unnecessary for prevention of CMV reactivation and TA-GVHD, respectively, in high-risk patients. FFP should be ABO compatible with recipient RBCs; however, Rh type does not need to be considered nor does a crossmatch need to be done before administering [43]. FFP is the blood product used most commonly. Indications include [18,21]

Multiple coagulation factor deficiencies (eg, liver failure, vitamin K deficiency from malabsorption or biliary disease, or DIC)

Reversal of warfarin emergently when vitamin K is deemed untimely

Dilutional coagulopathy from massive transfusion

Replacement of rare single congenital factor deficiencies when specific concentrates are not available (eg, protein C or factor II, V, X, XI, or XIII deficiency)

Replacement of C1 esterase inhibitor in patients who have hereditary angioedema

As a component of WB priming for small children for apheresis

Thrombotic thrombocytopenic purpura as simple transfusion, as part of therapeutic plasma exchange, or as “cryopoor plasma” (prepared by removing cryoprecipitate that is rich in high molecular weight von Willebrand multimers from FFP)

FFP should not be used before invasive procedures for patients who have less than 1.5 times the midpoint of normal range for prothrombin time (PT) or activated partial thromboplastin time (aPTT) because clinical experience suggests that FFP does not prevent bleeding in this setting. FFP also is contraindicated for intravascular volume expansion, correction/prevention of protein malnutrition, and when specific factor concentrates are available; alternative products that have undergone viral inactivation through complex manufacturing processes are preferable.

When single factor replacement is needed, the amount of FFP needed can be calculated based on the following, where *HCT* is hematocrit and *TPV* is total plasma volume:

1 mL of factor activity = 1 mL FFP

TBV = weight $\times$ 70 mL/kg

TPV = TBV $\times$ (1 – HCT)

Unit of factor needed = TPV (desired factor [%] – initial factor [%])

For example, if a 10-kg child who has an initial FV of 10 U/mL and hematocrit 40% is going to surgery and the goal is a FV of greater than 50 U/mL for hemostasis, then

TBV = 700 mL and TPV = 420 mL

Units of factor needed = $420 \times (0.50 - 0.10) = 168$ mL

Amount of FFP needed = 170 mL (or 17 mL/kg)

Using these calculations, it is evident that 20 mL/kg of FFP replaces approximately 50% of most factors immediately after transfusion. It is important for clinicians to know the half-lives of the factors for which replacement is sought to plan a dosing schedule because not all factors have equivalent half-lives (eg, FVII half-life: 2 to 6 hours versus FV: 20 hours) [21]. It also is important to know that normal values of certain factors (eg, vitamin K-dependent factors) in neonates may be lower than in older children and

adults; therefore, the PT and aPTT are prolonged similarly, rendering correlation of laboratory values to clinical status of patients more complicated.

Cryoprecipitate

Cryoprecipitated antihemophilic factor, or cryoprecipitate, is prepared by thawing FFP at 1°C to 6°C, removing the supernatant, and refreezing at -18°C for up to 1 year. The resulting small volume of precipitate contains concentrated levels of factor VIII, factor XIII, factor VIII: von willebrand's factor (VWF), fibrinogen, and fibronectin. Each cryoprecipitate unit (sometimes referred to as a "bag" of cryoprecipitate, 10 to 15 mL) contains a minimum of 80 units of factor VIII activity and 150 mg of fibrinogen. Because there are no standards for the quantity of the other factors, and because the Food and Drug Administration has licensed viral-inactivated, pooled, plasma-derived and recombinant factor concentrates, cryoprecipitate should not be considered first-line treatment for hemophilia A and B or von Willebrand disease (VWD). In emergent cases of bleeding, however, when these commercially available products are unavailable, cryoprecipitate may be used for replacement. Cryoprecipitate is indicated for treatment for active bleeding in patients who have dysfibrinogenemia, hypofibrinogenemia (<150 mg/dL), or afibrinogenemia with active bleeding. For complex coagulation factor deficiency states (ie, DIC and dilutional coagulopathy), cryoprecipitate may be needed along with FFP to normalize fibrinogen levels. For correcting states of hypofibrinogenemia, the same replacement formula can be applied, but in general, 1 U/5 kg should increase a small child's fibrinogen by approximately 100 mg/dL (see [Table 1](#)).

Plasma derivatives

Plasma derivatives are concentrates of plasma proteins prepared from large donor pools (10,000 to 60,000) of plasma or cryoprecipitate. The specific protein of interest is purified and concentrated and cell fragments, cytokines, and viruses are inactivated or removed. Methods of viral inactivation include solvent-detergent treatment, pasteurization, immunoaffinity chromatography, and nanofiltration. Factor concentrates can be human plasma derived or produced in vitro using genetically engineered cell lines (recombinant). Human-derived and recombinant factor VIII and IX preparations are available for short-term and prophylactic treatment of bleeding in patients who have hemophilia A or B. Because the newer recombinant products (Recombinate, Kogenate, Advate, Benefix, and Novoseven) have limited or no albumin as a human protein, they are considered extremely safe for transmitting human infectious organisms and, therefore, are the preferred products when available for specific single factor replacement. Certain selected human-derived factor VIII preparations (Humate-P and Koate-HP) contain significant amounts of VWF and are used for

treatment of significant bleeding in VWD rather than cryoprecipitate when available. The VWF activity and dosing are expressed as ristocetin cofactor units. Recombinant factor VIIa (Novoseven) is indicated for the use of acute bleeding and prophylaxis for patients with hemophilia A or B, who have inhibitors to FVIII and FIX, respectively, and congenital factor VII deficiency. Reports also have documented off-label use for treatment of acute bleeding in patients who have qualitative platelet disorders, such as Glanzmann's thrombasthenia, severe liver disease, and massive bleeding in the trauma setting [44,45]. Activated prothrombin complex (FEIBA) is a human plasma-derived factor IX complex that in addition to factor IX contains various amounts of activated factors II, VII, and X and trace amounts of factor VIII. Although traditionally used for patients who have hemophilia A and who have inhibitors, FEIBA has been replaced by recombinant factor VIIa because of a higher thrombotic risk at higher doses and because the small amounts of factor VIII present within the product can stimulate anamnesis, thereby increasing inhibitor titers in patients who have hemophilia and who are considered for immune tolerance therapy [46].

Granulocytes

Granulocytes are the least used blood component for many reasons, including the logistics of collection, limited storage viability (24 hours), and lack of conclusive evidence of efficacy in various clinical settings. Granulocytes are collected by apheresis from "stimulated" donors to collect higher numbers and more activated granulocytes. Donors can be stimulated with steroids, granulocyte colony-stimulating factor (GCSF), or both. Although studies show that costimulation with GCSF and steroids is superior in terms of granulocyte yield (increase collections to 6 to 8×10^{10} granulocytes per procedure), stimulation of donors is not performed by all blood banks and transfusion centers. All granulocyte components are stored at 20°C to 24°C without agitation, and contain at least 1×10^{10} granulocytes per product, with variable numbers of lymphocytes, platelets, and RBCs in 200 to 400 mL plasma. Because of this, units must be ABO compatible and preferably RhD negative for RhD-negative recipients. Granulocyte function deteriorates rapidly during storage and, therefore, should be transfused as soon as possible after collection and no later than 24 hours after collection. This may require that physicians waive, in writing, viral serologic testing of the product and obtain separate consent from recipients.

Granulocyte transfusion should be used as an adjunct to other medical therapies, including the use of granulocyte-stimulating factors, antibiotics, and antifungals. Because of the lack of randomized controlled trials addressing efficacy and the recent developments of better antimicrobial agents, the Infectious Disease Society of America does not recommend the routine use of granulocyte transfusions for prolonged refractory neutropenic infections

[21]. Meta-analysis of the efficacy and safety of granulocyte infusion as adjuncts to antibiotic therapy in treatment of neutropenic neonates who have sepsis was inconclusive that granulocyte infusions reduce morbidity and mortality in septic neutropenic newborns [47]. It generally is accepted, however, to strongly consider granulocyte transfusion in severe (or progressive) bacterial or fungal infection in patients who are severely neutropenic and who have no response to appropriate aggressive antimicrobial treatment and no expected recovery of neutrophil count for more than 7 days [48,49]. For neonates and small children, daily infusion of 1 to 2×10^9 polymorphonuclear cells (PMNs)/kg, and for larger children, an absolute daily dosage of at least 4 to 8×10^{10} PMNs, are recommended until recovery (see Table 1) [18,21,48].

Granulocyte transfusions frequently are accompanied by fevers, chills, and allergic reactions. More severe reactions, such as hypotension, respiratory distress, and lung injury, occur in 1% to 5% of transfusions; previously HLA-alloimmunized patients are at the greatest risk [48]. Patients should be tested for the presence of HLA and antineutrophil antibodies before the first granulocyte transfusion and periodically during prolonged courses of transfusions or when there is concern for alloimmunization (eg, poor post-transfusion increments in WBC or platelets, pulmonary infiltrates, or frequent febrile transfusion reactions). An additional concern regarding alloimmunization entails the likelihood of future patients who have bone marrow transplantation of finding a suitable HLA match. This is important especially when family members are considered as donors; these individuals should not be considered as granulocyte donors for patients before bone marrow transplantation. If alloimmunization does occur, HLA-matched granulocytes may be sought. Because granulocyte concentrates contain lymphocytes, all components should be gamma irradiated and CMV negative if appropriate to recipients, because leukoreduction is contraindicated.

Acute transfusion reactions

There are many benefits to transfusion therapy; however, there are risks that may be incurred acutely or in the long term. It is important for physicians to be aware of their incidence and to be able to recognize these adverse reactions swiftly so as to take proper action to prevent significant morbidity and mortality as a result of them. Some adverse reactions are discussed previously (eg, TA-GVHD, alloimmunization, and CMV reactivation) and are not discussed further. Discussed later are adverse reactions that take place at the time of, or within 24 hours after, transfusion. Although most acute reactions in pediatric patients are immune related, nonimmune-related complications, such as bacterial contamination, transfusion-associated circulatory overload (TACO), and thermal/mechanical hemolysis, always should be considered. When an acute transfusion reaction occurs, it is

imperative to stop the transfusion immediately, maintain intravenous access, verify that the correct unit was transfused to the patient, treat the patient's symptoms, and notify the transfusion service for further investigation.

Febrile reactions

Fever is a common symptom of transfusion reactions. When a fever develops, serious transfusion reactions, such as bacterial contamination, acute hemolysis of ABO incompatible red cells, or transfusion-related acute lung injury (TRALI), should be considered; the transfusion should be stopped and the transfusion service notified so as to initiate the appropriate evaluation and quarantine any further products from the suspected donor unit. A common less severe etiology includes FNHTRs, which can result from the transfusion of RBCs, platelets, or plasma [16]. In the past, FNHTRs occurred in up to 30% of transfusions; however, since the advent of leukoreduction, the incidence is only 0.1% to 3% for all products [6–8,16]. Although FNHTRs are relatively harmless, they may be uncomfortable for recipients. A fever ($>1^{\circ}\text{C}$ increase in temperature) often is accompanied by chills, rigors, and overall discomfort making it difficult to discern this entity from other more serious etiologies. FNHTRs are believed to result from the release of pyrogenic cytokines, interleukin (IL)- 1β , IL-6, and IL-8 and tumor necrosis factor α , by leukocytes within the plasma during storage. Prestorage leukoreduction is shown to decrease the incidence of FNHTRs in patients receiving RBCs and platelet products [6–8]. In severe or recalcitrant cases, washing the blood product may be considered. The usefulness of premedication with antipyretics to prevent FNHTRs is controversial. Retrospective analysis showed no difference in the incidence of FNHTRs between those who received premedication versus those who received placebo [50].

Allergic reactions

Allergic transfusion reactions (ATRs) are the most common of all acute transfusion reactions. The severity of the allergic reaction can range from mild localized urticaria, pruritis, and flushing to bronchospasm and anaphylaxis. Unlike other acute transfusion reactions, fever usually is absent, and if the symptoms are mild and resolve with stopping the transfusion and administering antihistamines, the transfusion may be restarted. Most patients who have ATRs respond to antihistamines and pretreatment may help to prevent recurrence. These reactions are caused by an antibody response in recipients to soluble plasma proteins within the blood product. Leukoreduction is not shown to decrease the incidence of ATRs as it has for FNHTRs [8,51]. Severe ATRs leading to anaphylaxis often are the result of the development of anti-IgA antibodies in recipients who are IgA deficient. Long-term management of individuals who have had severe ATRs is difficult.

Pretransfusion medication with antihistamines and steroids is recommended and washed RBCs and platelets should be used because they remove most of the plasma responsible for the ATR. Epinephrine should be readily available during subsequent transfusions. In patients who are IgA deficient and have documented anti-IgA antibodies, IgA-deficient plasma products may be obtained through rare donor registries if time permits [51].

Acute hemolytic transfusion reactions

An acute hemolytic transfusion reaction (AHTR) occurs when RBCs are transfused to a recipient who has preformed antibodies to antigens on the transfused RBCs. Most reactions are the result of antibodies to the RBC major blood group antigens A or B resulting from clerical errors. Infants under 4 months are not considered at risk for AHTRs because of the absence of A and B isoagglutinins and other RBC antigens (alloantibodies); however, maternal IgG antibodies can cross the placenta causing hemolysis of transfused RBCs and, therefore, should be considered when transfusing infants. Less commonly, nonimmune causes of acute hemolysis may occur. These include hemolysis from mechanical devices, such as blood warmers, infusion devices, filters, and catheters; improper storage; or bacterial contamination [10].

Signs and symptoms of AHTRs include fever, chills, nausea, vomiting, shortness of breath, chest pain, hypotension, vasoconstriction, and hemoglobinuria, with potential progression to DIC and acute renal failure. When AHTR is suspected, the transfusion should be stopped immediately and a full transfusion evaluation initiated, which includes obtaining blood cultures from the units, comparing the direct antibody test from the patient's pretransfusion crossmatch to the post-transfusion direct antibody test, and a clerical check to verify the correct unit was given to the correct patient. Aggressive intravenous fluid therapy is required to maintain intravascular volume and to prevent acute renal failure. The severity of the reaction and mortality rate are correlated directly to the rate and amount of incompatible blood transfused. Mortality reaches 44% in individuals receiving larger volumes of incompatible blood [51].

Transfusion-related acute lung injury

TRALI is an uncommon yet potentially fatal acute immune-related transfusion reaction that recently has become the leading cause of death from transfusion in the United States. It typically occurs during or within 4 hours of transfusion and presents with respiratory distress resulting from noncardiogenic pulmonary edema (normal central venous pressure and pulmonary capillary wedge pressure), hypotension, fever, and severe hypoxemia (O_2 saturation $< 90\%$ in room air) [10,52]. Transient leukopenia can be observed within a few hours of the reaction and can distinguish

TRALI from TACO, an acute, nonimmune transfusion reaction that presents with respiratory distress, cardiogenic pulmonary edema, and hypertension resulting from volume overload. TRALI usually improves after 48 to 96 hours from onset of symptoms, but aggressive respiratory support is required in 75% of patients and 10% to 15% of patients who have TRALI have a fatal outcome. Although patients who have TACO often respond to diuresis, patients who have TRALI may require fluid or vasopressor support in the face of hypotension, and diuretics should be avoided [52].

Although the exact mechanism of TRALI remains uncertain, two not mutually exclusive hypotheses are proposed: the antibody-mediated hypothesis and the neutrophil priming hypothesis. According to the antibody-mediated hypothesis, antineutrophil or anti-HLA I or II antibodies (from donor or recipient) attach to the corresponding antigen on neutrophils, causing sequestration and activation of neutrophils within the lungs, resulting in endothelial damage and vascular leakage. Many reports clearly document the presence of these antibodies in TRALI reactions [53]. In 85% to 90% of the cases, the antibodies were present within the donor blood unit, whereas in approximately 10% of the cases, the antibodies were found present in the recipient. Leukoreduction of cellular blood products decreases the incidence of TRALI caused by recipient leukocyte antibodies to incompatible donor leukocyte antigens [6,52]. The neutrophil priming hypothesis is proposed to account for the cases of TRALI in which no antibody is identified. In this two-hit mechanism, the first event is the clinical situation within the recipient surrounding the transfusion, which primes neutrophils (eg, surgery, infection, or trauma). The second event consists of the transfusion of “bioactive factors,” such as cytokines, IL-6, IL-8, bioactive lipids (ie, lysophosphatidylcholines), or anti-HLA/antineutrophil antibodies, which produces neutrophil sequestration with the endothelium of the lungs. Some reports show that cases of TRALI in adults, in which antibodies were not identified in the donor or recipient, had less severe courses than those associated with antibodies [52,53].

TRALI is reported as a consequence of all blood product transfusions; however, plasma products (FFP and FP) account for the majority (50%–63%) of TRALI fatalities [52,53]. TRALI is reported in pediatric patients, albeit in a limited number of case reports. High-risk pediatric populations consist of those with hematologic malignancy, post-bone marrow transplant, and autoimmune disorders. In the largest epidemiologic study on TRALI, which included 15 pediatric patients, the most common setting surrounding the reaction in children was induction chemotherapy for acute lymphoblastic leukemia [54]. There are no definitive cases of TRALI documented in the neonatal population.

Recent data from the United Kingdom’s serious hazards of transfusion initiative and the American Red Cross have shown that the majority of TRALI cases resulting from high-volume plasma products (FFP and apheresis platelets) involved an antileukocyte antibody-positive female donor

[55,56]. This is attributed to an increase in antileukocyte and anti-HLA antibodies present in multiparous women. Although the United Kingdom has adopted a policy of minimizing transfusion of high-volume plasma products from female donors and subsequently has seen a dramatic decrease in the incidence of TRALI, somewhat different procedures have been adopted in the United States [55]. These include use of male-only, high-volume plasma products or the use of male and female donor products after selecting for donors who have a low likelihood of having been alloimmunized by pregnancy or transfusions. Performing leukocyte antibody testing on female-donor, high-volume plasma products is a suggested alternative measure [57].

Future directions

Since the advent of transfusion medicine, many technologic advances have made the collection of blood products safer and more efficient. Ongoing research, however, is underway to improve several aspects of blood component collection and administration. Advances in DNA technology are changing the understanding of blood group antigens and HLA serotypes and allowing blood centers to solve compatibility problems among alloimmunized/refractory patients. The implications of DNA-based RBC and HLA genotyping are only beginning to become apparent in clinical practice. Nucleic acid amplification testing is beginning to replace serologic testing for several blood-borne infectious agents in blood products, and ongoing research involving multipathogen microarray technology for donor screening may reform the current infectious disease donor screening interventions. Pathogen inactivation is successful in eliminating enveloped virus transmission in plasma derivatives. Considerable effort continues to be invested in the development of universal pathogen inactivation techniques using nucleic acid inactivating agents, given that no single technique has proved effective for all blood components, and their effect on the final blood product is not fully known.

As a result of dramatic developments in apheresis technology, separation of every blood component, including HPCs, can be accomplished from a single donor. HPC transplantation increasingly is used in place of bone marrow transplantation in childhood malignancies and other diseases because of the increased safety and availability of this technique of stem cell collection. In addition, the use of umbilical cord blood as a source of HPCs, whose collection and processing parallels that of peripheral blood stem cell techniques, rapidly is expanding the inventory of viable graft options for children and adults who have these disorders. Refinements in bioengineering and apheresis technology are expanding the ability to grow, proliferate, and collect many bone marrow-derived cells, which may show promise in cellular immunotherapy.

Lastly, a call for a national hemovigilance system, similar to those established in European countries, has been proposed for the United States. Once established, transfusion safety can be monitored at several levels to prevent adverse transfusion events with ongoing monitoring and early recognition of undesirable trends within the community.

References

- [1] Luban NL. Basics of transfusion medicine. In: Furman B, Zimmerman JJ, editors. *Pediatric critical care*. 3rd edition. Philadelphia: Mosby; 2006. p. 1185–98.
- [2] Luban NL, Strauss RG, Hume HA. Commentary on the safety of red cells preserved in extended storage media for neonatal transfusions. *Transfusion* 1991;31:229–35.
- [3] Strauss RG, Burneister LF, Johnson K, et al. Feasibility and safety of AS-3 red blood cells for neonatal transfusions. *J Pediatr* 2000;136:215–9.
- [4] Jain R, Jarosz C. Safety and efficacy of AS-1 red blood cell use in neonates. *Transfus Apher Sci* 2001;24(2):111–5.
- [5] Price TH, editor. *Standards for blood banks and transfusion services*. 25th edition. Bethesda (MD): American Association of Blood Banks; 2008.
- [6] Yazer MH, Podlosky L, Clarke G, et al. The effect of prestorage leukoreduction on the rates of febrile nonhemolytic transfusion reactions to PC and RBC. *Transfusion* 2004;44:10–5.
- [7] Paglino JC, Pomper GJ, Fisch G, et al. Reduction of febrile but not allergic reactions to red cells and platelets following conversion to universal prestorage leukoreduction. *Transfusion* 2004;44:16–24.
- [8] King TE, Tanz W, Shirey S, et al. Universal leukoreduction decreases the incidence of febrile nonhemolytic transfusion reactions to red cells. *Transfusion* 2004;44:25–9.
- [9] *Technical manual of the American Association of Blood Banks*. 14th edition. Bethesda (MD): American Association of Blood Banks; 2003.
- [10] Luban NL, Wong EC. Hazards of transfusion. In: Arceci RJ, Hann IM, Smith OP, editors. *Pediatric hematology*. 3rd edition. New York: Wiley Blackwell; 2006. p. 724–44.
- [11] Bowden RA, Slichter SJ, Sayers M, et al. A comparison of filtered leukocyte-reduced and cytomegalovirus (CMV) seronegative blood products for the prevention of transfusion-associated CMV infection after marrow transplant. *Blood* 1995;86:3598–603.
- [12] Nichols WG, Price TH, Gooley T, et al. Transfusion-transmitted cytomegalovirus infection after receipt of leukoreduced blood products. *Blood* 2003;101:4195–220.
- [13] Narvios AB, de Lima M, Shah H, et al. Transfusion of leukoreduced cellular blood components from cytomegalovirus-unscreened donors in allogeneic hematopoietic transplant recipients: analysis of 72 recipients. *Bone Marrow Transpl* 2005;35:499–501.
- [14] Special products. In: Roseff SD, editor. *Pediatric transfusion: a physician's handbook*. 2nd edition. Bethesda (MD): American Association of Blood Banks; 2006. p. 179–94.
- [15] Strauss RG. Data-driven blood banking practices for neonatal RBC transfusions. *Transfusion* 2000;40(12):1528–40.
- [16] Pelsynski MM, Moroff G, Luban NL, et al. Effect of gamma irradiation of red blood cell units on T-cell inactivation as assessed by limiting dilution analysis: implications for preventing transfusion-associated graft-versus-host disease. *Blood* 1994;83(6):1683–9.
- [17] Davey RJ, McCoy NC, Yu M, et al. The effect of prestorage irradiation on postransfusion red cell survival. *Transfusion* 1992;32(6):525–8.
- [18] Blood components. In: Roseff SD, editor. *Pediatric transfusion: a physician's handbook*. 2nd edition. Bethesda (MD): American Association of Blood Banks; 2006. p. 1–52.
- [19] Weiskopf RB, Schnapp S, Rouine-Rapp K, et al. Extracellular potassium concentration in red blood cell suspensions after irradiation and washing. *Transfusion* 2005;45:1295–301.

- [20] Roseff SD, Luban NL, Manno CS. Guidelines for assessing appropriateness of pediatric transfusion. *Transfusion* 2002;42:1398–413.
- [21] Robitaille N, Hume HA. Blood components and fractionated plasma products: preparations, indications, and administration. In: Arceci RJ, Hann IM, Smith OP, editors. *Pediatric hematology*. 3rd edition. New York: Wiley Blackwell; 2006. p. 693–706.
- [22] Vichinsky EP, Haberkern CM, Neumayer L, et al. A comparison of conservative and aggressive transfusion regimens in the perioperative management of sickle cell disease. *N Engl J Med* 1995;333:206–13.
- [23] Scotborn DJ, Price C, Schwartz D, et al. Risk of recurrent stroke in children with sickle cell disease receiving blood transfusion therapy for at least five years after initial stroke. *J Pediatr* 2002;140:348–54.
- [24] Adams RJ, McKie VC, Hsu L, et al. Prevention of first stroke by transfusions in children with sickle cell anemia and abnormal results on transcranial Doppler ultrasonography. *N Engl J Med* 1998;339:5–11.
- [25] Adams RJ, Brambilla D. Discontinuing prophylactic transfusions used to prevent stroke in sickle cell disease. *N Engl J Med* 2005;353:2769–78.
- [26] Smith-Whitley K. Alloimmunization in patients with sickle cell disease. In: Manno CS, editor. *Pediatric transfusion therapy*. Bethesda (MD): AABB Press; 2002. p. 249–82.
- [27] Vichinsky EP, Luban NC, Wright E, et al. Prospective RBC phenotype matching in a stroke-prevention trial in sickle cell anemia: a multicenter transfusion trial. *Transfusion* 2001;41:1086–92.
- [28] Alloimmune cytopenias. In: Roseff SD, editor. *Pediatric transfusion: a physician's handbook*. 2nd edition. Bethesda (MD): American Association of Blood Banks; 2006. p. 53–97.
- [29] British Committee for Standards in Hematology, Blood Transfusion Task Force. Transfusion guidelines for neonates and older children. *Br J Haematol* 2004;124:433–53.
- [30] Kirpalani H, Whyte RK, Anderson C, et al. The Premature Infants in Need of Transfusion (PINT) study: a randomized, controlled trial of a restrictive (low) versus liberal (high) transfusion threshold for extremely low birth weight infants. *J Pediatr* 2006;149:301–7.
- [31] Bell EF, Strauss RG, Widness JA, et al. Randomized trial of liberal versus restrictive guidelines for red blood cell transfusion in preterm infants. *J Pediatr* 2005;115:1685–91.
- [32] Cid J, Lozano M. Risk of Rh(D) alloimmunization after transfusion of platelets from D+ donors to D- recipients. *Transfusion* 2005;45:453.
- [33] Klein HG, Anstee DJ, editors. *Mollison's blood transfusion in clinical medicine*. 11th edition. Blackwell; 2005. p. 187–91.
- [34] Molnar R, Johnson R, Sweat LT, et al. Absence of D alloimmunization in D- pediatric oncology patients receiving D-incompatible single-donor platelets. *Transfusion* 2002;42:177–82.
- [35] Gil-Fernandez JJ, Alegre A, FernandezVillalta MJ, et al. Clinical results of a stringent policy on prophylactic platelet transfusion: Non-randomized comparative analysis of 190 bone marrow transplant patients from a single institution. *Bone Marrow Transplant* 1996;18:931–5.
- [36] Heckman KD, Weiner GJ, Davis CS. Randomized study of prophylactic platelet transfusion threshold during induction therapy for adult acute leukemia: 10,000 microL versus 20,000 microL. *J Clin Oncol* 1997;15:1143–9.
- [37] Wandt H, Frank M, Ehninger G, et al. Safety and cost effectiveness of $10 \times 10^9/L$ trigger for prophylactic platelet transfusion compared with the traditional $20 \times 10^9/L$ trigger: a prospective comparative trial in 105 patients with acute myeloid leukemia. *Blood* 1998;91:3601–6.
- [38] Murray NA, Horwarth LJ, McCloy MP, et al. Platelet transfusion in the management of severe thrombocytopenia in neonatal intensive care unit patients. *Transfus Med* 2002;12:35–41.
- [39] Vassallo RR. New paradigms in the management of alloimmune refractoriness to platelet transfusions. *Curr Opin Hematol* 2007;14:655–63.

- [40] Perotta PL, Pisciotto PT, Snyder EL. Platelets and related products. In: Hillyer CD, Silberstein LE, Ness PM, et al, editors. *Blood banking and transfusion medicine basic principles and practice*. 1st edition. Philadelphia: Churchill Livingstone; 2003. p. 181–206.
- [41] Petz LD, Garatty G, Calhoun L, et al. Selecting donors of platelets for refractory patients on the basis of HLA antibody specificity. *Transfusion* 2000;40:1446–56.
- [42] Delaflor-Weiss E, Mintz PD. The evaluation and management of platelet refractoriness and alloimmunization. *Transfus Med Rev* 2000;14:180–96.
- [43] British Committee for Standards in Hematology, Blood Transfusion Task Force. Amendments and corrections to the ‘transfusion guidelines for neonates and older children’ (BCSH, 2004a); and to the ‘Guidelines for the use of fresh frozen plasma, cryoprecipitate and cryosupernatant’ (BCSH, 2004b). *Br J Haematol* 2006;136:514–6.
- [44] Mathew P. The use of rVIIa in non-hemophilia bleeding conditions in paediatrics. A systematic review. *Thromb Haemost* 2004;92:738–46.
- [45] Mathew P, Young G. Recombinant factor VIIa in paediatric bleeding disorders—a 2006 review. *Haemophilia* 2006;12:457–72.
- [46] Green D. Complications associated with the treatment of haemophiliacs with inhibitors. *Haemophilia* 1999;5(Suppl 3):11–7.
- [47] Mohan P, Brocklehurst P. Granulocyte transfusions for neonates with confirmed or suspected sepsis and neutropenia. *Cochrane Database Syst Rev* 2003;4:CD003956.
- [48] Bishton M, Chopra R. The role of granulocyte transfusions in neutropenic patients. *Br J Haematol* 2004;127:501–8.
- [49] Vamvakas EC, Pineda AA. Determinants of the efficacy of prophylactic granulocyte transfusions: a meta-analysis. *J Clin Apheresis* 1997;12:74–81.
- [50] Sanders RP, Maddirala SD, Geiger TL, et al. Premedication with acetaminophen or diphenhydramine for transfusion with leucoreduced blood products in children. *Br J Haematol* 2005;130:781–7.
- [51] Davenport RD. Hemolytic transfusion reactions. In: Popovsky MA, editor. *Transfusion reactions*. 3rd edition. 2007. p. 1–56.
- [52] Kopko PM, Popovsky MA. Transfusion related acute lung injury. In: Popovsky MA, editor. *Transfusion reactions*. 3rd edition. 2007. p. 207–28.
- [53] Sanchez R, Toy P. Transfusion related acute lung injury: a pediatric perspective. *Pediatr Blood Cancer* 2005;45:248–55.
- [54] Silliman CC, Boshkov LK, Meddizadehkashi Z, et al. Transfusion-related acute lung injury: epidemiology and a prospective analysis of etiologic factors. *Blood* 2003;101:454–62.
- [55] Serious Hazards of Transfusion (SHOT). Annual report. 2006. Manchester, UK: SHOT Scheme, 2006. Available at: <http://www.shotuk.org/SHOTREPORT2006.PDF>. Accessed March 12, 2008.
- [56] Eder AF, Herron R, Strupp A, et al. Transfusion related acute lung injury surveillance (2003–2005) and the potential impact of the selective use of plasma from male donors in the American Red Cross. *Transfusion* 2007;47:599–607.
- [57] Transfusion-related acute lung injury Association bulletin #06-07. Bethesda (MD): AABB; 2006. Available at: http://www.aabb.org/content/Members_Area/Association_Bulleins/ab06-07.htm. Accessed March 12, 2008.