Concise Definitive Review

Series Editor, Jonathan E. Sevransky, MD, MHS

Transfusion in Critically Ill Children: Indications, Risks, and Challenges

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Objective: To provide a concise review of transfusion-related issues and practices in the pediatric patient population, with a focus on those issues of particular importance to the care of critically ill children.

Data Source: Electronic search of the PubMed database using the search terms "pediatric transfusion," "transfusion practices," "transfusion risks," "packed red blood cell transfusion," "white blood cell transfusion," "platelet transfusion," "plasma transfusion," and "massive transfusion" either singly or in combination.

Study Selection and Data Extraction: All identified articles published since 2000 were manually reviewed for study design, content, and support for indicated conclusions, and the bibliographies were scrutinized for pertinent references not identified in the PubMed search. Selected studies from this group were then manually reviewed for possible inclusion in this review.

Data Synthesis: Well-designed studies have demonstrated the benefit of "restrictive" transfusion practices across the entire age spectrum of pediatric patients across a wide spectrum of pediatric illness. However, clinician implementation of the more restrictive transfusion practices supported by these studies is variable. Additionally, the utilization of both platelet and plasma transfusions in either a "prophylactic" or "therapeutic" setting appears to be greater than that supported by published data.

Conclusions: The preponderance of prospective, randomized trials and retrospective analyses support the use of a restrictive packed RBC transfusion policy in most clinical conditions in children. Neonatal transfusions guidelines rely largely on "expert opinion" rather than experimental data. Current transfusion practices for both platelets and coagulant products (e.g., fresh-frozen plasma and recombinant-activated factor VII) are poorly aligned with recommended transfusion guidelines. As with adults, current transfusion practices in children often do not reflect implementation of our current knowledge on the need for transfusion. Greater efforts to implement current evidence-based transfusion practices are needed. (*Crit Care Med* 2014; 42:675–690)

Key Words: clotting factor concentrates; pediatrics; plasma; platelets; red blood cells; transfusion

Transfusion of blood products to critically ill and injured patients has been attempted for centuries, but it was not until the issues of blood compatibility and typing were recognized and addressed in the early 1900s, and methods to effectively separate and store blood components were subsequently developed that this therapy entered into the mainstream of medical care. The goal in transfusion of RBCs has always been to normalize oxygen delivery to the tissues, although at times blood transfusions have been used as a means of supporting intravascular volume. To meet both of these goals, a hemoglobin (hematocrit) target of 10 g/dL (30%) has historically been cited as the "optimal" value when transfusing critically ill or injured patients. However, over the past 10–15 years, several studies have been published calling into question the benefit of aggressive RBC transfusion and the appropriateness of this transfusion target. Although there is a developing consensus around transfusion practices, controversy still exists with regard to the application of data-driven guidelines for specific patients. Indeed, the implementation of new practices that conform with published data remains slow. I will review the current knowledge of the risks and benefits of blood transfusion and the practice guidelines that have developed from these data focusing on the clinical situations that can be reasonably generalized from those data, including current thoughts on the prevention and support of the patient requiring "massive transfusion." Where there is no pediatric literature on which to rely, experience in adult patients will be used to fill this knowledge gap. This review will not cover perinatal transfusion practices and guidelines, the use of erythropoietin to treat anemia, or blood transfusions for clinical conditions in which the transfusion practices cannot be generalized to a broader patient population (e.g., transfusion in neurosurgical, extracorporeal membrane oxygenation, and cardiopulmonary bypass patients). Additionally, the use of albumin, and other blood products, as a plasma expander will not be addressed in this review, as a thorough discussion of the uses of albumin is beyond the scope of this review.

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TRANSFUSION RISKS

Transfusion of blood products is known to carry risks to the recipient. Among these are acute and delayed hemolytic reactions, alloimmunization, fever, allergic reactions, transmission of certain infections (HIV, hepatitis B & C, cytomegalovirus [CMV], malaria, babesiosis, etc.), volume overload with cardiac decompensation (transfusion-associated cardiac overload), acute lung injury (transfusion-related acute lung injury [TRALI]), and immunosuppression (transfusion-related immunomodulation [TRIM]) (1–8) (**Fig. 1**). Additional risks include the development of transfusion-associated graft-versus-host disease (TA-GvHD) and transfusion-associated microchimerism resulting from the transfusion of immunocompetent cells (or DNA) into an immunoincompetent patient. The fatality rate of TA-GvHD approaches 100%, whereas the clinical/immune consequences of transfusion-associated microchimerism are unknown. Even with extended cross matching in patients at risk for frequent transfusions and consequent alloimmunization (e.g., patients with sickle cell disease or thalassemia syndromes), approximately at least 1 new alloantibody develops in 14% of patients as a consequence of repeated transfusion (9, 10). This may result in an increased difficulty in identifying cross-match compatible blood for transfusion. It is estimated that up to one-half of multiply transfused patients will experience a transfusion reaction (11).

Transfusion of large volumes of blood products, in the setting of massive transfusion (see below), when multiple units are administered over several days, or with therapeutic apheresis, may result in the development of metabolic derangements. These include hyperkalemia, particularly in the setting of antecedent renal insufficiency, and metabolic alkalosis, hypocalcemia, and hypochloremia due to accumulation of calcium-citrate complex. This latter complication is more pronounced in the setting of liver failure or liver transplantation (12–14).

Infection

Prior to current viral testing procedures (including donor self-deferral), viruses presented the greatest risk for transfusion-transmitted infection (TTI) (**Table 1**). However, at the present time, bacterial contamination of blood products presents the greatest risk for TTI (15–20). This risk has been documented in several developed countries worldwide, with risk of infection ranging from 0.2 to 7.4 events per million RBC units. The greatest risk for bacterial TTI is consistently demonstrated for platelet concentrates stored at room temperature with an incidence of 1:2,000–3,000 platelet transfusions. Gram-positive organisms, particularly those that represent normal skin flora including *Staphylococcus epidermidis* and *Staphylococcus aureus*, represent the predominant bacteria contaminating platelet transfusions. Transfusion-transmitted bacterial infection (TTBI) resulting from platelet transfusions is less in apheresis obtained platelet units when compared with platelet units obtained from whole blood donation. Transmission of gram-negative bacteria is an even rarer event and is thought primarily to result from units collected from a donor with asymptomatic bacteremia. Although bacterial contamination more commonly occurs with platelet units, gram-negative contamination is more often associated with transfusion of packed RBC (pRBC) units (15–20). However, the greatest risk of infection from RBC transfusion is with the use of cell-saver blood transfused intraoperatively or postoperatively (21, 22). When a TTBI is suspected, the clinician must promptly notify the blood bank to minimize the chance that other patients will be exposed to blood products obtained from that donor during the same collection (i.e., when units are "split" for multiple transfusions).

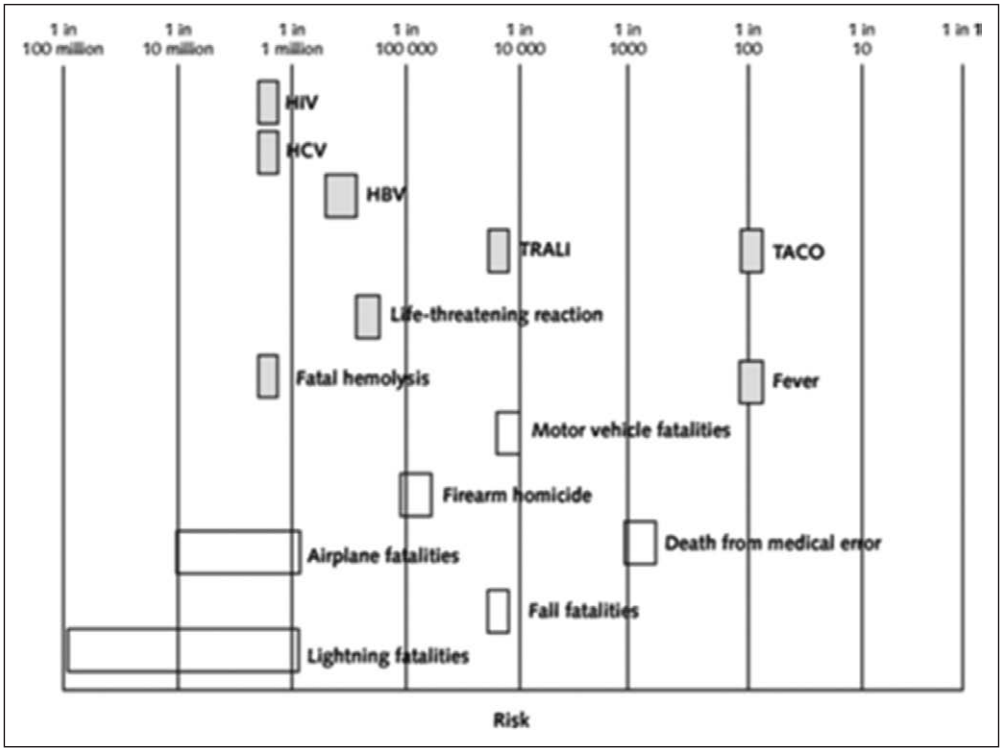

Figure 1. Adverse effects of RBC transfusion contrasted with other risks. HCV = hepatitis C virus, HBV = hepatitis B virus, TRALI = transfusion-related acute lung injury, TACO = transfusion-associated circulatory overload. Reproduced with permission from Carson et al (1).

Viral transmission from blood product transfusion remains a risk, particularly for CMV. In most urban areas, 50% of blood donors (or more) will be CMV positive by young adulthood. Transmission of

TABLE 1. Infectious Agents Transmittable in Blood

Viruses	Parasitic Diseases	Bacteria
Hepatitis A, B[a], C[a], E	Malaria	Gram positive[a]
Human immunodeficiency virus[a]	Babesiosis	Staphylococcus species
Human T-lymphotropic virus I/II[a]	Chagas	Streptococcus species
Herpes simplex virus	Leishmaniasis	Bacillus species
Dengue	Toxoplasmosis	*Propionibacterium acnes*
West Nile[a]	*Treponema pallidum*[a]	*Enterococcus faecalis*
Cytomegalovirus[a]	Trypanosomiasis	Gram negative[a]
Epstein-Barr virus	**Prions**	*Escherichia coli*, Acinetobacter, Klebsiella
Parvovirus B-19	Variant Creutzfeldt-Jakob	Pseudomonas, Serratia, Enterobacter species
Human herpes virus-8	**Nematodes**	*Pasturella multocida, Yersinia enterocolitica*
	Microfilariasis	*Providencia rettgeri, Proteus mirabilis*
		Anaplasma phagocytophilum (Anaplasmosis)
		Rickettsia

[a]Those pathogens routinely found in the United States.

CMV by transfusion of blood products from a CMV-positive donor to nonimmune individuals is assumed but can be reduced to a level approaching that noted with the transfusion of "CMV-negative" blood products through leukodepletion of the cellular blood product unit; approximately 2.5% of CMV-negative individuals will be found to seroconvert to CMV positive following transfusion of CMV-negative blood products. Such blood products are frequently referred to as being "CMV safe" (23–25). The risk of hepatitis B virus transmission through blood transfusion is essentially at the incidence in the general (nontransfused) population (< 1:200,000–500,000), whereas that for HIV or hepatitis C virus is approximately 1:1,000,000–2,000,000 (Fig. 1). With greater ease of rapid intranational and international travel, there is an increased/continued risk of transfusion of regional infectious diseases (e.g., malaria) outside of its usual geographic containment. Other protozoal disorders with an intraerythrocytic stage (e.g., babesiosis) have also been shown to be transmitted by transfusion, although exact risks for transmission of these organisms cannot be calculated due to their limited geographic distribution (1, 26–28).

The methods for pathogen reduction in blood products currently approved in the United States or under study are listed in **Table 2** (reviewed in [29]). However, clinicians can also minimize the secondary contamination of blood products by following current requirements that all blood products be transfused within 4 hours of the blood product unit being entered (i.e., spiked) on the clinical unit or returned to the blood bank within 30 minutes if it is not spiked and not to be immediately transfused. Additional potential benefits to pathogen reduction techniques may also exist. These include enhanced leukocyte inactivation, reduced microparticle load of the blood product, and decreased risk of TRALI resulting from a decrease in antileukocyte and anti-human leukocyte antigen antibodies with the use of solvent/detergent–treated plasma. However, cost-benefit analyses are needed to determine if the added costs are justified (30).

Hemolysis

Acute hemolytic events may be life threatening and are often the result of human error in which a noncompatible unit of blood is given to the wrong patient. These reactions almost exclusively occur when ABO incompatible blood is transfused, although infrequent cases of acute hemolytic events have been reported with minor blood group incompatibility. It is estimated that the risk of an acute hemolytic transfusion reaction is 1:70,000 per unit, whereas that for a delayed hemolytic transfusion reaction is 1:1,500 transfusions. The likelihood of an adverse outcome from the reaction is higher in children and neonates than in adults: 13:100,000 in adults, 18:100,000 in children less than 18 years, and 37:100,000 in infants (31, 32). The event is heralded by fever, chills, hypotension, back pain, passage of dark (tea colored) urine, and then oliguria. Symptoms generally develop after only a few milliliters of blood (generally < 10 mL) have been transfused. Management requires discontinuance of the unit of blood being transfused, and the infusion of large volumes of normal saline (with or without diuretics) to maintain adequate urine output. It is important to note that acute hemolytic transfusion reactions can occur with the transfusion of any cellular blood product due to the presence of high-titer isohemagglutinins in the donor plasma, although the anti-ABO antibody titer in the donor blood unit is not always predictive of the risk of hemolysis (33–37). The second group of hemolytic reactions is those referred to as "delayed hemolytic reactions." These result from the development of alloantibodies (typically directed against minor blood groups such as Jk and Fy RBC antigens), which

TABLE 2. Methods of Pathogen Inactivation in Blood Products

Method	Description	Useful for; Effective Against	Status
Solvent-detergent	Inactivates enveloped but not nonenveloped viruses	Plasma; lipid enveloped viruses only	Food and Drug Administration approved
Methylene blue	Dimethylmethylene blue binds to nucleic acids and activated on visible light exposure	Plasma; most viruses and bacteria	No longer under study
Helinx	Psoralen S-59 and UV-A light exposure causes cross-linking with pathogen DNA; process not effective in RBC units	Plasma and platelets; most viruses and bacteria	Licensed in Europe; under study in the United States
Antimicrobial peptides	Bind to specific microbes and result in membrane disruption and microbial death	Platelets; most bacteria	Under study
Inactine	PEN111 binds to guanine residues in DNA, is effective against cell-free pathogens, interferes with leukocyte function in vivo, and has resulted in RBC antibodies against neoantigens	RBCs	Under study
FRALE	FRALE, S-303 method cross-links both DNA and RNA and has resulted in RBC antibodies against neoantigens	RBCs; most viruses and bacteria	Under study
Mirasol	Riboflavin absorbs visible and UV light at 419 nm and intercalates DNA and RNA causing guanine oxidation and single-strand breaks	RBCs; most viruses and bacteria	Under study in the United States; licensed in Europe for RBCs; licensed for platelets and plasma in some European and Asian countries

UV = ultraviolet, FRALE = frangible anchor linker effector.
Data are from Sobral et al (29).

develop during transfusion and typically result in hemolysis occurring within 10 days following transfusion. These patients are "cross-match" compatible but experience an anamnestic response upon transfusion with development of increased antibody titers and consequent hemolysis. The rate of hemolysis is generally relatively mild but does result in a shortened survival of transfused RBC. However, a rapid anamnestic response may infrequently occur that can produce marked hemolysis with hemoglobinuria and risk for kidney damage.

Fever

Fever occurring late in the course of a transfusion is the most common adverse event associated with transfusion of pRBCs, occurring in up to 1% of transfusions (38). These are generally caused by contaminating leukocytes in the transfusion product. The risk of transfusion-associated febrile episodes can be reduced though prestorage leukoreduction of the transfusion product. The use of in-line leukocyte filters for transfusion of units of blood not leukodepleted at the time of collection has been shown to have some, though limited, effect as well (39–41). The greater efficacy in the prevention of transfusion-associated febrile reactions with the use of prestorage leukoreduced blood products is thought to result from a reduction in inflammatory cytokines produced by contaminating leukocytes during the storage period. Although these febrile episodes are generally not reflective of infection, they may result in some degree of morbidity and frequently result in additional medical costs from investigation into the cause of the fever.

Transfusion-Associated Circulatory Overload

A similar incidence of 1% exists for transfusion-associated circulatory overload, although the careful clinician should be able to anticipate volume overload in "at-risk" patients and minimize the risk by altering the transfusion rate, volume, or the concomitant use of diuretics (7, 8).

Allergy

Late allergic reactions (e.g., hives) are the result of exposure to plasma proteins or proteins adsorbed onto the RBC membrane. These rarely result in severe reactions but may require short-term treatment with antihistamines and/or corticosteroids. These types of reactions are generally "donor specific," but in individuals who experience repeated episodes with transfusion products obtained from different donors, the reactions can be minimized by washing the pRBC unit free of plasma and adsorbed plasma proteins (42, 43). Severe anaphylactic or anaphylactoid reaction may occur in individuals who are severely IgA deficient (estimated incidence 1:1,200); however, less than 5% of IgA deficient individuals are at risk for these reactions (44, 45). Approximately one third of these reactions are the result of IgE-mediated histamine release from mast cells, whereas the mechanism for the remaining two-thirds of cases is not clear.

TRALI

The prevalence and pathophysiology of TRALI have recently been reviewed (4, 5). This appears to be predominantly an antibody-mediated process resulting from the presence of anti-neutrophil and/or anti-HLA antibodies present in the donor plasma. Exclusion of plasma and platelets from multiparous women has significantly decreased the prevalence of TRALI as reported in national blood surveillance programs. However, even with this strategy, cases of TRALI occur, particularly when type AB blood product is required (46–48). Recently, the American Association of Blood Banks (AABB) has issues of new guidelines for identification and potential exclusion of high-risk blood products obtained from donors who have had prior donated units implicated in an episode of TRALI. These include high-volume plasma products (defined as whole blood, plasma, and "unmanipulated" apheresis platelet units obtained from multiparous women). Units obtained from men, never pregnant women, or women who have been tested since their last pregnancy and found to be negative for anti-HLA antibodies are acceptable. In addition, platelet units with reduced plasma volume due to collection with an approved platelet additive product are deemed to be low risk for TRALI. It is anticipated that implementation of these guidelines (scheduled for October 2014) will reduce the risk of TRALI with type AB high plasma volume blood products. Limited reports of TRALI in the pediatric population place the incidence below that in adults at approximately 1.8 per 100,000 transfusions (6).

RBC STORAGE LESION

Multiple studies have demonstrated changes in the ability of stored RBCs to effectively deliver oxygen to tissues following transfusion (reviewed in [49, 50]). These changes have collectively been termed the RBC storage lesion. Current lines of investigation identify many different aspects of RBC physiology and cell biology as contributing to the abnormalities noted in RBC function following storage after collection. These abnormalities include membrane changes resulting in decreased RBC deformability, aggregation, and adhesion; altered intracellular constituents resulting in decreased oxygen delivery (e.g., decreased RBC 2,3-diphosphoglycerate); and the effects of free Hb, iron, and RBC microparticles on nitric oxide availability, immune regulation, and coagulation. What has not been determined, however, is the relative clinical and physiologic importance played by each of these defects, under what conditions each is generated during RBC storage, and which patients are most susceptible to the RBC lesion produced (49–55). Although some studies have demonstrated an association of duration of storage with the magnitude of the defect, clinical studies assessing outcome as a function of the age of transfused blood have produced differing conclusions (56–62) (please see following section).

TRIM

Transfusion of stored RBCs has been shown to increase the risk of nosocomial infections and sepsis in ICU patients, and studies have demonstrated some impairment of immune response in patients who have been multiply transfused. Additionally, in vitro studies have confirmed an immunomodulatory effect of stored RBCs (63–68). A meta-analysis by Hill et al (69) in 2003 concluded that the transfusion of allogeneic blood represented a significant risk for nosocomial infection in trauma patients. Initially, contaminating leukocytes (or leukocyte-derived cytokines) in RBC units were hypothesized to be a primary source of TRIM. The subsequent availability of prestorage leukodepletion has decreased the prevalence of infectious and non-infectious morbidity of RBC transfusions (70, 71). Indeed, a prospective study investigating the effect on leukodepleted stored RBCs on outcome of transfused trauma patients concluded that the transfusion of prestorage pRBCs prevented the deleterious effect of RBC age on outcome (72). Although prestorage leukodepletion reduces the number of contaminating leukocytes in a unit of RBCs, some leukocytes remain and can potentially contribute to TRIM.

The exact mechanism by which transfusion of stored RBCs contribute to TRIM is not clear, but one hypothesis is that the damage incurred by RBCs during storage produces hemolysis in the microvasculature and spleen which in turn causes local release of iron. This may also be augmented by free iron contained in the RBC unit. As a consequence, a cascade of events resulting in a proinflammatory response and inhibition of iron-modulated antimicrobial processes is then initiated (73–76). There are some evidences that RBC microparticles may also play a role in this process (30). Multiple studies looking at outcome as affected by the age of pRBCs transfused in adult patients have suggested a correlation with the age of stored RBCs (older RBCs associated with worse outcome), but the findings are not consistent and cannot be interpreted as being conclusive (reviewed in [77]). Recent reports have suggested that the transfusion of "older" stored pRBCs is associated with a poorer outcome in pediatric cardiac patients and in adult trauma patients (78, 79). However, a similar effect was not noted in very low-birth-weight neonates (58). A single study in adult trauma patients has also shown a similar effect on outcome (particularly an increased prevalence of sepsis) when older stored platelet concentrates were transfused (80). Two recently published prospective observational studies have addressed the question of age of transfused blood and outcome (81, 82). Karam et al (81) in a prospective observational study demonstrated an increase in multiple organ failure in those children who received pRBCs stored for more than or equal to 14 days before transfusion, whereas in a cohort analysis of patients enrolled on the Transfusion in Pediatric Intensive Care Units (TRIPICU) study, Gauvin et al (82) found a suggestion of greater risk of multiple organ failure in children who received blood stored for more than 2–3 weeks before transfusion. Given the complex heterogeneity of many of these patient groups, it is not unreasonable to expect that although some patients may benefit from the transfusion of younger blood, identification of who those patients are will be exceedingly difficult. Conclusions to be drawn from these reports are limited owing to the retrospective, nonrandomized nature of many of these studies, but age of stored blood products to be transfused may be an

important factor affecting outcome. A thorough discussion of this topic is beyond the scope of this review, and I refer the interested reader to the listed references.

BLOOD PRODUCT TRANSFUSION

Both cellular (i.e., RBCs, WBCs, and platelets) and acellular (fresh-frozen plasma [FFP] and cryoprecipitate) blood products can be used to replace deficient blood components. RBC products (whole blood and pRBCs) make up approximately 63% of transfused units with the remainder comprised FFP (20%), platelets (9%), cryoprecipitate (5%), and granulocytes (3%) (83). Commonly applied indications and transfusion thresholds for transfusion of each of these products are shown in **Table 3**. Although there are strong data supporting a restrictive RBC transfusion threshold (see below) and for a platelet prophylactic transfusion threshold of 10,000/mL, these data were obtained in well-defined patient populations and these transfusion thresholds may not be appropriate for all patients and in all clinical settings. Consequently, the clinician must exercise clinical judgment in deciding on the need for transfusion. That being said, the AABB has published guidelines for transfusion of blood products in neonates and children that take into account the currently available evidence (84) (**Tables 4–7**). It must be pointed out, however, that particularly when directed toward neonates, the data supporting many of these recommendations are limited and rely largely on "expert opinion." Several of these transfusion triggers appear to be higher than needed (e.g., platelet transfusion trigger of 100,000/mL in a nonbleeding infant or transfusion of pRBCs at a hematocrit of 30% [i.e., Hb of 10 g/dL] with mild respiratory dysfunction) in light of our newer understanding of the benefits and risks of blood product transfusion. Consequently, clinicians must apply these recommendations with caution. It is this author's opinion that many of these recommended transfusion thresholds represent a starting point at which a transfusion should be considered, but that lower Hb or platelet transfusion triggers may be appropriate depending on the patient's specific clinical setting.

RBC TRANSFUSION: LIBERAL VERSUS RESTRICTIVE TRANSFUSION PRACTICES

Recently, two excellent reviews on transfusion practices in PICU patients have been published, and I refer the reader

TABLE 3. Blood Products and Indications for Use

Product	General Goal or Indication	Transfusion Threshold[a]
Whole blood	The replacement of plasma and all cellular blood components	
Packed RBCs	To increase the O_2 carrying capacity of blood	Hb < 7 g/dL
Platelets	To treat or prevent bleeding secondary to critical thrombocytopenia or in the presence of a qualitative platelet defect	Bleeding patient: platelets < 40–50,000 Prophylactic: platelets < 10,000
Granulocytes	To treat bacterial or fungal infections not responsive to usual antimicrobial agents in the presence of critical neutropenia or the presence of qualitative granulocyte defects	Neutropenia: defined as an absolute neutrophil count < 500/μL
FFP	To replace deficient clotting factors when a clotting factor concentrate is not available, when multiple clotting factors are deficient (e.g., disseminated intravascular coagulation, massive transfusion), when the cause of the coagulopathy is not known, or emergency treatment of warfarin-associated bleeding (e.g., intracranial hemorrhage) FFP for volume support is not an accepted indication Note: product is not treated to minimize viral transmission	
Cryoprecipitate	In the presence of hypo- or dysfibrinogenemia when fibrinogen concentrate is not available; for the prophylactic or therapeutic management of factor XIII deficiency in the absence of factor XIII concentrate; or for treatment of factor VIII deficiency or von Willebrand disease in infants Note: product is not treated to minimize viral transmission	Fibrinogen < 75–100 mg/dL
Clotting factor concentrates	To replace a specific, identified individual clotting factor or correction of warfarin-associated prolongation of the international normalized ratio (four-factor prothrombin complex concentrate preferred)	Variable

FFP = fresh-frozen plasma.

[a]Transfusion threshold may be higher depending on the clinical status of the patient.

to these reviews for a more in-depth treatment of the topic (85, 86). In 1999, Hébert et al (87) published a multicenter randomized trial of pRBC transfusion threshold in nonbleeding adult ICU patients in which they found that the outcome of patients assigned to a "restrictive" transfusion policy (i.e., a transfusion trigger of 7 g/dL) was no worse (possibly better) than that for patients who were assigned to the "liberal" transfusion group (i.e., transfusion trigger of Hb < 10 g/dL). Subsequently, this study was repeated in neonates (88), in older children (89), and in a broad spectrum of hospitalized adult patients (90, 91) with similar conclusions being reached in each study. This same lack of harm with the implementation of a restrictive transfusion policy was also shown in patients with sepsis (92) and in postoperative general and cardiac surgical patients in the pediatric population (93–96). The results of a subgroup analysis of patients from the TRIPICU study have subsequently been confirmed in two single institution studies in which patients were randomized to either a restrictive or liberal transfusion strategy. Although the exact transfusion triggers were not identical (< 8.0 and < 10.8 g/dL for the study by de Gast-Bakker et al [94] and < 9.0 and < 13.0 g/dL for the study by Cholette et al [94]), the findings were similar demonstrating no relative benefit from a liberal transfusion policy versus a more restrictive one with those patients in the restrictive group having fewer transfusion events and donor exposures. Analysis of outcomes in pediatric cardiac surgery patients has demonstrated a worse outcome for those patients who received more pRBC transfusions, and this worse outcome was not due to identifiable patient characteristics (97–99). Whether the transfusions themselves were the cause of the poorer outcome or merely a marker for it is not clear (100), although the findings of similar disparities in outcomes in more heavily transfused patient groups across age and disease categories suggests that the transfusion of pRBCs has a negative effect on outcome (see below).

In the neonatal ICU (NICU), a restrictive transfusion policy has been shown to result in a small reduction in allogeneic blood exposure for infants and no worsening of clinical outcomes when compared with traditional liberal transfusion policies (88). However, in contrast to the hemoglobin thresholds describing restrictive and liberal transfusion cohorts employed in studies with adults and older children (i.e., restrictive cohort = Hb < 7 g/dL; liberal cohort = Hb < 10 g/dL), hemoglobin thresholds triggering a pRBC transfusion in the Premature Infants Needing Transfusion study were dependent on the age and clinical status of the infant (i.e., need for respiratory support) (4). This has led to a reassessment of current transfusion practices in the NICU with the goal being a cleared assessment of the risks and benefits of transfusion in this patient population (101). In several retrospective studies investigating the outcome of very low-birth-weight infants as a function of pRBC transfusion, transfusion of pRBCs has been shown to carry an increased risk of neurocognitive abnormalities, the development of necrotizing enterocolitis, and severe intraventricular hemorrhage (102–108). In spite of the strength of these data supporting the use of a more restrictive transfusion protocol (i.e., use of a lower Hb level to trigger transfusion), adult and pediatric critical care, neonatology, and pediatric hematology/oncology practitioners have been slow to adopt restrictive transfusion practices across patient populations (109–115). An element of this resistance may be the difficulty in identifying which patients may require a higher transfusion threshold because of specific patient characteristics. These factors include, but are not limited to, the need for supplemental oxygen and/or mechanical ventilatory support, the presence of cardiomyopathy, hemodynamic instability or need for vasopressor support, and active bleeding (Table 4). Although it is attractive to assume that intensivists have been more willing to adopt a restrictive transfusion policy in those of their patients deemed to be "stable," the published studies have not addressed this question. Consequently, as many of the published guidelines in neonates and younger children rely heavily on expert opinion, it is very likely that the transfusion thresholds were set arbitrarily higher than needed in order to reach consensus while recognizing that identification of the specific factors that would indicate the need for a transfusion of RBCs (e.g., evidence of anaerobic metabolism in specific tissues) is difficult if not impossible with available technology in individual patients. As we are better able to identify those patients who require and will benefit from a higher circulating oxygen carrying capacity, it is anticipated that transfusion thresholds will become better defined.

TRANSFUSION OF FFP AND CRYOPRECIPITATE

FFP is second only to RBCs in the frequency of transfusion. However, most studies have shown that it is frequently transfused with weak or no accepted indication. FFP is commonly infused in nonbleeding patients to provide intravascular volume, to correct a prolonged prothrombin time (PT), or to decrease the risk of bleeding with a planned invasive procedure (116–120). The evidence supporting these practices and the anticipated benefit is frequently outweighed by the potential risk of FFP infusion (121–123). Correction of a prolonged PT or activated partial thromboplastin time by FFP infusion generally requires a large volume of FFP relative to the patient's blood volume given the low concentration of each clotting factor contained in FFP (i.e., 1 U clotting factor/mL plasma); to increase a deficient clotting factor level by 0.1 U/mL (10% of normal activity level) would require an infusion of approximately 3–5 mL FFP/kg body weight. Randomized clinical trials investigating the efficacy of prophylactic FFP infusions across a broad range of patient age and clinical settings are limited, and those studies when taken in toto have failed to consistently demonstrate benefit (123, 124). Indeed, in a retrospective analysis of adult ICU patients who received FFP prior to central venous cannula placement, those patients who did receive FFP experienced a similar prevalence of bleeding when compared with patients who did not receive FFP, and the prevalence of "acute lung injury" in the 48 hours following FFP infusion was much higher in the transfused group (18% vs 4%; p = 0.02) (125). Other studies have failed to demonstrate a predictable

TABLE 4. American Association of Blood Banks Transfusion Guidelines for RBCs in Infants Younger Than 4 Months

1. Hematocrit < 20% with low reticulocyte count and symptomatic anemia (tachycardia, tachypnea, poor feeding)
2. Hematocrit < 30% and any of the following:
   a. On < 35% oxygen hood[a]
   b. On oxygen by nasal cannula[a]
   c. On continuous positive airway pressure and/or intermittent mandatory ventilation on mechanical ventilation with mean airway pressure < 6 cm of water
   d. With significant tachycardia or tachypnea (heart rate > 180 breaths/min for 24 hr, respiratory rate > 80 breaths/min for 24 hr)
   e. With significant apnea or bradycardia (> 6 episodes in 12 hr or 2 episodes in 24 hr requiring bag and mask ventilation while receiving therapeutic doses of methylxanthines)
   f. With low weight gain (< 10 g/d observed over 4 d while receiving ≥ 100 kcal/kg/d)
3. Hematocrit < 35% and either of the following:
   a. On > 35% oxygen hood[a]
   b. On continuous positive airway pressure/intermittent mandatory ventilation with mean airway pressure ≥ 6–8 cm of water
4. Hematocrit < 45% and either of the following:
   a. On extracorporeal membrane oxygenation[a]
   b. With congenital cyanotic heart disease[a]

[a]These represent weak recommendations with limited supporting data and a wide range of clinical practice. A lower transfusion threshold may be appropriate after careful evaluation of any individual patient.
Data are from Josephson (85).

correction of a prolonged PT with FFP infusions (85, 126, 127). Additionally, these studies have also failed to demonstrate a benefit of prophylactic FFP infusions in patients with an international normalized ratio (INR) between 1.5 and 2.0 calling into question the need to provide FFP support for these patients. Many clinicians use the INR as a surrogate measure of the PT and as such an indicator of a coagulopathic state. However, although the INR is calculated from the PT, it has never been validated as an indicator of bleeding risk (128, 129). A recent consensus conference supported by the AABB addressing the use of FFP (130) found two clinical settings (in addition to the treatment of a bleeding patient with a coagulopathy for which a specific clotting factor concentrate was not available) in which the use of FFP was indicated (Table 3). These were 1) massive transfusion and 2) patients with warfarin-associated intracranial hemorrhage. The group specifically recommended against prophylactic FFP infusions for patients not in these two groups. The AABB guidelines for plasma transfusions in children are similar (Table 5). In spite of these recommendations, plasma usage continues to increase with the primary cause being infusions administered in "nonindicated" clinical settings (131). A solvent/detergent–treated pooled human plasma product has recently been approved for use in the United States by the FDA. It is anticipated that its use will reduce the risk of viral transmission in patients who receive large quantities of plasma in the treatment of undefined or multiple clotting factor deficiencies as can be present in patients with liver disease or trauma requiring massive transfusion. Although this product was developed to reduce FFP-associated pathogen transmission, extensive use of this product in Europe has demonstrated a dramatic reduction in the prevalence of TRALI. Possible mechanisms for this effect include dilution of anti-HLA and antineutrophil antibodies implicated in the induction of TRALI through the pooling of several thousand donors in the production of each batch of solvent/detergent–treated plasma and the removal of any residual contaminating leukocytes in the processed plasma (132).

Recently, a new recombinant clotting factor concentrate of activated factor VII (recombinant-activated human factor VII [rhFVIIa]) has become available and is frequently used in the treatment of refractory bleeding. The approved indications for this agent in the United States and Europe are for the treatment or prevention of bleeding in patients with congenital hemophilia A (factor VIII deficiency) or B (factor IX deficiency) with inhibitors to factor VIII or factor IX, patients with congenital factor VII deficiency, and in acquired hemophilia. An additional indication in Europe is the treatment of bleeding in patients with Glanzmann thrombasthenia. Prothrombin complex concentrates (specifically four-factor concentrates) are the recommended treatment of bleeding in patients on vitamin K antagonist anticoagulation or correction of a prolonged PT secondary to warfarin anticoagulation (133). However, recent statistics from the United States show that less than 5% of rhFVIIa use is for approved indications (133). Although there have been several randomized controlled trials investigating the usefulness of rhFVIIa demonstrating decreased blood loss in several clinical settings, effect on outcome (i.e., mortality) in patients with refractory or severe bleeding has generally not been demonstrated. Additionally, results of this analysis indicated an increased risk of arterial thrombotic events in patients receiving rhFVIIa. Consequently, a large meta-analysis of the use of rhFVIIa for the prevention or treatment of bleeding has failed to support the use of rhFVIIa outside of its current approved indications (134). This lack of documented efficacy of rhFVIIa may reflect limitations in identifying patients who would benefit from this product rather than a lack of efficacy of the product itself. Until those patients who will benefit from this agent can be clearly identified, off-label use of rhFVIIa and other similarly hemostatic blood products should be used with caution.

Cryoprecipitate is a plasma fraction produced by the controlled thawing of frozen plasma that is enriched in factor VIII, von Willebrand factor (vWf), factor XIII, and fibronectin as a result of its production. In addition, cryoprecipitate

TABLE 5. American Association of Blood Banks Transfusion Guidelines for Plasma Products in Neonates and Older Children

FFP

1. Support during treatment of disseminated intravascular dissemination
2. Replacement therapy
   a. When specific factor concentrates are not available, including, but not limited to, antithrombin; protein C or S deficiency; and factor II, factor V, factor X, and factor XI deficiencies
   b. During therapeutic plasma exchange when FFP is indicated (cryoprecipitate-poor plasma, plasma from which the cryoprecipitate has been removed)
3. Reversal of warfarin in an emergency situation, such as before an invasive procedure with active bleeding[a]

Cryoprecipitate

1. Hypofibrinogenemia or dysfibrinogenemia with active bleeding
2. Hypofibrinogenemia or dysfibrinogenemia while undergoing an invasive procedure
3. Factor XIII deficiency with active bleeding or while undergoing an invasive procedure in the absence of factor XIII concentrate
4. Limited directed-donor cryoprecipitate for bleeding episodes in small children with hemophilia A (when recombinant and plasma-derived factor VIII products are not available)
5. In the preparation of fibrin sealant
6. von Willebrand disease with active bleeding but only when both of the following are true:
   a. Desamino-D-arginine vasopressin is contraindicated, not available, or does not elicit response
   b. Virus-inactivated plasma-derived factor VIII concentrate (which contains von Willebrand factor) is not available

FFP = fresh-frozen plasma.

[a]Current recommendations for reversal of warfarin in emergency situations or for bleeding is to infuse four-factor prothrombin complex concentrates (PCC) when available. As of this writing, there are no four-factor PCCs available in the United States. A four-factor PCC product is currently undergoing regulatory review for use in the United States with an indication of emergency reversal of warfarin-induced coagulopathy (Beriplex; CSL Behring, King of Prussia, PA).

FFP is not indicated for volume expansion or enhancement of wound healing. Data are from Josephson (85).

also contains fibrinogen at approximately one-third plasma levels (i.e., 150–350 mg/bag; 1 bag cryoprecipitate is derived from 1 U of plasma). As there are plasma-derived concentrates for vWf and both plasma and recombinant sources for factor VIII, the usual setting in which cryoprecipitate is infused is in individuals with hypofibrinogenemia who cannot tolerate large volumes of plasma. Cryoprecipitate is not appropriate for treatment of global coagulopathies due to the limited spectrum of clotting factors contained (123). The use of cryoprecipitate for the treatment of hypofibrinogenemia may be supplanted by fibrinogen concentrates now being used in Europe and recently approved for use in the United States (135, 136).

PLATELET TRANSFUSIONS

Platelets are obtained either from a single-donated unit of whole blood or by the process of platelet apheresis (thrombocytapheresis). The latter involves processing all of one donor's blood volume (also known as "single donor volume") commonly via a continuous flow cell separator. Platelets harvested from a single unit of donated whole blood are often referred to as "random donor" platelets, whereas those obtained by apheresis are referred to as "single donor" platelets. The latter contain at least 3×10^{11} platelets/container or unit, the precise yield depending on the donor's predonation platelet count. A single donor platelet unit is equivalent to 6–8 random donor platelet units. Donated platelets are stored in an incubator with a slow back-and-forth agitation (to prevent aggregation) with controlled room temperature. Platelets are the only blood component routinely tested for bacterial contamination. As with FFP, platelet transfusions may be administered to prevent/reduce the risk of bleeding (i.e., prophylactic transfusions) or to treat clinically significant bleeding in the presence of thrombocytopenia (i.e., therapeutic transfusions). The indications for each type of platelet transfusion are different with the data supporting prophylactic platelet transfusion guidelines generally being stronger. Prophylactic platelet transfusions to prevent bleeding in patients receiving cancer chemotherapy have represented the standard of care for over 30 years. The data supporting this approach date back to the 1960s and were initially obtained in children and adolescents undergoing induction chemotherapy for acute leukemia (137–139). These data have since been generalized to support the use of platelet transfusions in virtually all thrombocytopenic patients. Although the initial studies produced a recommendation for prophylactic platelet transfusions once the platelet count fell below 20,000/μL (140, 141), subsequent data have resulted in a generally accepted transfusion threshold of 10,000/μL (142, 143). This threshold is commonly increased under conditions assumed to be associated with an increased risk of bleeding (e.g., uncontrolled hypertension, intracranial mass lesion, recent hemorrhage or surgery, recent gastrointestinal hemorrhage, anticipated invasive procedure, etc.). Published guidelines frequently recommend a higher transfusion threshold prior to invasive procedures (e.g., 50,000/μL for procedures such as percutaneous central venous catheter placement, bronchoscopy, endoscopy and solid organ biopsy, and 100,000/mL for CNS procedures) (144–146). However, the data supporting a higher transfusion threshold for prophylactic platelet transfusions for invasive procedure are weak, and a recent retrospective review concluded that higher platelet transfusion threshold (i.e., 50,000/μL) is not superior to a 20,000/μL threshold for prevention of procedural bleeding (137, 147). It must be noted, however, that empiric, uncontrolled data suggest that the risk of bleeding with thrombocytopenia appears to be increased in children younger than 4 years when compared with adults (141, 148), and consequently, a higher threshold for

platelet support may be appropriate in these children. A recent Cochrane Database analysis of published randomized clinical trials addressing efficacy and dosing of prophylactic platelet transfusions in patients with chemotherapy-induced thrombocytopenia concluded that there is no evidence that prophylactic platelet transfusions prevent bleeding, that there is no evidence to support a change in current recommendations of a 10,000/μL platelet count transfusion threshold for prophylactic platelet transfusions (even though the evidence suggesting that a threshold of 10,000/μL is equivalent to a threshold of 20,000/μL is weak), and that the dose of platelets given does not affect the prevalence of patients with major bleeding in patients (149). Two randomized trials comparing therapeutic versus prophylactic platelet transfusions in chemotherapy-induced thrombocytopenia have recently been completed (150, 151). Although all the patients in these studies were adults (i.e., ≥ 16 yr), the findings may in practice be generalized to younger children even in the absence of age-specific data. Each study used a transfusion threshold of 10,000/μL, and neither study demonstrated differences in overall bleeding between the two treatment groups in patients who had undergone an autologous hematopoietic stem cell transplant. However, the authors reached different conclusions. The study reported by Wandt et al (150) concluded that a no-prophylaxis strategy was appropriate for all patients except those receiving treatment for acute myeloid leukemia who did, as a group, experience increased bleeding with the "no-prophylaxis" strategy. However, Stanworth et al (151), in a study comprised similar patient populations, concluded that prophylactic platelet transfusions were still clinically indicated and resulted in a superior outcome (i.e., decreased bleeding) for patients, even though prophylactic platelet transfusions did not prevent bleeding. At the present time, a modification of prophylactic platelet transfusion strategies for thrombocytopenic cancer patients does not appear warranted. Currently, the majority of prophylactic platelet transfusions administered to hematology patients do not conform to recommended guidelines (152).

The evidence defining platelet transfusion practices in neonates is even weaker and more scarce that those for older children with expert opinion setting transfusion practices (153, 154). Current AABB guidelines for platelet transfusions in newborns and children are noted in Table 6. In the only randomized trial assessing the efficacy of platelet transfusions in neonates with moderate thrombocytopenia (platelet count 50,000–150,000/μL), this degree of thrombocytopenia was not found to have a negative effect on outcome of intraventricular/periventricular hemorrhage (155). However, newborns with lower platelet counts were excluded from the study because of a perceived higher risk of hemorrhage. Not surprisingly, surveys of NICUs in the United States, Canada, and Western Europe reveal marked variations in platelet transfusion practice with the most common transfusion threshold at 50,000/μL (or greater) in nonbleeding patients in spite of the lack of data supporting this practice (156–158). Causes for lower than expected rise in platelet count following platelet transfusion include the presence of platelet alloantibodies, splenomegaly, the transfusion of ABO mismatched platelets, and increased platelet consumption as might occur with bleeding, graft-versus-host disease, and vasoocclusive disease (36, 159).

GRANULOCYTE TRANSFUSIONS

The data supporting the transfusion of granulocytes in patients with either neutrophil function defects or neutropenia secondary to cancer chemotherapy are limited (Table 7) (160, 161). Most randomized studies were performed over two decades ago and a relatively small number of granulocytes were infused per transfusion. Consequently, applying the largely negative results from those studies to the current era when our ability to collect greater number of granulocytes may not be appropriate as recent (limited) studies suggest that infusion of a greater number of granulocytes (e.g., > 6 × 109/kg or > 1 × 1010 per infusion) may result in an improved outcome (162–164).There is a similar lack of conclusive evidence supporting granulocyte infusions in septic neonates (165).

MASSIVE TRANSFUSION SUPPORT

Massive transfusion had generally been defined, in adults, as the transfusion of more than 10 U of RBCs within 24 hours,

TABLE 6. Transfusion Guidelines for Platelets in Neonates and Older Children

With thrombocytopenia

1. Platelet count 5,000–10,000/μL with failure of platelet production
2. Platelet count < 30,000/μL in neonate with failure of platelet production
3. Platelet count < 50,000/μL in stable premature infant:
   a. With active bleeding or
   b. Before an invasive procedure, with failure of platelet production
4. Platelet count < 100,000/μL in sick premature infant:
   a. With active bleeding or
   b. Before an invasive procedure in patient with disseminated intravascular coagulation

Without thrombocytopenia

1. Active bleeding in association with qualitative platelet defect
2. Unexplained excessive bleeding in a patient undergoing cardiopulmonary bypass[a]
3. Patient undergoing extracorporeal membrane oxygenation with:
   a. A platelet count of < 100,000/μL or[a]
   b. Higher platelet counts and bleeding[a]

[a]These represent controversial recommendations with little data supporting platelet transfusions under these conditions. A lower transfusion threshold may be appropriate after careful evaluation of any individual patient.

Data are from Josephson (85).

more than 4 U of RBCs in 1 hour, or more than 50% blood volume replacement within 3 hours. However, this definition was not useful in children due to their smaller total blood volume (TBV), and a blood volume–based definition was needed. In children, it has been suggested that massive transfusion occurs when transfusion needs result in the replacement of 1 TBV within 24 hours, 50% TBV within 3 hours, or transfusion rate equal to 10% of TBV every 10 minutes (166). Alternatively, a definition of massive transfusion has been suggested if transfusion needs reach 80 mL/kg body weight of blood products over a 24-hour period. Over the past two to three decades, the approach to transfusion support in individuals who require multiple blood transfusions acutely for the treatment of trauma or massive surgical hemorrhage has evolved from a policy of 1 U of FFP and 1 U of platelets for every 4–5 U of pRBCs transfused to a current 1:1:1 ratio of pRBC:FFP:platelets (166–168). The goal of this approach has been to prevent the development of a coagulopathy as a consequence of platelet and clotting factor depletion secondary to transfusion restricted to pRBCs. Although the transfusion of whole blood could mitigate the development of a coagulopathic state, this would require the transfusion of large volumes (mL for mL) of fresh (< 24 hr old) whole blood which is not generally available in most centers. Although early experience with the more plasma- and platelet-rich transfusion mixture has been positive, it remains to be fully validated by clinical trials. Most of the reports assessing the effectiveness of a "high ratio" blood support program (i.e., a ratio of units of platelets and plasma to RBC units approaching 1:1:1) are retrospective and nonrandomized. To date, only a single randomized trial of a high ratio transfusion support program is found in the literature, and this did not include pediatric patients (169). A recently published prospective observational (nonrandomized) study assessing plasma:RBC transfusion ratios on the outcome of adult trauma patients has confirmed the benefit of high plasma support (plasma:RBC ratio approximately 1:1) during the first 24 hours of care showing an increase in survival (170). This benefit is largely due to improved control of bleeding in these patients. However, for those patients who survived 24 hours, the amount of initial plasma support showed no association with outcome. Observational studies have demonstrated a greater prevalence of acute lung injury (presumably TRALI) in those survivors who received more plasma in their resuscitation fluids. A recently published systematic review of publications reporting on the use of a high platelet:RBC transfusion regimen concluded that at this time, there were insufficient evidence to "strongly support" the routine use of high platelet:RBC ratio resuscitation regimens in trauma patients and that further randomized trials were needed to determine safety and efficacy of such approaches (171).

Due to the lack of high-quality data addressing massive transfusion support in pediatric and neonatal medicine, practices vary widely between institutions, and there is no evidence-based consensus. The reader is referred to the report by Diab et al (166) for an in-depth review of massive transfusion in children and neonates. They present an institutional massive transfusion protocol for infants and children that is weight based and aims to achieve a pRBC:FFP:cryoprecipita te:platelet ratio of approximately 1:1:1.3:1.3. Although they do not report outcomes from this protocol, other institutions have shown that implementation of a massive transfusion protocol can result in more efficient utilization of blood products and reduced hospital expenses (172, 173). Two recently published single-institution retrospective series in which children were treated according to a massive transfusion protocol have demonstrated the feasibility of such a program even if an effect on outcome could not be demonstrated (174, 175). Of interest, in the study by Chidester et al (174), thromboembolic events were noted only in the group of patients whose transfusions were not determined by their transfusion protocol, even though almost all patients in each transfusion group manifested at least one coagulation test abnormality. How to monitor individuals receiving multiple blood product transfusions in order to better determine what products are needed continues to be actively debated without consensus being reached. Several investigators believe methodologies such as thromboelastography or thromboelastometry may ultimately allow clinicians to better direct blood product usage (166, 167). However, further studies are still required to validate the utility of these studies in determining transfusion needs.

TABLE 7. Transfusion Guidelines for Granulocytes in Neonates and Older Children

1. Neonates or children with neutropenia or granulocyte dysfunction with bacterial sepsis and lack of responsiveness to standard therapy
2. Neutropenic neonates or children with fungal disease not responsive to standard therapy

Data are from Josephson (85).

SPECIAL BLOOD PREPARATIONS

The number of blood product units that undergo some sort of special preparation has increased significantly over the past several years. Canada and most European Union countries have moved to a policy of universal leukocyte depletion of RBC units at collection, and this is becoming the norm across the United States. At centers that do not have the capability to leukocyte deplete at collection, the use of leukocyte filters at the time of transfusion is near universal. Although leukocyte depletion at collection was hypothesized to result in a decrease in TRIM and has been associated with decreased morbidity (70–73), this has not been confirmed in other clinical studies (98, 176). However, leukocyte depletion of cellular blood products has resulted in decreased CMV seroconversion of CMV-negative recipients (24, 25, 84). Irradiated blood products are given to immunecompromised patients when there is a risk of engraftment of transfused donor immune-competent cells and the development of TA-GvHD (25, 84, 177). Patients undergoing hematopoietic stem cell transplantation,

TABLE 8. American Association of Blood Banks Guidelines for Irradiation of Blood Products

1. Premature infants weighing < 1,200 g at birth
2. Any patient with
a. Known or suspected cellular immune deficiency
b. Significant immunosuppression related to chemotherapy or radiation treatment
3. Any patient receiving
a. Components from blood relatives
b. HLA-matched or cross-matched platelet components

Data are from Josephson (85).

aggressive combination chemotherapy, or receiving blood from first-degree, second-degree, and third-degree relatives are generally considered candidates to receive irradiated blood products. Additionally, sick, premature infants also fall into this category (**Table 8**). However, just what constitutes "aggressive chemotherapy" and a "sick newborn" is open to interpretation and consequently practices vary. Some centers routinely irradiate all directed-donor blood out of concern that they may not have complete clinical or family information. Individuals who have acquired multiple alloantibodies making identification of cross-match compatible blood difficult may have compatible units of blood stored frozen in glycerin. These units are then thawed and "deglycerolized" before transfusion with acceptable in vivo function (178, 179). Washing units of pRBCs has been shown to decrease the prevalence of allergic reactions by eliminating plasma proteins and has also shown to decrease the potassium concentration in the pRBC unit (180, 181). In addition, washing of cell-saver blood has recently been shown to decrease postoperative inflammation and possibly decrease mortality in pediatric cardiac surgery patients (182, 183). An added benefit of the use of washed cell-saver blood in cardiac surgery is a reduction in donor exposure to patients (183, 184).

CONCLUSIONS

Although progress has been made to develop evidence-based transfusion practices, implementation of these recommendations has been slow, even in medically advanced societies, and when the data supporting these guidelines are strong. Many transfusion guidelines in pediatric populations are similar to those in adult medicine practices. However, in the neonatal population, published recommendations largely rely on expert opinion and are less firm, in spite of good prospective observational studies demonstrating the benefit (or at least lack of harm) with a more restrictive RBC transfusion policy. Across all age groups (neonatal to adult), transfusion practices for platelets and plasma are less likely to conform to published guidelines. In spite of the strength of data addressing RBC transfusion practices, there remains a need for high-quality studies to shape platelet and plasma transfusion practice and guide pediatricians in the transfusion needs of children. Although the studies forming the basis for recommended transfusion practices in adult patients may be appropriate for older children and adolescents, they may not be for newborns and younger children because of developmental differences in physiology. Consequently, there remains a great need for pediatric-specific studies to develop "best practices" in transfusion medicine for children. Furthermore, across all age groups, there needs to be more work directed toward implementation of better evidence-based transfusion practices.

REFERENCES

1. Carson JL, Grossman BJ, Kleinman S, et al; Clinical Transfusion Medicine Committee of the AABB: Red blood cell transfusion: A clinical practice guideline from the AABB. *Ann Intern Med* 2012; 157:49–58
2. Zou S, Dorsey KA, Notari EP, et al: Prevalence, incidence, and residual risk of human immunodeficiency virus and hepatitis C virus infections among United States blood donors since the introduction of nucleic acid testing. *Transfusion* 2010; 50:1495–1504
3. Zou S, Stramer SL, Notari EP, et al: Current incidence and residual risk of hepatitis B infection among blood donors in the United States. *Transfusion* 2009; 49:1609–1620
4. Toy P, Gajic O, Bacchetti P, et al; TRALI Study Group: Transfusion-related acute lung injury: Incidence and risk factors. *Blood* 2012; 119:1757–1767
5. Sayah DM, Looney MR, Toy P: Transfusion reactions: Newer concepts on the pathophysiology, incidence, treatment, and prevention of transfusion-related acute lung injury. *Crit Care Clin* 2012; 28:363–372, v
6. Gauvin F, Robillard P, Hume H, et al: Transfusion-related acute lung injury in the Canadian paediatric population. *Paediatr Child Health* 2012; 17:235–239
7. Li G, Rachmale S, Kojicic M, et al: Incidence and transfusion risk factors for transfusion-associated circulatory overload among medical intensive care unit patients. *Transfusion* 2011; 51:338–343
8. Murphy EL, Kwaan N, Looney MR, et al; TRALI Study Group: Risk factors and outcomes in transfusion-associated circulatory overload. *Am J Med* 2013; 126:357.e29–357.e38
9. Miller ST, Kim HY, Weiner DL, et al; Investigators of the Sickle Cell Disease Clinical Research Network (SCDCRN): Red blood cell alloimmunization in sickle cell disease: Prevalence in 2010. *Transfusion* 2013; 53:704–709
10. O'Suoji C, Liem RI, Mack AK, et al: Alloimmunization in sickle cell anemia in the era of extended red cell typing. *Pediatr Blood Cancer* 2013; 60:1487–1491
11. Vichinsky E, Neumayr L, Trimble S, et al; CDC Thalassemia Investigators: Transfusion complications in thalassemia patients: A report from the Centers for Disease Control and Prevention. *Transfusion* 2013 Jul 25 [Epub ahead of print]
12. Sihler KC, Napolitano LM: Complications of massive transfusion. *Chest* 2010; 137:209–220
13. Diaz J, Acosta F, Parrilla P, et al: Citrate intoxication and blood concentration of ionized calcium in liver transplantation. *Transplant Proc* 1994; 26:3669–3670
14. Marlow SD, House M: Managing apheresis complications during the hematopoietic stem cell collection. *Methods Mol Biol* 2012; 904:93–96
15. Bihl F, Castelli D, Marincola F, et al: Transfusion-transmitted infections. *J Transl Med* 2007; 5:25
16. Abrol P, Lal H: Transfusion-transmitted bacterial, viral and protozoal infections. *In*: Blood Transfusion in Clinical Practice. Kochhar P (Ed). Ninth Edition. Rijeka, Croatia, 2012, pp 143–154
17. Perez P, Salmi LR, Folléa G, et al; BACTHEM Group; French Haemovigilance Network: Determinants of transfusion-associated bacterial contamination: Results of the French BACTHEM Case-Control Study. *Transfusion* 2001; 41:862–872

18. Williamson LM, Lowe S, Love EM, et al: Serious hazards of transfusion (SHOT) initiative: Analysis of the first two annual reports. *BMJ* 1999; 319:16–19
19. Kuehnert MJ, Roth VR, Haley NR, et al: Transfusion-transmitted bacterial infection in the United States, 1998 through 2000. *Transfusion* 2001; 41:1493–1499
20. Blajchman MA, Goldman M: Bacterial contamination of platelet concentrates: Incidence, significance, and prevention. *Semin Hematol* 2001; 38:20–26
21. Wagner SJ: Transfusion-transmitted bacterial infection: Risks, sources and interventions. *Vox Sang* 2004; 86:157–163
22. Eder AF, Kennedy JM, Dy BA, et al; American Red Cross Regional Blood Centers: Limiting and detecting bacterial contamination of apheresis platelets: Inlet-line diversion and increased culture volume improve component safety. *Transfusion* 2009; 49:1554–1563
23. Nichols WG, Price TH, Gooley T, et al: Transfusion-transmitted cytomegalovirus infection after receipt of leukoreduced blood products. *Blood* 2003; 101:4195–4200
24. Vamvakas EC: Is white blood cell reduction equivalent to antibody screening in preventing transmission of cytomegalovirus by transfusion? A review of the literature and meta-analysis. *Transfus Med Rev* 2005; 19:181–199
25. Luban NL, McBride E, Ford JC, et al: Transfusion medicine problems and solutions for the pediatric hematologist/oncologist. *Pediatr Blood Cancer* 2012; 58:1106–1111
26. Zou S, Stramer SL, Dodd RY: Donor testing and risk: Current prevalence, incidence, and residual risk of transfusion-transmissible agents in US allogeneic donations. *Transfus Med Rev* 2012; 26:119–128
27. Attaullah S, Khan S, Khan J: Trend of transfusion transmitted infections frequency in blood donors: Provide a road map for its prevention and control. *J Transl Med* 2012; 10:20
28. Batista-dos-Santos S, Raiol M, Santos S, et al: Real-time PCR diagnosis of Plasmodium vivax among blood donors. *Malar J* 2012; 11:345
29. Sobral PM, Barros AE, Gomes AM, et al: Viral inactivation in hemotherapy: Systematic review on inactivators with action on nucleic acids. *Rev Bras Hematol Hemoter* 2012; 34:231–235
30. Tissot JD, Rubin O, Canellini G: Analysis and clinical relevance of microparticles from red blood cells. *Curr Opin Hematol* 2010; 17:571–577
31. Strobel E: Hemolytic transfusion reactions. *Transfus Med Hemother* 2008; 35:346–353
32. Lavoie J: Blood transfusion risks and alternative strategies in pediatric patients. *Paediatr Anaesth* 2011; 21:14–24
33. Pandey S, Vyas GN: Adverse effects of plasma transfusion. *Transfusion* 2012; 52(Suppl 1):65S–79S
34. Berséus O, Boman K, Nessen SC, et al: Risks of hemolysis due to anti-A and anti-B caused by the transfusion of blood or blood components containing ABO-incompatible plasma. *Transfusion* 2013; 53(Suppl 1):114S–123S
35. Kleinman S, Chan P, Robillard P: Risks associated with transfusion of cellular blood components in Canada. *Transfus Med Rev* 2003; 17:120–162
36. Dunbar NM, Ornstein DL, Dumont LJ: ABO incompatible platelets: Risks versus benefit. *Curr Opin Hematol* 2012; 19:475–479
37. Karafin MS, Blagg L, Tobian AA, et al: ABO antibody titers are not predictive of hemolytic reactions due to plasma-incompatible platelet transfusions. *Transfusion* 2012; 52:2087–2093
38. Heddle NM: Pathophysiology of febrile nonhemolytic transfusion reactions. *Curr Opin Hematol* 1999; 6:420–426
39. King KE, Shirey RS, Thoman SK, et al: Universal leukoreduction decreases the incidence of febrile nonhemolytic transfusion reactions to RBCs. *Transfusion* 2004; 44:25–29
40. Paglino JC, Pomper GJ, Fisch GS, et al: Reduction of febrile but not allergic reactions to RBCs and platelets after conversion to universal prestorage leukoreduction. *Transfusion* 2004; 44:16–24
41. Wang RR, Triulzi DJ, Qu L: Effects of prestorage vs poststorage leukoreduction on the rate of febrile nonhemolytic transfusion reactions to platelets. *Am J Clin Pathol* 2012; 138:255–259
42. Hirayama F: Current understanding of allergic transfusion reactions: Incidence, pathogenesis, laboratory tests, prevention and treatment. *Br J Haematol* 2013; 160:434–444
43. Gilstad CW: Anaphylactic transfusion reactions. *Curr Opin Hematol* 2003; 10:419–423
44. Sandler SG, Mallory D, Malamut D, et al: IgA anaphylactic transfusion reactions. *Transfus Med Rev* 1995; 9:1–8
45. Vassallo RR: Review: IgA anaphylactic transfusion reactions. Part I. Laboratory diagnosis, incidence, and supply of IgA-deficient products. *Immunohematology* 2004; 20:226–233
46. Chapman CE, Stainsby D, Jones H, et al; Serious Hazards of Transfusion Steering Group: Ten years of hemovigilance reports of transfusion-related acute lung injury in the United Kingdom and the impact of preferential use of male donor plasma. *Transfusion* 2009; 49:440–452
47. Wiersum-Osselton JC, Middelburg RA, Beckers EA, et al: Male-only fresh-frozen plasma for transfusion-related acute lung injury prevention: Before-and-after comparative cohort study. *Transfusion* 2011; 51:1278–1283
48. Eder AF, Dy BA, Perez JM, et al: The residual risk of transfusion-related acute lung injury at the American Red Cross (2008-2011): Limitations of a predominantly male-donor plasma mitigation strategy. *Transfusion* 2013; 53:1442–1449
49. Pavenski K, Saidenberg E, Lavoie M, et al: Red blood cell storage lesions and related transfusion issues: A Canadian Blood Services research and development symposium. *Transfus Med Rev* 2012; 26:68–84
50. Doctor A, Spinella P: Effect of processing and storage on red blood cell function in vivo. *Semin Perinatol* 2012; 36:248–259
51. Donadee C, Raat NJ, Kanias T, et al: Nitric oxide scavenging by red blood cell microparticles and cell-free hemoglobin as a mechanism for the red cell storage lesion. *Circulation* 2011; 124:465–476
52. Roback JD: Vascular effects of the red blood cell storage lesion. *Hematology Am Soc Hematol Educ Program* 2011; 2011:475–479
53. Kim-Shapiro DB, Lee J, Gladwin MT: Storage lesion: Role of red blood cell breakdown. *Transfusion* 2011; 51:844–851
54. Weinberg JA, MacLennan PA, Vandromme-Cusick MJ, et al: Microvascular response to red blood cell transfusion in trauma patients. *Shock* 2012; 37:276–281
55. Alexander JT, El-Ali AN, Newman JL, et al: Red blood cells stored for increasing periods produce progressive impairments in nitric oxide-mediated vasodilation. *Transfusion* 2013; 53:2619–2628
56. Tinmouth A, Fergusson D, Yee IC, et al; ABLE Investigators; Canadian Critical Care Trials Group: Clinical consequences of red cell storage in the critically ill. *Transfusion* 2006; 46:2014–2027
57. Lelubre C, Vincent JL: Relationship between red cell storage duration and outcomes in adults receiving red cell transfusions: A systematic review. *Crit Care* 2013; 17:R66
58. Fergusson DA, Hébert P, Hogan DL, et al: Effect of fresh red blood cell transfusions on clinical outcomes in premature, very low-birth-weight infants: The ARIPI randomized trial. *JAMA* 2012; 308:1443–1451
59. Weinberg JA, McGwin G Jr, Vandromme MJ, et al: Duration of red cell storage influences mortality after trauma. *J Trauma* 2010; 69:1427–1431
60. Spinella PC, Carroll CL, Staff I, et al: Duration of red blood cell storage is associated with increased incidence of deep vein thrombosis and in hospital mortality in patients with traumatic injuries. *Crit Care* 2009; 13:R151
61. Katsios C, Griffith L, Spinella P, et al: Red blood cell transfusion and increased length of storage are not associated with deep vein thrombosis in medical and surgical critically ill patients: A prospective observational cohort study. *Crit Care* 2011; 15:R263
62. Cywinski JB, You J, Argalious M, et al: Transfusion of older red blood cells is associated with decreased graft survival after orthotopic liver transplantation. *Liver Transpl* 2013; 19:1181–1188
63. Horvath KA, Acker MA, Chang H, et al: Blood transfusion and infection after cardiac surgery. *Ann Thorac Surg* 2013; 95:2194–2201
64. Purohit S, Alvarez O, O'Brien R, et al: Durable immune response to inactivated H1N1 vaccine is less likely in children with sickle cell anemia receiving chronic transfusions. *Pediatr Blood Cancer* 2012; 59:1280–1283
65. Yazdanbakhsh K, Bao W, Zhong H: Immunoregulatory effects of stored red blood cells. *Hematology Am Soc Hematol Educ Program* 2011; 2011:466–469

66. Neal MD, Raval JS, Triulzi DJ, et al: Innate immune activation after transfusion of stored red blood cells. *Transfus Med Rev* 2013; 27:113–118
67. Howard-Quijano K, Schwarzenberger JC, Scovotti JC, et al: Increased red blood cell transfusions are associated with worsening outcomes in pediatric heart transplant patients. *Anesth Analg* 2013; 116:1295–1308
68. Muszynski J, Nateri J, Nicol K, et al: Immunosuppressive effects of red blood cells on monocytes are related to both storage time and storage solution. *Transfusion* 2012; 52:794–802
69. Hill GE, Frawley WH, Griffith KE, et al: Allogeneic blood transfusion increases the risk of postoperative bacterial infection: A meta-analysis. *J Trauma* 2003; 54:908–914
70. Hébert PC, Fergusson D, Blajchman MA, et al; Leukoreduction Study Investigators: Clinical outcomes following institution of the Canadian universal leukoreduction program for red blood cell transfusions. *JAMA* 2003; 289:1941–1949
71. Friese RS, Sperry JL, Phelan HA, et al: The use of leukoreduced red blood cell products is associated with fewer infectious complications in trauma patients. *Am J Surg* 2008; 196:56–61
72. Phelan HA, Eastman AL, Aldy K, et al: Prestorage leukoreduction abrogates the detrimental effect of aging on packed red cells transfused after trauma: A prospective cohort study. *Am J Surg* 2012; 203:198–204
73. Benson AB, Burton JR Jr, Austin GL, et al: Differential effects of plasma and red blood cell transfusions on acute lung injury and infection risk following liver transplantation. *Liver Transpl* 2011; 17:149–158
74. Hod EA, Zhang N, Sokol SA, et al: Transfusion of red blood cells after prolonged storage produces harmful effects that are mediated by iron and inflammation. *Blood* 2010; 115:4284–4292
75. Hod EA, Spitalnik SL: Stored red blood cell transfusions: Iron, inflammation, immunity, and infection. *Transfus Clin Biol* 2012; 19:84–89
76. Ozment CP, Mamo LB, Campbell ML, et al: Transfusion-related biologic effects and free hemoglobin, heme, and iron. *Transfusion* 2013; 53:732–740
77. Aubron C, Nichol A, Cooper DJ, et al: Age of red blood cells and transfusion in critically ill patients. *Ann Intensive Care* 2013; 3:2
78. Juffermans NP, Vlaar AP, Prins DJ, et al: The age of red blood cells is associated with bacterial infections in critically ill trauma patients. *Blood Transfus* 2012; 10:290–295
79. Manlhiot C, McCrindle BW, Menjak IB, et al: Longer blood storage is associated with suboptimal outcomes in high-risk pediatric cardiac surgery. *Ann Thorac Surg* 2012; 93:1563–1569
80. Inaba K, Branco BC, Rhee P, et al: Impact of the duration of platelet storage in critically ill trauma patients. *J Trauma* 2011; 71:1766–1773
81. Karam O, Tucci M, Bateman ST, et al: Association between length of storage of red blood cell units and outcome of critically ill children: A prospective observational study. *Crit Care* 2010; 14:R57
82. Gauvin F, Spinella PC, Lacroix J, et al; Canadian Critical Care Trials Group and the Pediatric Acute Lung Injury and Sepsis Investigators (PALISI) Network: Association between length of storage of transfused red blood cells and multiple organ dysfunction syndrome in pediatric intensive care patients. *Transfusion* 2010; 50: 1902–1913
83. Whitaker BI, Schlumpf K, Schulman J, et al: Report of the US Department of Health and Human Services. The 2009 National Blood Collection and Utilization Survey Report. Washington, DC, US Department of Health and Human Services, Office of the Assistant Secretary for Health, 2011
84. Josephson, C: Neonatal and pediatric transfusion practice. *In*: AABB Technical Manual. Roback JD (Ed). 17th Edition. Bethesda, MD, AABB, 2011, pp 645–760
85. Istaphanous GK, Wheeler DS, Lisco SJ, et al: Red blood cell transfusion in critically ill children: A narrative review. *Pediatr Crit Care Med* 2011; 12:174–183
86. Sloniewsky D: Anemia and transfusion in critically ill pediatric patients: A review of etiology, management, and outcomes. *Crit Care Clin* 2013; 29:301–317
87. Hébert PC, Wells G, Blajchman MA, et al: A multicenter, randomized, controlled clinical trial of transfusion requirements in critical care. Transfusion Requirements in Critical Care Investigators, Canadian Critical Care Trials Group. *N Engl J Med* 1999; 340:409–417
88. Kirpalani H, Whyte RK, Andersen 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; 149:301–307
89. LacroixJ, Hepert PC, Hutchison JS, et al: Transfusion strategies for patients in pediatric intensive care units. TRIPICU Investigators, the Canadian Critical Care Trials Group, and the Pediatric Acute Lung Injury and Sepsis Investigators Network. *N Engl J Med* 2007; 356:1609–1619
90. Carson JL, Carless PA, Hebert PC: Transfusion thresholds and other strategies for guiding allogeneic red blood cell transfusion. *Cochrane Database Syst Rev* 2012; 4:CD002042
91. Villanueva C, Colomo A, Bosch A, et al: Transfusion strategies for acute upper gastrointestinal bleeding. *N Engl J Med* 2013; 368:11–21
92. Rouette J, Trottier H, Ducruet T, et al; Canadian Critical Care Trials Group; PALISI Network: Red blood cell transfusion threshold in postsurgical pediatric intensive care patients: A randomized clinical trial. *Ann Surg* 2010; 251:421–427
93. Willems A, Harrington K, Lacroix J, et al; TRIPICU investigators; Canadian Critical Care Trials Group; Pediatric Acute Lung Injury and Sepsis Investigators (PALISI) Network: Comparison of two red-cell transfusion strategies after pediatric cardiac surgery: A subgroup analysis. *Crit Care Med* 2010; 38:649–656
94. Cholette JM, Rubenstein JS, Alfieris GM, et al: Children with single-ventricle physiology do not benefit from higher hemoglobin levels post cavopulmonary connection: Results of a prospective, randomized, controlled trial of a restrictive versus liberal red-cell transfusion strategy. *Pediatr Crit Care Med* 2011; 12:39–45
95. de Gast-Bakker DH, de Wilde RB, Hazekamp MG, et al: Safety and effects of two red blood cell transfusion strategies in pediatric cardiac surgery patients: A randomized controlled trial. *Intensive Care Med* 2013; 39:2011–2019
96. Karam O, Tucci M, Ducruet T, et al; Canadian Critical Care Trials Group; PALISI Network: Red blood cell transfusion thresholds in pediatric patients with sepsis. *Pediatr Crit Care Med* 2011; 12:512–518
97. Guzzetta NA: Benefits and risks of red blood cell transfusion in pediatric patients undergoing cardiac surgery. *Paediatr Anaesth* 2011; 21:504–511
98. Kneyber MC, Grotenhuis F, Berger RF, et al: Transfusion of leukocyte-depleted RBCs is independently associated with increased morbidity after pediatric cardiac surgery. *Pediatr Crit Care Med* 2013; 14:298–305
99. Lacroix J: Red cell transfusion: Risk marker or risk factor in cardiac children? *Pediatr Crit Care Med* 2013; 14:330–331
100. Valieva OA, Strandjord TP, Mayock DE, et al: Effects of transfusions in extremely low birth weight infants: A retrospective study. *J Pediatr* 2009; 155:331–337.e1
101. Christensen RD, Del Vecchio A, Ilstrup SJ: More clearly defining the risks of erythrocyte transfusion in the NICU. *J Matern Fetal Neonatal Med* 2012; 25:90–92
102. Whyte R, Kirpalani H: Low versus high hemoglobin concentration threshold for blood transfusion for preventing morbidity and mortality in very low birth weight infants. *Cochrane Database Syst Rev* 2011; 11:CDC000512
103. Christensen RD: Associations between "early" red blood cell transfusion and severe intraventricular hemorrhage, and between "late" red blood cell transfusion and necrotizing enterocolitis. *Semin Perinatol* 2012; 36:283–289
104. Paul DA, Mackley A, Novitsky A, et al: Increased odds of necrotizing enterocolitis after transfusion of red blood cells in premature infants. *Pediatrics* 2011; 127:635–641
105. Demirel G, Celik IH, Aksoy HT, et al: Transfusion-associated necrotising enterocolitis in very low birth weight premature infants. *Transfus Med* 2012; 22:332–337
106. Bak SY, Lee S, Park JH, et al: Analysis of the association between necrotizing enterocolitis and transfusion of red blood cell in very

low birth weight preterm infants. *Korean J Pediatr* 2013; 56: 112–115

107. McCoy TE, Conrad AL, Richman LC, et al: Neurocognitive profiles of preterm infants randomly assigned to lower or higher hematocrit thresholds for transfusion. *Child Neuropsychol* 2011; 17:347–367
108. Whyte RK: Neurodevelopmental outcome of extremely low-birth-weight infants randomly assigned to restrictive or liberal hemoglobin thresholds for blood transfusion. *Semin Perinatol* 2012; 36:290–293
109. Spinella PC, Dressler A, Tucci M, et al; Pediatric Acute Lung Injury and Sepsis Investigators Network: Survey of transfusion policies at US and Canadian children's hospitals in 2008 and 2009. *Transfusion* 2010; 50:2328–2335
110. Leal-Noval SR, Arellano-Orden V, Maestre-Romero A, et al: Impact of national transfusion indicators on appropriate blood usage in critically ill patients. *Transfusion* 2011; 51:1957–1965
111. Guillén U, Cummings JJ, Bell EF, et al: International survey of transfusion practices for extremely premature infants. *Semin Perinatol* 2012; 36:244–247
112. Dallman MD, Liu X, Harris AD, et al: Changes in transfusion practice over time in the PICU. *Pediatr Crit Care Med* 2013; 14:843–850
113. Murphy DJ, Needham DM, Netzer G, et al: RBC transfusion practices among critically ill patients: Has evidence changed practice? *Crit Care Med* 2013; 41:2344–2353
114. Wong EC, Perez-Albuerne E, Moscow JA, et al: Transfusion management strategies: A survey of practicing pediatric hematology/oncology specialists. *Pediatr Blood Cancer* 2005; 44:119–127
115. Bercovitz RS, Quinones RR: A survey of transfusion practices in pediatric hematopoietic stem cell transplant patients. *J Pediatr Hematol Oncol* 2013; 35:e60–e63
116. Muntean W: Fresh frozen plasma in the pediatric age group and in congenital coagulation factor deficiency. *Thromb Res* 2002; 107(Suppl 1):S29–S32
117. Goldenberg NA, Manco-Johnson MJ: Pediatric hemostasis and use of plasma components. *Best Pract Res Clin Haematol* 2006; 19:143–155
118. Karam O, Lacroix J, Robitaille N, et al: Association between plasma transfusion and clinical outcome in critically ill children: A prospective observational study. *Vox Sang* 2013; 104:1–8
119. Puetz J, Witmer C, Huang YS, et al: Widespread use of fresh frozen plasma in US children's hospitals despite limited evidence demonstrating a beneficial effect. *J Pediatr* 2012; 160:210–215.e1
120. Motta M, Del Vecchio A, Radicioni M: Clinical use of fresh-frozen plasma and cryoprecipitate in neonatal intensive care unit. *J Matern Fetal Neonatal Med* 2011; 24(Suppl 1):129–131
121. Gajic O, Dzik WH, Toy P: Fresh frozen plasma and platelet transfusion for nonbleeding patients in the intensive care unit: Benefit or harm? *Crit Care Med* 2006; 34:S170–S173
122. Verghese SG: Elective fresh frozen plasma in the critically ill: What is the evidence? *Crit Care Resusc* 2008; 10:264–268
123. Stanworth SJ: The evidence-based use of FFP and cryoprecipitate for abnormalities of coagulation tests and clinical coagulopathy. *Hematology Am Soc Hematol Educ Program* 2007; 179–186
124. Stanworth SJ, Brunskill SJ, Hyde CJ, et al: Is fresh frozen plasma clinically effective? A systematic review of randomized controlled trials. *Br J Haematol* 2004; 126:139–152
125. Dara SI, Rana R, Afessa B, et al: Fresh frozen plasma transfusion in critically ill medical patients with coagulopathy. *Crit Care Med* 2005; 33:2667–2671
126. Abdel-Wahab OI, Healy B, Dzik WH: Effect of fresh-frozen plasma transfusion on prothrombin time and bleeding in patients with mild coagulation abnormalities. *Transfusion* 2006; 46:1279–1285
127. Chowdhury P, Saayman AG, Paulus U, et al: Efficacy of standard dose and 30 ml/kg fresh frozen plasma in correcting laboratory parameters of haemostasis in critically ill patients. *Br J Haematol* 2004; 125:69–73
128. Segal JB, Dzik WH; Transfusion Medicine/Hemostasis Clinical Trials Network: Paucity of studies to support that abnormal coagulation test results predict bleeding in the setting of invasive procedures: An evidence-based review. *Transfusion* 2005; 45:1413–1425
129. Keeling D: International normalized ratio in patients not on vitamin K antagonists. *J Thromb Haemost* 2007; 5:188–189
130. Roback JD, Caldwell S, Carson J, et al; American Association for the Study of Liver; American Academy of Pediatrics; United States Army; American Society of Anesthesiology; American Society of Hematology: Evidence-based practice guidelines for plasma transfusion. *Transfusion* 2010; 50:1227–1239
131. Stanworth SJ, Walsh TS, Prescott RJ, et al; Intensive Care Study of Coagulopathy (ISOC) Investigators: A national study of plasma use in critical care: Clinical indications, dose and effect on prothrombin time. *Crit Care* 2011; 15:R108
132. Flesland O: A comparison of complication rates based on published haemovigilance data. *Intensive Care Med* 2007; 33(Suppl 1):S17–21
133. Goodnough LT: A reappraisal of plasma, prothrombin complex concentrates, and recombinant factor VIIa in patient blood management. *Crit Care Clin* 2012; 28:413–426, vi
134. Simpson E, Lin Y, Stanworth S, et al: Recombinant factor VIIa for the prevention and treatment of bleeding in patients without haemophilia. *Cochrne Database Syst Rev* 2012; 3:CDC005011
135. Kozek-Langenecker S, Sørensen B, Hess JR, et al: Clinical effectiveness of fresh frozen plasma compared with fibrinogen concentrate: A systematic review. *Crit Care* 2011; 15:R239
136. Warmuth M, Mad P, Wild C: Systematic review of the efficacy and safety of fibrinogen concentrate substitution in adults. *Acta Anaesthesiol Scand* 2012; 56:539–548
137. Bercovitz RS, Josephson CD: Thrombocytopenia and bleeding in pediatric oncology patients. *Hematology Am Soc Hematol Educ Program* 2012; 2012:499–505
138. Freireich TJ, Klimann A, Gaydos LA, et al: Response to repeated platelet transfusions from the same donor. *Ann Intern Med* 1963; 59:277–87
139. Djerassi I, Farber S, Evans AE: Transfusions of fresh platelet concentrates to patients with secondary thrombocytopenia. *N Engl J Med* 1963; 268:221–226
140. Gaydos LA, Freireich EJ, Mantel N: The quantitative relation between platelet count and hemorrhage in patients with acute leukemia. *N Engl J Med* 1962; 266:905–909
141. Roy AJ, Jaffe N, Djerassi I: Prophylactic platelet transfusions in children with acute leukemia: A dose response study. *Transfusion* 1973; 13:283–290
142. Heddle NM, Cook RJ, Tinmouth A, et al; SToP Study Investigators of the BEST Collaborative: A randomized controlled trial comparing standard- and low-dose strategies for transfusion of platelets (SToP) to patients with thrombocytopenia. *Blood* 2009; 113:1564–1573
143. Slichter SJ, Kaufman RM, Assmann SF, et al: Dose of prophylactic platelet transfusions and prevention of hemorrhage. *N Engl J Med* 2010; 362:600–613
144. Schiffer CA, Anderson KC, Bennett CL, et al; American Society of Clinical Oncology: Platelet transfusion for patients with cancer: Clinical practice guidelines of the American Society of Clinical Oncology. *J Clin Oncol* 2001; 19:1519–1538
145. British Committee for Standards in Hematology, Blood Transfusion Task Force: Guidelines for the use of platelet transfusions. *Br J Haematol* 2003; 122:10–23
146. Razzaghi A, Barkun AN: Platelet transfusion threshold in patients with upper gastrointestinal bleeding: A systematic review. *J Clin Gastroenterol* 2012; 46:482–486
147. Zeidler K, Arn K, Senn O, et al: Optimal preprocedural platelet transfusion threshold for central venous catheter insertions in patients with thrombocytopenia. *Transfusion* 2011; 51:2269–2276
148. Josephson CD, Granger S, Assmann SF, et al: Bleeding risks are higher in children versus adults given prophylactic platelet transfusions for treatment-induced hypoproliferative thrombocytopenia. *Blood* 2012; 120:748–760
149. Estcourt L, Stanworth S, Doree C, et al: Prophylactic platelet transfusion for prevention of bleeding in patients with haematological disorders after chemotherapy and stem cell transplantation. *Cochrane Database Syst Rev* 2012; 5:CD004269
150. Wandt H, Schaefer-Eckart K, Wendelin K, et al; Study Alliance Leukemia: Therapeutic platelet transfusion versus routine

prophylactic transfusion in patients with haematological malignancies: An open-label, multicentre, randomised study. *Lancet* 2012; 380:1309–1316

151. Stanworth SJ, Estcourt LJ, Powter G, et al; TOPPS Investigators: A no-prophylaxis platelet-transfusion strategy for hematologic cancers. *N Engl J Med* 2013; 368:1771–1780
152. Estcourt LJ, Birchall J, Lowe D, et al: Platelet transfusions in haematology patients: Are we using them appropriately? *Vox Sang* 2012; 103:284–293
153. Del Vecchio A, Motta M: Evidence-based platelet transfusion recommendations in neonates. *J Matern Fetal Neonatal Med* 2011; 24(Suppl 1):38–40
154. Stanworth SJ: Thrombocytopenia, bleeding, and use of platelet transfusions in sick neonates. *Hematology Am Soc Hematol Educ Program* 2012; 2012:512–516
155. Andrew M, Vegh P, Caco C, et al: A randomized, controlled trial of platelet transfusions in thrombocytopenic premature infants. *J Pediatr* 1993; 123:285–291
156. Josephson CD, Su LL, Christensen RD, et al: Platelet transfusion practices among neonatologists in the United States and Canada: Results of a survey. *Pediatrics* 2009; 123:278–285
157. Dohner ML, Wiedmeier SE, Stoddard RA, et al: Very high users of platelet transfusions in the neonatal intensive care unit. *Transfusion* 2009; 49:869–872
158. Cremer M, Sola-Visner M, Roll S, et al: Platelet transfusions in neonates: Practices in the United States vary significantly from those in Austria, Germany, and Switzerland. *Transfusion* 2011; 51:2634–2641
159. Slichter SJ: Evidence-based platelet transfusion guidelines. *Hematology Am Soc Hematol Educ Program* 2007:172–178
160. Massey E, Paulus U, Doree C, et al: Granulocyte transfusions for preventing infections in patients with neutropenia or neutrophil dysfunction. *Cochrane Database Syst Rev* 2009; 1:005341
161. Strauss RG: Role of granulocyte/neutrophil transfusions for haematology/oncology patients in the modern era. *Br J Haematol* 2012; 158:299–306
162. Seidel MG, Minkov M, Witt V, et al: Granulocyte transfusions in children and young adults: Does the dose matter? *J Pediatr Hematol Oncol* 2009; 31:166–172
163. Ofan Y, Aviv I, Oliven A, et al: Granulocyte transfusions for neutropenic patients following life-threatening infections: A single centre experience in 47 patients, who received 348 granulocyte transfusions. *Vox Sang* 2007; 93:363–369
164. Cherif H, Axdorph U, Kalin M, et al: Clinical experience of granulocyte transfusion in the management of neutropenic patients with haematological malignancies and severe infection. *Scand J Infect Dis* 2013; 45:112–116
165. Pammi M, Brocklehurst P: Granulocyte transfusions for neonates with confirmed or suspected sepsis and neutropenia. *Cochrane Database Syst Rev* 2011; 10:CDC003956
166. Diab YA, Wong EC, Luban NL: Massive transfusion in children and neonates. *Br J Haematol* 2013; 161:15–26
167. Spinella PC, Holcomb JB: Resuscitation and transfusion principles for traumatic hemorrhagic shock. *Blood Rev* 2009; 23: 231–240
168. Ledgerwood AM, Blaisdell W: Coagulation challenges after severe injury with hemorrhagic shock. *J Trauma Acute Care Surg* 2012; 72:1714–1718
169. Reed RL 2nd, Ciavarella D, Heimbach DM, et al: Prophylactic platelet administration during massive transfusion. A prospective, randomized, double-blind clinical study. *Ann Surg* 1986; 203:40–48
170. Holcomb JB, del Junco DJ, Fox EE, et al; PROMMTT Study Group: The prospective, observational, multicenter, major trauma transfusion (PROMMTT) study: Comparative effectiveness of a time-varying treatment with competing risks. *JAMA Surg* 2013; 148: 127–136
171. Hallet J, Lauzier F, Mailloux O, et al: The use of higher platelet: RBC transfusion ratio in the acute phase of trauma resuscitation: A systematic review. *Crit Care Med* 2013; 41:2800–2811
172. Brown RE, Dorion RP, Trowbridge C, et al: Algorithmic and consultative integration of transfusion medicine and coagulation: A personalized medicine approach with reduced blood component utilization. *Ann Clin Lab Sci* 2011; 41:211–216
173. Khan S, Allard S, Weaver A, et al: A major haemorrhage protocol improves the delivery of blood component therapy and reduces waste in trauma massive transfusion. *Injury* 2013; 44:587–592
174. Chidester SJ, Williams N, Wang W, et al: A pediatric massive transfusion protocol. *J Trauma Acute Care Surg* 2012; 73:1273–1277
175. Hendrickson JE, Shaz BH, Pereira G, et al: Implementation of a pediatric trauma massive transfusion protocol: One institution's experience. *Transfusion* 2012; 52:1228–1236
176. Tasaki T, Ohto H, Sasaki S, et al: Significance of pre-storage leucoreduction for autologous blood. *Vox Sang* 2009; 96:226–233
177. Fast LD: Developments in the prevention of transfusion-associated graft-versus-host disease. *Br J Haematol* 2012; 158:563–568
178. Valeri CR, Pivacek LE, Gray AD, et al: The safety and therapeutic effectiveness of human red cells stored at –80 degrees C for as long as 21 years. *Transfusion* 1989; 29:429–437
179. Henkelman S, Lagerberg JW, Graaff R, et al: The effects of cryopreservation on red blood cell rheologic properties. *Transfusion* 2010; 50:2393–2401
180. Tobian AA, Savage WJ, Tisch DJ, et al: Prevention of allergic transfusion reactions to platelets and red blood cells through plasma reduction. *Transfusion* 2011; 51:1676–1683
181. Vraets A, Lin Y, Callum JL: Transfusion-associated hyperkalemia. *Transfus Med Rev* 2011; 25:184–196
182. Waters JH, Tuohy MJ, Hobson DF, et al: Bacterial reduction by cell salvage washing and leukocyte depletion filtration. *Anesthesiology* 2003; 99:652–655
183. Cholette JM, Henrichs KF, Alfieris GM, et al: Washing red blood cells and platelets transfused in cardiac surgery reduces postoperative inflammation and number of transfusions: Results of a prospective, randomized, controlled clinical trial. *Pediatr Crit Care Med* 2012; 13:290–299
184. Cholette JM, Powers KS, Alfieris GM, et al: Transfusion of cell saver salvaged blood in neonates and infants undergoing open heart surgery significantly reduces RBC and coagulant product transfusions and donor exposures: Results of a prospective, randomized, clinical trial. *Pediatr Crit Care Med* 2013; 14:137–147