Guidelines for assessing appropriateness of pediatric transfusion

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Recent advances in donor screening, blood testing before transfusion, and modifications made to collected components, with irradiation as an example, make the blood supply safer than ever before. Nonetheless, blood components should only be transfused when risks and benefits have been carefully weighed.[1-5] Particular consideration is required when transfusing preterm infants, the most heavily transfused patient group in the tertiary care setting, with the greatest potential for longevity.[6-9] Recent data have demonstrated that transfusion practices vary tremendously, particularly in preterm infants.[10] Establishing criteria for appropriate transfusion practice is important to ensure that clear-cut benefits are derived from the administration of this sometimes limited resource. In addition, the Joint Commission for the Accreditation of Health Care Organizations requires review of the appropriateness of all transfusions to correct transfusion practices that deviate from standard practice and that the use of blood and blood components be reviewed on a continuing basis, as part of a required performance-improvement function.[11] Review for under-transfusion should also be considered.

ABBREVIATIONS: DIC = disseminated intravascular coagulation; ECMO = extracorporeal membrane oxygenation; ITP = idiopathic thrombocytopenic purpura; PCC = prothrombin complex concentrates; TA-GVHD = transfusion-associated GVHD; UCB = umbilical cord blood; WB = whole blood.

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This paper has been written to help transfusion services and transfusion committees have a starting point to establish their own audit guidelines. References are included for each institution to evaluate as they embark upon this process. Transfusion medicine specialists who are not well versed in the special needs of neonates, as well as generalists who direct the transfusion service but lack specific expertise, can use this document and its references to initiate guideline development. These guidelines, representing the opinions of the authors and incorporating evidence-based data where it exists, have been designed to facilitate uniform transfusion practice whenever possible. Elements of transfusion practice, which should also be reviewed, include the documentation of informed consent as well as completion of transfusion records.[11,12]

Transfusion practice guidelines *should not serve* as medical indications for transfusion, nor can they be all inclusive. The appropriateness for most of these transfusion guidelines has been demonstrated in published reports. It should be pointed out that neonatal transfusion medicine is an evolving discipline. Because of the fragile clinical status of these small patients, it is difficult to design randomized controlled trials with enough statistical power to produce ironclad data. A great majority of the papers written about neonatal transfusion are practice oriented and derived by consensus. Therefore, adapting published literature to be used when creating transfusion audit guidelines for neonates should be done on an individualized basis.[13-15] In certain selected clinical situations, transfusion events that deviate from the proposed guidelines may be considered appropriate. Scientific data, as well as a review of the patient's chart, can be helpful in evaluating the appropriateness of transfusion events that deviate from guidelines.[16,17]

Physicians should clearly document, in writing, the indication for each transfusion administered and perform an assessment of the efficacy of the transfusion (e.g., relief of symptoms of anemia, cessation of bleeding). Parental informed consent, a process that includes delineating risks, benefits, and alternatives to transfusion, must be obtained in accordance with all applicable local, state, and national regulatory requirements. Ob-

taining proper informed consent is also an ethical and moral obligation.[11,18]

The following suggested criteria for reviewing appropriateness of pediatric transfusions apply to infants and children of all ages except when otherwise stated. Statements found in tables *in italics* require additional definition(s) by a local transfusion committee. Such additional definition(s) should be consistent with the general objective of these guidelines, namely the intent to provide optimal patient care consistent with local standards of practice, in each institution. The current edition of the *Standards of the American Association of Blood Banks* can be used in conjunction with this document to supplement related topics.[19] General textbooks and review articles cited throughout can also be helpful. A list of these is extracted at the end of the text. Alternatives to transfusion, as well as specialized components and their indications, are also included for completeness, as transfusion committees consider what to incorporate into their own audit guidelines.

TRANSFUSION OF WHOLE BLOOD OR RECONSTITUTED WHOLE BLOOD

Before the introduction of component therapy, whole blood (WB) was the mainstay of transfusion support. The storage requirements of WB prevent optimal recovery of the labile clotting FV (in vivo t_{50} = 4.5-36 hr, in vitro t_{50} = 10-14 days) and FVIII (in vivo t_{50} = 8-12 hr, in vitro t_{50} = 7 days).[20] Likewise, platelets lose their discoid shape, resulting in acceleration of the platelet storage defect that leads to decreased in vivo survival, when stored in a refrigerated environment.[21] While trying to optimize the number of transfusable components obtained from a single blood donor and to treat patients' specific needs, most blood collected is now made into components. Therefore, WB is considered a special request and usually must be ordered in advance. If it is not available, it can be reconstituted by combining a unit of RBCs with a compatible unit of FFP or plasma frozen within 24 hours (frozen plasma). Frozen plasma contains all the stable clotting proteins found in FFP but in one study was found to have 15 to 20 percent lower levels of FVIII after 24 hours of liquid storage. This difference was felt to be significant only in the setting of FVIII replacement but would not pose a problem for other indications for FFP replacement.[20,22] Because reconstitution in this manner will double the number of donors the patient is exposed to, the potential benefits should be weighed against this increased risk of exposure. In the setting of massive transfusion or acute blood loss, WB, if available, is used by many practitioners as the component of choice as opposed to replacement with individual components. The transfusion of WB may be appropriate in the circumstances listed in Table 1.[23]

TABLE 1. Guidelines for transfusion of WB or reconstituted WB

1. Exchange transfusion for
   - HDN
   - *Hyperbilirubinemia* with risk of kernicterus
2. After cardiopulmonary bypass[24,25]
3. ECMO
4. Massive transfusion*

* Defined as transfusion of >1 blood volume in 24 hr.

One of the more controversial aspects of WB transfusion is the use of fresh WB after cardiopulmonary bypass in patients undergoing complex cardiac surgery. Some investigators found improved hemostasis in the perioperative period when WB, less than 48 hours old, was transfused.[24,25] Data suggest that improved platelet function was responsible for the lower blood loss seen in children under 2 years old undergoing complex cardiac surgery.[24,25] Obviously, the logistics of obtaining blood less than 48 hours old with current blood-manufacturing requirements makes it difficult to meet these needs on a consistent basis.

TRANSFUSION OF RBCS IN PATIENTS LESS THAN 4 MONTHS OF AGE

Criteria for transfusion of patients less than 4 months of age are different from those for older children. Infants of this age group are considered separately, not only due to their small blood volume but also due to unique physiologic factors, such as decreased production of endogenous EPO in the premature infant in response to anemia and physiologic anemia of infancy. Another important difference is their humoral immune systems, making them inefficient at forming antibodies in response to antigenic RBC challenges, when compared with older infants and children.[7,8] Because these infants are some of the most heavily transfused patients in the hospital, their needs require special attention.[9] Practice is variable and criteria should be developed for each institution. There are a variety of published guidelines available, many derived empirically by panels of "experts" without rigorous scientific methods. Of note, the practice of transfusing RBCs solely for the purpose of replacing iatrogenic blood loss is no longer common.[13,26-29] Transfusion may be appropriate as summarized in Table 2.[9,29]

RBCs are routinely produced from WB collection and are stored in one of several anticoagulant and/or preservative solutions, which have varying compositions and shelf lives. For simple, small-volume transfusion, a dose of 5 to 15 mL per kg is administered, whereas larger-volume transfusions are used in hypotensive shock, extracorporeal membrane oxygenation (ECMO), exchange transfusion, and cardiopulmonary bypass. Donor expo-

TABLE 2. Guidelines for transfusion of RBCs in patients less than four months of age

1. Hct <20% with *low reticulocyte count* and symptoms of anemia*
2. Hct <30% with an infant:
   - On <35% hood O_2
   - On O_2 by nasal cannula
   - On continuous positive airway pressure and/or intermittent mandatory ventilation with mechanical ventilation with mean airway pressure <6 cm H_2O
   - With *significant* apnea or bradycardia†
   - With *significant* tachycardia or tachypnea‡
   - With low weight gain§
3. Hct <35% with an infant:
   - On >35% hood O_2
   - On continuous positive airway pressure/intermittent mandatory ventilation with mean airway pressure ≥6-8 cm H_2O
4. Hct <45% with an infant:
   - On ECMO
   - With congenital cyanotic heart disease

* Tachycardia, tachypnea, poor feeding.
† More than six episodes in 12 hr or two episodes in 24 hr requiring bag and mask ventilation while receiving therapeutic doses of methylxanthines.
‡ Heart rate >180 beats/min for 24 hr; respiratory rate >80 breaths/min for 24 hr.
§ Gain of <10 g/day observed over 4 days while receiving ≥100 kcal/kg/day.

sure has been reduced by dedicating specific units to neonates, while taking advantage of the longer shelf life and improved viability of RBCs stored in additive solutions, which prolong the RBC shelf life to 42 days.[30-33] Initially, there were concerns about the use of AS-1 in premature infants due to the presence of mannitol with its concomitant diuretic effects (750 mg/100 mL AS-1 vs. none in CPDA-1) and higher quantities of adenine (27 mg/100 mL AS-1 vs. 17.3 mg/63 mL CPDA-1). Both adenine and mannitol have been associated with renal toxicity in high concentrations.[20,34-36] A variety of clinical trials and mathematical models have concluded that blood preserved in AS is safe when used for small-volume (5-15 mL/kg) transfusions and may actually improve blood glucose homeostasis.[35,36] The safety and efficacy of the use of AS-3, which contains no mannitol but 30 mg per 100 mL AS-3 of adenine, has also been shown to be safe for small-volume neonatal transfusion.[37,38] AS-5 is also used in blood collection, but there are currently no published studies in the neonatal population. Because its composition is similar to the other solutions, it may prove to have a similar safety profile. The transfusion service should make the clinician aware of the anticoagulant and/or preservative used for storage of RBCs, particularly for transfusion of the neonate.

Many transfusion services provide blood that lacks Hb S for select neonatal patients. Though there are no randomized controlled trials supporting or refuting this practice, it is generally recommended that blood lacking Hb S be used in massive or exchange transfusion of the newborn, based on isolated case reports of donor blood sickling in patients with poor oxygenation.[26]

TRANSFUSION OF RBCs IN CHILDREN GREATER THAN 4 MONTHS OF AGE

The guidelines for assessing transfusion in this group of patients are found in Table 3[5,26,39] and reflect those used for adults. As with other forms of transfusion therapy, RBC transfusion should be based on clinical signs and symptoms of anemia, not laboratory values alone.[5,40-44]

RBC transfusion plays an integral role in the treatment of many clinical complications of sickle cell disease.[45,46] Raising the Hct and lowering the percentage of Hb S to levels between 20 and 50 percent are important in the management of complications.[45-48] These complications include cerebrovascular accident, acute chest syndrome, splenic sequestration, and recurrent priapism. Preoperative transfusion, aimed at achieving a Hb level of 10 g per dL in patients who will undergo general anesthesia, has been shown to decrease the risk of perioperative complications, regardless of percentages.[47-49] Simple or exchange transfusion, to reach a Hb S of less than 30 percent, followed by transfusion every 3 to 4 weeks, has also been shown to reduce the risk of first stroke in children with abnormally high blood-flow velocity on transcranial Doppler ultrasonography.[50]

In this population, failure to achieve expected increments or decreases in Hb concentrations after transfusion may be due to delayed hemolytic transfusion reactions in the absence of detectable antibody.[51-53]

TABLE 3. Guidelines for transfusion of RBCS in patients more than four months of age (details in text)

1. Emergency surgical procedure in patient with *significant preoperative anemia*
2. Preoperative *anemia* when other corrective therapy is not available
3. Intraoperative blood loss ≥15% total blood volume
4. Hct <24%:
   - In perioperative period, with *signs and symptoms of anemia*
   - While on chemotherapy/radiotherapy
   - Chronic congenital or acquired *symptomatic* anemia
5. Acute blood loss with *hypovolemia* not responsive to other therapy
6. Hct <40% with:
   - *Severe pulmonary disease*
   - ECMO
7. Sickle cell disease:
   - Cerebrovascular accident
   - Acute chest syndrome
   - Splenic sequestration
   - Recurrent priapism
   - Preoperatively when general anesthesia is planned to reach Hb = 10 g/dL
8. Chronic transfusion programs for disorders of RBC production (such as β-thalassemia major and Diamond-Blackfan syndrome unresponsive to therapy)[39]

Therefore, conservative transfusion management, including refraining from transfusion in asymptomatic individuals, is crucial. In various case reports, corticosteroids have been used successfully to treat this immune-based hemolysis.[53] Baseline RBC antigen typing (e.g., Rh, Kell) should be obtained before transfusion to aid in subsequent selection of blood as antibodies develop.

TRANSFUSION OF PLATELET CONCENTRATES

The guidelines for transfusion in older infants and children are adapted from those used for adults.[42,54,55] Platelet transfusion guidelines are summarized in Tables 4 and 5. Note that routine use of platelets is not indicated in patients with autoimmune thrombocytopenia and/or idiopathic thrombocytopenic purpura (ITP) on the basis of platelet count alone because the autoantibodies present in the patient will most likely destroy the transfused platelets. In addition, some of these patients will have normal bleeding times with adequate hemostasis in the face of thrombocytopenia.[9,23,56] Platelet transfusion is also contraindicated for patients with thrombotic thrombocytopenic purpura because this has been associated with thrombosis after administration.[20]

The normal platelet count of a neonate is the same as that of older children and adults. When calculating the dose of platelets for a child, 5 to 10 mL per kg of either a random donor or apheresis unit should result in a rise in platelet count of 50 to 100 $\times$ 10^9 per L. For children over 10 kg, a dose of 1 unit per 10 kg should produce the same results. This response can be blunted if the infant or child is septic, febrile, has disseminated intravascular coagulation, or shows other evidence of consumptive coagulopathy.[56] Volume reduction of platelet concentrates is not usually necessary because using the recommended dosages should yield an adequate rise. For small-volume patients, though, it can be helpful as a means to remove incompatible plasma given that there have been published reports of hemolysis after transfusion of platelets that are ABO mismatched.[57-59] Volume reduction is also indicated in premature infants with renal ischemia, or compromised cardiac function, who are at risk for volume instability.[7] Methods for volume reduction of platelets have been published, but there is no consensus regarding optimal centrifugation rates and practice varies.[20]

TABLE 4. Guidelines for platelet transfusion in children

1. Platelet count 5-10 $\times$ 10^9/L with failure of platelet production
2. Platelet count <30 $\times$ 10^9/L in neonate with failure of platelet production[56]
3. Platelet count <50 $\times$ 10^9/L in stable premature infant:
   - With *active bleeding*
   - Invasive procedure with failure of platelet production
4. Platelet count <100 $\times$ 10^9 in *sick* premature infant:
   - With *active bleeding*
   - Invasive procedure in patient with DIC

TABLE 5. Guidelines for platelet transfusion in patients with a normal platelet count

1. Active bleeding in association with a qualitative platelet defect
2. Unexplained, *excessive bleeding* in a patient undergoing cardiopulmonary bypass
3. Patient undergoing ECMO:
   - With a platelet count of <100 $\times$ 10^9/L
   - With *higher platelet counts* and bleeding

Premature infants (gestational age <37 weeks) who are ill deserve special attention. The sick preterm infant, with comorbid disease, is at greater risk for intracranial hemorrhage due to poor platelet function and decreased levels of plasma coagulation proteins. In addition, the underdeveloped subependymal matrix with endothelial lining capillaries are poorly supported and predisposed to rupture in the preterm brain[7,9,56] Platelet transfusion is generally recommended in a sick premature infant when the platelet count is below 100 $\times$ 10^9 per L and in a stable premature infant when the platelet count is below 50 $\times$ 10^9 per L, provided there is active bleeding or an invasive procedure is planned.[9,23,56,60-62] A multicenter prospective randomized controlled trial of 252 infants, all of whom were less than 33 weeks gestational age and had platelet counts below 150 $\times$ 10^9 per L, assessed the benefit of prophylactic transfusion in infants with platelet counts maintained above 150 $\times$ 10^9 per L. The authors concluded that there was no reduction in the rate of intracranial hemorrhage for the group with higher platelet counts when compared with the group transfused with counts of 50 $\times$ 10^9 per L.[61] Therefore, intracranial bleeding may still occur in the premature infant whose platelet count is maintained above 100 $\times$ 10^9 per L.[60-62] Levels for prophylaxis in older children generally reflect those used for adults.[26,63,64]

Standard guidelines for transfusion of blood components during ECMO do not exist. ECMO is a form of cardiopulmonary bypass used to support patients with reversible pulmonary disease or temporary cardiac insufficiency. The process can be done through either venoarterial access or venovenous access. Due to the risk of platelet activation as blood flows through the extensive tubing and membrane of the ECMO circuitry, patients must be heparinized to prevent thrombosis. Again, there are no data on the optimum platelet level required to prevent bleeding and reduce the risks of serious hemorrhagic sequelae, though most centers keep patients at levels of 100 $\times$ 10^9 per L and transfuse to higher levels when there is active bleeding.[65-69]

TRANSFUSION OF GRANULOCYTE CONCENTRATES

All transfusions of granulocyte concentrates should be evaluated in light of current available information. For infants, a dose of 10 to 15 mL per kg is recommended, which is about 1 to 2 $\times$ 10^9 PMN per kg.[9] Studies of the efficacy of granulocyte transfusion in septic neutropenic neonates have reached conflicting conclusions. Because neonatal neutrophil function is often abnormal, the use of granulocyte transfusions in this age group may be beneficial.[9,70-76] There has been speculation that the lack of proven efficacy of granulocytes is due to limitations in collecting a high-enough dose, one that would be similar to the endogenous response of normal individuals fighting an infection. Therefore, due to the smaller blood volume of infants and young children, they may have better response to this form of therapy. A meta-analysis published in 1996 looked at the collective data of 7 adult and 5 neonatal clinical studies. The authors concluded that the efficacy of granulocyte transfusion in neonates appeared to be dose dependent, with doses greater than 1 $\times$ 10^9 PMN per kg offering better clinical response.[70] Granulocyte concentrates prepared by apheresis are more desirable than those prepared from buffy coats because they produce a higher yield.[9,70]

Likewise, studies of the efficacy of granulocyte transfusion in septic older children and adults have yielded conflicting results. For adults and larger children, a dose of 1 $\times$ 10^{10} PMN per kg is recommended.[70,77] Components collected from donors on a regimen of both G-CSF and steroid mobilization can yield higher numbers of granulocytes than those collected from an unstimulated donor. There is hope that these higher-dose components will be more effective in larger patients.[20]

G-CSF and GM-CSF are also used in the treatment of neutropenic children with malignancies, reflecting the use in adults.[78] Additional indications may be developed in neonates and children as the field evolves.[75-81] The use of IVIG for prevention of neonatal sepsis and as an adjunct to treatment has been investigated. The results of various studies have yielded conflicting data, and its use varies per institution.[8,9,53,82-85] Guidelines for granulocyte transfusion are listed in Table 6.

AABB requires that all allogeneic units for transfusion are tested with all FDA-required tests. Because granulocytes must be used within 24 hours of collection, the occasion may arise when infectious disease testing is not completed, but the unit must be transfused. The risks and benefits of transfusing an untested component must be weighed by the transfusing physician, in conjunction with the patient's parents. Some blood-collection facilities will attempt to obtain granulocytes from frequent platelet donors who have been appropriately tested in the preceding 10 days and found acceptable for donation. On other occasions, a granulocyte donor is asked to submit a blood sample for testing before collection and, if negative for all infectious disease markers, serves as a donor. The component can then immediately be shipped and transfused. In an emergency situation, when appropriately labeled, AABB Standard 5.8.4.1 does allow the distribution of blood before completion of tests. The tests must be performed as soon as possible, and any reactive results must be reported to the recipient's physician as soon as possible.[19]

TABLE 6. Guidelines for granulocyte transfusion in 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*

TRANSFUSION OF FFP

The transfusion of FFP is indicated when there is bleeding, or when an invasive procedure is planned in a patient with documented coagulation factor deficiency, or a significantly prolonged prothrombin time and/or partial thromboplastin time. The sample for coagulation testing must be obtained from a heparin-free source to assure that the laboratory values are representative of the patient's ability to form thrombi. FFP should *only* be used if a specific factor concentrate is not available or in the case of liver failure where multiple factors are simultaneously decreased. FFP is administered in doses of 10 to 15 mL per kg.[20]

FFP is not indicated for volume expansion.[86] A large multicenter study investigated the prophylactic use of FFP for volume expansion in infants less than 32 weeks of gestational age. Routine use of FFP did not reduce the mortality of premature infants.[87] Prophylactic use of FFP or any pharmacologic intervention to expand intravascular volume had no effect on the risk of death or subsequent disability in this population.[88]

The treatment of DIC must be tailored to the clinical situation, while weighing the risks and benefits of anticoagulation against the need for hemostasis. FFP is used in the treatment of DIC, confirmed or suspected, when therapy of the underlying illness has begun and there is acute bleeding, along with a prolonged prothrombin time and/or partial thromboplastin time more than two times the age-related normal values. Note that a positive D-dimer and/or fibrin degradation products in this setting provides laboratory confirmation of DIC.[86] Other guidelines are summarized in Table 7.[42,55,86,89-91]

S/D plasma is manufactured from approximately 2500 units of pooled, thawed FFP. The mixture is treated with the solvent tri(n-butyl) phosphate and the detergent Triton X-100 to destroy the lipid coat of enveloped vi-

TABLE 7. Guidelines for the transfusion of FFP*

1. Support during the management of disseminated intravascular coagulation
2. Replacement therapy:
   - When specific factor concentrates are not available, including but not limited to, antithrombin III, protein C or S deficiency, FII, FV, FX, and FXI
   - During therapeutic plasma exchange when FFP is indicated (cryo-poor plasma, plasma from which the cryoprecipitate has been removed, or S/D plasma may be beneficial in thrombotic thrombocytopenic purpura not responsive to conventional plasma exchange)[90,91]
3. Reversal of coumadin in an emergency situation, such as before an invasive procedure with *active bleeding*

* FFP is not indicated for volume expansion or enhancement of wound healing.

TABLE 8. Guidelines for the use of cryoprecipitate

1. *Hypofibrinogenemia* or dysfibrinogenemia with active bleeding.
2. *Hypofibrinogenemia* or dysfibrinogenemia, undergoing an invasive procedure
3. FXIII deficiency with active bleeding or undergoing an invasive procedure in the absence of FXIII concentrate
4. Limited directed donor cryoprecipitate for bleeding episodes in small children with hemophilia A (Note: previously untreated children should receive recombinant FVIII)
5. In the preparation of fibrin sealant
6. vWD:
   Active bleeding
   - Before an invasive procedure
   - Cryoprecipitate is only used in vWD disease when:
     - Deamino-D-arginine vasopressin (vasopressin) is contraindicated, not available or does not elicit response
     - Virally inactivated plasma-derived FVIII concentrate, which contains vWF, is not available

ruses, resulting in inactivation. Published data have reported this component to be safe and efficacious to use in the same settings as FFP (with the exception of DIC, which is not an approved indication) but with reduced risk of viral transmission. Due to the pooling process, the levels of factor levels are more consistent than those seen in FFP.[92-94] The National Hemophilia Foundation Medical and Scientific Advisory Council recommended that either S/D plasma or donor-retested plasma be used as plasma alternatives when FFP is indicated, unless there are emergency situations where these components are not readily available.[95] Of note, S/D plasma has been found to have decreased amounts of protein S and antiplasmin when compared with FFP, raising concerns about an increase in the risk of thrombosis.[96,97] On March 29, 2002, the FDA issued a warning to physicians advising that S/D plasma not be used for patients undergoing liver transplant or for patients with other forms of liver disease or coagulopathy.[98] In addition, despite the presence of neutralizing antibodies, there has been transmission of both HAV and parvovirus B-19.[94] At the current time, S/D plasma is not being manufactured.

TRANSFUSION OF CRYOPRECIPITATE

Cryoprecipitate contains the same levels of FVIII, FXIII, fibrinogen, vWF, and fibronectin as FFP, but in a much smaller volume. This reduced volume (15 mL) allows more rapid replacement of these specific factors than a single unit of FFP (200 mL), while reducing the risk of volume overload. This is especially important for the small-volume patient. Due to patterns of inappropriate use of cryoprecipitate in some institutions, transfusion services may choose to evaluate all cryoprecipitate transfusions. In infants, a single unit of 10 to 15 mL as a standard dose is usually sufficient to achieve hemostasis. Table 8 summarizes its uses.[8,20,23,42,55,89]

Fibrin sealants have been used during surgery to achieve rapid topical hemostasis. In the past, a variety of homegrown methods employed for the preparation of fibrin sealant have required mixing cryoprecipitate, containing fibrinogen, with bovine thrombin and calcium, causing the activation of fibrinogen.[99,100] In 1998, the FDA approved the first commercially manufactured fibrin sealants, Tisseel, distributed by Baxter Healthcare Corporation (Deerfield, IL) and HemaSeel APR, distributed by the Hemacure Corporation (Montreal, Canada). The advantage of the commercially prepared component is its greater bonding strength, more rapid preparation time, and increased safety profile due to viral inactivation processes during manufacturing, when compared with those preparations made at the bedside. In addition, the use of a human source of thrombin prevents the development of sensitization to bovine thrombin that has been seen in the homegrown preparations. Patients exposed to bovine thrombin are at risk for developing antibodies to bovine FV that cross-reacts with human FV and can lead to serious hemorrhage.[101-103] There is limited experience with fibrin sealants in pediatric patients.[104,105]

TRANSFUSION OF CLOTTING FACTOR CONCENTRATES

Bleeding or thrombosis in patients with documented coagulation or antithrombotic factor deficiencies may require factor replacement. Specific clotting concentrates will be the component of choice as they become commercially available. In situations where these components are not available, blood components that contain multiple coagulation factors, such as FFP, may be used.

Many factor concentrates are still derived from human plasma. A variety of processes are used (e.g., ion exchange chromatography, cyroprecipitation) to fractionate plasma. The goal is to isolate the specific coagulation proteins in high concentration while removing impurities. In addition, by using heat, S/D treatment, or

both, enveloped viruses are inactivated. Within the past several years, the use of molecular techniques has provided a growing supply of recombinant coagulation components to treat both hemophilia A and B. Recombinant clotting factor components have not been associated with any infectious disease transmission to date.[106]

FVIII concentrate

FVIII concentrate is the component of choice in patients with documented hemophilia A (classic hemophilia). FVIII is indicated before an invasive procedure, in response to a bleeding episode, or for prevention of chronic joint disease (so called prophylaxis). For children with severe hemophilia A, routine infusion of FVIII may provide primary or secondary prophylaxis to prevent bleeding episodes. The Medical and Scientific Advisory Council of the National Hemophilia Foundation recommends recombinant FVIII as the component of choice for these patients; human-derived FVIII is only indicated when the patient prefers to continue its use or when recombinant VIII is not available.[107] Plasma-derived FVIII concentrates, which retain vWF activity, are also indicated in patients with severe or variant forms of vWD, when deamino-D-arginine vasopressin is ineffective or contraindicated, and should be used for prevention of bleeding at surgery.[20]

F IX concentrate

F IX concentrates are indicated for bleeding or before invasive procedures in patients with documented hemophilia B (Christmas disease). There are three types of F IX concentrates available: recombinant F IX, coagulation F IX (a purer plasma-derived component), and prothrombin complex concentrates (PCC). All are used for treatment of F IX deficiency either for on-demand needs or prophylaxis. Recombinant F IX, licensed in 1995, is the component of choice for young children with hemophilia B. Rare patients with hemophilia B are treated with PCC, which contain FII, FVII, F IX, and FX. When there is no clinical response to PCC, activated PCC can be used. Both components are known to carry a risk of thrombosis.[108,109]

When a hemophilia patient develops an inhibitory antibody to FVIII or F IX, routine doses of factor concentrate will not result in hemostasis. For patients with low titer inhibitors (<5 BU) bleeding episodes may be successfully treated with higher-than-routine doses of factor. For patients with higher titer inhibitors, hemostasis may require the infusion of factor concentrates that bypass the need for FVIII or F IX. Concentrates with bypass activity include rVIIa and PCCs. Porcine FVIII might also be useful in this context. The production of high titer inhibitors may be eliminated or reduced by institution of immune tolerance protocols that require routine infusion of FVIII or F IX in higher-than-routine doses until the inhibitor titer falls to undetectable levels.[109-111] Frequent large-volume exchange with FFP can also overcome factor inhibition.[112]

Select coagulation concentrates

Patients with deficiencies of the naturally occurring anticoagulants antithrombin III, protein C, and protein S may require prophylaxis in the following conditions:[113]

Antithrombin III concentrate. This component is indicated in patients with documented congenital deficiency who have had thrombosis.

Protein S concentrate. This component is indicated in patients with documented congenital deficiency and thrombosis. This component is currently available in Europe.

Protein C concentrate. This component is indicated in patients with documented congenital deficiency and thrombosis. This component is only available for compassionate use but is being evaluated in phase II clinical trials in the US as a treatment for sepsis.[114]

TRANSFUSION OF ALBUMIN (5%, 25%)

Transfusion of albumin, manufactured from human plasma pools, is indicated when there is need for volume expansion and colloid replacement. There is no evidence that albumin serves a role either as a nutritional supplement or as correction for ascites and peripheral edema secondary to portal hypertension. In addition, there has been concern raised that transfused albumin can leak into alveoli, further reducing oxygenation in respiratory distress syndrome. The benefits and risks of albumin should be weighed.[115] The guidelines for its use are summarized in Table 9.[20,23]

IMMUNE GLOBULIN PREPARATIONS

IVIG

IVIG is derived from pooled human plasma that has undergone Cohn fractionation. The development of complement-activating IgG aggregates during the manufacturing process has been associated with side effects such as anaphylaxis and severe hypotension. Efforts to further purify the component are ongoing.[116] Current uses of IVIG are summarized in Table 10.

Neonatal sepsis deserves special consideration. Several studies have supported the use of IVIG to increase opsonization and phagocytosis in neonates with age-specific abnormalities of granulocyte function,[82-84] although its use to prevent sepsis has not been proven.[84] As stated earlier, clinical trials looking at the role of IVIG in the treatment and prevention of neonatal sepsis have yielded conflicting results and its use varies.[77,82] The uses for IVIG are constantly expanding; therefore, it is important to modify guidelines as more information becomes available.[85,117,118]

TABLE 9. Guidelines for the use of albumin*

1. *Acute hypotension* in patients with one of the following conditions:
   - *Acute or chronic* liver failure
   - After paracentesis for ascites
   - Newborns with sepsis and/or hyaline membrane disease
2. To maintain blood volume in selected patients during
   - Therapeutic phlebotomy for polycythemia
   - Plasma exchange procedures
3. To induce diuresis in combination with a diuretic in patients with fluid overload and:
   - Protein-losing enteropathy or nephropathy
   - *Acute chronic* liver failure
4. To elevate protein when total protein <52 g/L (5.2 g/dL) and/or albumin <18 g/L (1.8 g/dL) in cases of:
   - Burns, after the first 24 hr
   - Nonhemorrhagic shock
   - Acute respiratory distress syndrome in selected patients
   - *Severe* periphera edema
5. Cardiovascular compromise secondary to hypovolemia associated with:
   - Surgery with extracorporeal circulation
   - *Shock/preshock*
   - *Significant tachycardia*

* Albumin should be used with caution in certain patients (see text).

TABLE 10. Guidelines for the use of IVIG

1. Immune deficiency states—humoral
   - Primary, excluding patients with selective IgA deficiency
   - Secondary, including HIV infection, marrow transplant recipients
2. Hematologic diseases such as ITP, Evans syndrome, autoimmune hemolytic anemia (steroid resistant)
3. Prophylaxis to prevent opportunistic infection in marrow transplant patients
4. Sepsis neonatorum
5. Neonatal alloimmune thrombocytopenia
6. *Thrombocytopenia* secondary to maternal autoimmune disease (ITP, systemic lupus erythematosus)
7. Miscellaneous: Kawasaki syndrome, Guillain-Barré syndrome

Hyperimmune globulins

Hyperimmune globulins are derived from donors who have either been naturally immunized for commercial globulin production. Varicella-zoster immune globulin is indicated in neonates whose mothers have had varicella in the perinatal period, or in immune compromised children, without a history of varicella or protective antibodies to the virus (including those with HIV) exposed to varicella-zoster within the past 72 hours.[119]

Rh immune globulin (RhIG or anti-D) is used to prevent immunization in an D– mother immunized by a D+ fetus or after the transfusion of D+ blood and/or blood components to D– recipients, particularly female recipients. Rh immunization can result in HDN with subsequent pregnancies. In the US, two RhIG components are licensed for prevention of Rh immunization, an IM form and an IV preparation.[20]

Another indication for the IV preparation of RhIG is in the treatment of acute and/or chronic immune-mediated thrombocytopenic purpura in D+ patients only. Theoretically, the anti-D binds to the D antigen, and subsequently the coated RBC binds to the Fc receptor in the spleen, allowing antibody-coated platelets to bypass the blockade. This may be used as first-line treatment, not just for patients unresponsive to other treatments.[120,121]

WBC-REDUCED BLOOD COMPONENTS

Recently, many studies have evaluated the methods, benefits, and risks of WBC reduction. Research regarding additional benefits in the use of WBC reduction is actively evolving, and each institution will need to tailor their individual guidelines to reflect their interpretation of the current literature. In 1998 and again in 2001, advisory committees to the FDA voted unanimously to endorse universal WBC reduction of all cellular blood components, with the exception of granulocytes.[122,123] Canada and regions of Europe have adopted universal WBC reduction, the latter as a possible protection against vCJD.[124,125] Despite years of studies and discussions, controversy in the US continues.[126-128] Currently, some blood manufacturers produce WBC-reduced components exclusively and some hospital transfusion services, likewise, maintain a 100-percent WBC-reduced inventory. Components must contain less than 5×10^6 WBCs to be labeled as WBC reduced.[19]

WBC-reduced blood components have been demonstrated to prevent the recurrence of febrile nonhemolytic transfusion reactions, to reduce the risk of alloimmunization to HLAs in selected patients, and to reduce the risk of CMV in selected patients.[20,126-128] They have also been shown to prevent of postcardiopulmonary bypass lung injury.[129-132] Many institutions have chosen to use WBC-reduced blood components, in lieu of the traditional seronegative components, when CMV reduced-risk components are indicated. These groups cite prospective data that demonstrate an equivalent degree of protection against CMV transmission in several clinical situations, in conjunction with AABB recommendations. Since there is still some conflicting data regarding the comparison of rates of infection using seronegative versus WBC-reduced components, transfusion services must make their decisions based on evaluation of current data.[129,133-137]

WBC reduction can be accomplished before storage, at the collection facility, in the blood bank before release to the patient, or after storage using bedside filtration devices. Studies have shown that WBC reduction performed before storage, as part of component preparation, might be superior to bedside WBC reduction and confer additional benefits to the stored component as well as to the transfusion recipient. These benefits include a pos-

sible reduction in the bacterial load of components, when bacteria are present, reduced rates of HLA alloimmunization after transfusion, and a decreased incidence of transfusion reactions caused by cytokine release of aging WBCs.[138-142] WBC reduction before storage can also be accomplished through sterile docked filters in the blood bank after receipt from the collection facility. Depending on the age of the component at the time of filtration in the blood bank, some of the advantages discussed above may not apply.[143] The FDA's 2001 published draft guidance on prestorage leukocyte reduction states that WBC reduction before storage is favored over bedside WBC reduction.[144]

The role of WBCs in immunomodulation is also being investigated. There is evidence that transfusion of allogeneic WBCs down regulates the immune system, leading to increases in infectious complications after surgery and increased rates of recurrence of colorectal and other malignancies in adults. Conversely, transfusion of non-WBC-reduced cellular components can decrease the severity of Crohn's disease.[126,127,142-147]

Neonates rarely develop febrile nonhemolytic transfusion reactions and infrequently become alloimmunized. Hence, the need to provide WBC-reduced blood components in neonates may be less critical than in adults.[148-153] On the other hand, transfused WBCs have no proven benefit, and some argue that all the known deleterious effects of allogeneic WBCs dictate their removal. Because of the difficulty of recognizing the clinical stigmata of transfusion reactions in infants, there might actually be deleterious effects that go unrecognized. A summary of the guidelines, for those who do not maintain a 100-percent WBC-reduced blood inventory, is found in Table 11.

PREVENTION OF CMV TRANSMISSION

CMV is a DNA virus that resides in WBCs and has been demonstrated to be transmitted through transfusion of cellular blood components. Naturally occurring infection is very common during the course of an individual's lifetime, as demonstrated by seroprevalence rates of up to 80 percent in certain geographic locations. Immunocompetent individuals recover fully from an acute infection, with many infections being asymptomatic. As with other members of the herpes group of viruses, CMV remains in a latent state in the immune individual, residing within WBCs. Because it is very difficult to treat CMV infection, prevention of infection is important in patients considered to be at risk for serious sequelae. Those at risk for high morbidity and mortality are listed in Table 12.[19,20,129,133-137] Though babies born to mothers with IgG antibody against CMV are considered to be at lower risk for CMV infection than those whose mothers lack protective antibody, reinfection with different strains during pregnancy leading to clinically significant perinatal CMV infections has been reported.[154]

When a patient is at risk for transfusion-transmitted CMV disease, blood components should be selected or processed to reduce risk for CMV. Reduced-risk components are either seronegative or WBC reduced to less than 5×10^6 WBCs.[19] CMV transmission can still occur in seronegative components due to false-negative serology or various scenarios where antibody levels may be too low to be detected at the time of testing. CMV transmission through WBC-reduced components can occur if a higher-than-anticipated residual number of WBCs are retained in the component or if the filter fails. The use of WBC-reduced blood components in patients requiring CMV reduced-risk components is discussed in the previous section.[129,133-137,143]

PREVENTION OF GVHD

Transfusion-associated GVHD (TA-GVHD) occurs as the result of transfused lymphocytes engrafting and proliferating in the transfusion recipient. In contrast with GVHD after marrow transplant, untreated TA-GVHD is fatal in 90 percent of patients due to the resultant marrow hypoplasia. Because TA-GVHD rarely responds to treatment, other than marrow transplantation,[155] prevention is of paramount importance.[133,156] Irradiation of cellular blood components dramatically reduces the risk of TA-GVHD.[19,20,156]

Patients at risk for GVHD include those with decreased cellular immunity, premature infants, fetuses that receive in-utero transfusions, marrow transplant recipients, and patients receiving chemotherapy that results in severe immune suppression. An analysis of Japanese newborns with TA-GVHD concluded that newborns might be at increased risk for TA-GVHD. Of note, thymic abnormalities were observed in the infants at autopsy and some of these infants received blood from their par-

TABLE 11. Guidelines for WBC-reduced blood components

1. Prevent recurrence of febrile nonhemolytic transfusion reactions
2. Reduce the risk of HLA alloimmunization
3. To prevent CMV transmission (see text)
4. Prevent post cardiopulmonary bypass lung injury

TABLE 12. Patients requiring CMV reduced-risk components

1. Intrauterine transfusion
2. Premature infants weighing <1200 g at birth with
   - Either infant or mother seronegative
   - CMV status unknown
3. Any patient identified as at risk for transfusion-transmitted CMV infection

ents, pointing toward risk factors for development of GVHD independent of age.[14,157] Likewise, there are case reports describing TA-GVHD after transfusion in young children who had a previously undetected, underlying immune deficiency syndrome.[14,155]

It is important to note that immunocompetent individuals are also at risk for TA-GVHD in the setting when an HLA-homozygous individual donates components for a recipient who is HLA-heterozygous at that allele. When this occurs, the transfused lymphocytes will recognize the host as foreign. Since there is an increased likelihood of this scenario occurring in blood relatives and in HLA-matched components, irradiation of directed cellular blood components from family members is required.[19,20,156,157] Currently, there are no guidelines for universal irradiation of blood components transfused to all infants and/or children.[14]

Though current WBC-reduction filters are very efficient, WBC reduction has not been shown to prevent TA-GVHD.[158] The only known method of preventing TA-GVHD is irradiation at 2500 cGy using a device approved for blood irradiation by the FDA.[19,156-158] The shelf life of irradiated RBCs is reduced to 28 days after irradiation due to acceleration of the storage lesion.[19,159] Refer to Table 13 for a summary of the guidelines.

AUTOLOGOUS BLOOD AND BLOOD COMPONENTS

Autologous blood before deposit

Many studies document the safety of autologous donation, as well as its effectiveness in markedly decreasing allogeneic blood exposure in infants and children. Studies have looked at donations from as early as 3 months of age. The attached references cite some of these studies.[160-173]

Infants and small children represent a different group of autologous donors and patients than their adult counterparts. The major differences are decreased ability to compensate for volume changes in young children and infants, ability to cooperate, ability to understand the procedure, venous access, smaller blood volume, adjustment of anticoagulant ratio in the collection set, and ability to give informed consent.[20]

Autologous blood should only be ordered when there is a high likelihood of transfusion in a child who can safely self-donate blood. Self-donated blood may be an alternative for patients with multiple antibodies, for whom finding compatible blood is difficult.[166] As with any transfusion, autologous transfusion carries risks along with its benefits.[20,26,160-173] Therefore, criteria for transfusion should be the same as those for transfusion of allogeneic blood and blood components.

TABLE 13. Patients requiring irradiated blood components

1. Intra-uterine transfusion
2. Premature infants weighing <1200 g at birth
3. Patients with known or suspected cellular immune deficiencies
4. Patients undergoing marrow or peripheral blood progenitor cell transplant
5. Patients rendered *immunosuppressed* by chemotherapy or radiation treatment
6. Recipient of components from blood relatives
7. Recipients of HLA-matched or platelet crossmatch-compatible components

Perioperative blood

For the collection and infusion of blood components collected through intraoperative hemodilution and perioperative salvage, guidelines should be established in conjunction with the hospital transfusion service. There are limited studies in pediatric patients that have shown safety in the pediatric population, with decreases in allogeneic exposure. The role of blood obtained by salvage in conjunction with other forms of autologous donation has not yet been fully explored in this patient population. Contraindications to the use of perioperative salvage include gross contamination of the field with bacteria and/or tumor.[20,26,174-179]

Umbilical cord blood

Another approach that has been explored to meet transfusion needs of infants is the use of umbilical cord blood (UCB).[180-186] Since placental vessels contain anywhere from 75 to 125 cc of blood, it has been postulated that using this otherwise wasted resource could serve as a means of autologous transfusion. Concern has been raised about the risk of bacterial contamination during delivery, with rates up to 9.6 percent in one study,[181] as well as the viability and quality of UCB when compared with banked blood from adult, volunteer donors. In addition, those with the greatest need, the smallest infants, will have the smallest volumes of UCB available for postnatal transfusion. Whether or not the use of UCB as a form of autologous transfusion will prove to be beneficial by reducing overall donor exposure remains to be seen.[180-186] In lieu of using UCB after delivery, others have advocated delaying cord clamping at the time of delivery, to administer a generous placental-fetal transfusion. For infants without volume constraints, this may be the best way to deliver additional RBCs.[26,187]

AUTHORS' NOTE

For readers who would like further general information regarding pediatric transfusion therapy, the authors recommend cited references 6, 7, 8, 9, 13, 14, 16, 17, 20, 23, 26, 48, 56, 74, 77, 80, 113, 126, 137, and 164.

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