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Transfusion support: Considerations in pediatric populations

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ABSTRACT

Over 400,000 units of blood and blood products are transfused to pediatric patients annually, yet only sparse high-quality data exist to guide the preparation and administration of blood products in this population. The direct application of data from studies in adult patients should be undertaken with caution, as there are dissimilarities in the pathology and physiology between adult and pediatric patients. We provide an overview of available evidence in the field of pediatric transfusion medicine, summarizing indications for blood product transfusion, thresholds for transfusion and indications for blood product modifications.

Introduction

Blood product transfusion practice is an important component of the medical and surgical care delivered to children. The use of blood products in neonates and children differs from that in adults in terms of indication for transfusion, transfusion dose and frequency of adverse events. Dissimilarities in pathology and physiology between pediatric and adult patients underlie these differences. The appropriate use of blood products is imperative to avoid the addition of unnecessary exposure, adverse events and costs. Pediatric patients have more transfusion reactions than adults. In a study of >130,000 blood transfusions administered to pediatric and adult patients, the rate of acute transfusion reactions was higher in pediatric patients compared to adult patients (6.2 events vs 2.1 events per 1000 transfusions, respectively) [1]. According the 2013 National Blood Collection and Utilization Survey, pediatric transfusions comprised 5% of all whole blood/RBC transfusions, 9.4% of all platelet transfusions and 4.9% of all plasma products administered [2]. In addition, a multi-center study of all consecutive pediatric discharges in 35 academic children's hospitals over a 2-year period found that 4.8% of admitted patients received blood product transfusions during their hospital course [3]. Despite this, high-quality evidence to guide the use of blood product transfusions in pediatric patients is lacking. In this review, we describe the most current published evidence regarding indications for and administration of blood products in the pediatric population, with the goal of familiarizing practitioners with the available evidence in this field to guide decision-making.

Red blood cell transfusions

Red blood cell (RBC) units are the most commonly transfused blood product in pediatric patients, with a reported 306,000 units administered to pediatric patients in 2013 [2]. The volume selected for transfusion is typically determined based on the desired rise in hemoglobin, with the most commonly used formulas given in Table 1. All of these formulas make assumptions based on the recipient's total blood volume and the donor hemoglobin concentration [4,5]. In practice, more often a volume of 10-15 mL/kg is selected, with attention to prescribe no more than the maximum dose for an adult patient, and infused over a period of 2 to 4 hours [4,6]. Slower rates of transfusion may be desired in patients with chronic anemia to decrease the risk of cardiac failure. A review of pediatric patients with severe anemia of gradual onset found that transfusion at a rate of 2mL/kg/hr to the desired hemoglobin was well tolerated [7].

The most extensive research to determine appropriate transfusion thresholds in pediatric patients has taken place in the neonatal population. Anemia in neonates is related to a number of factors, including insufficient maternal iron transport in premature infants, iatrogenic blood losses, decreased lifespan of circulating RBCs, insufficient erythropoietin (EPO) production and superimposed physiologic anemia of infancy [8]. Over 90% of extremely low birth weight infants (ELBW) will receive at least one RBC transfusion following birth, as the risks associated with untreated

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Table 1
Recommendations for routine transfusion dose based on blood product.

Product	Population	Dose	Reference
Red blood cells	Neonate	10-20 mL/kg	[4,6,118]
	Child/adolescent	Volume = AHb(g/dL) x Weight (kg) x Factor (3-5) OR 10-15mL/kg* *No more than 20 mL/kg or standard adult volume	[4-6,119]
Platelets	Neonate	10-15 L/kg	[4,118]
	Child/adolescent	1 whole blood platelet concentrate (PC)/10 kg OR Platelet dose ($x10^9$/L) = Aplatelet count x Blood Volume (L) x 0.67 OR *No more than standard adult volume	[71,120]
FFP		10-20mL/kg	[4,6,118]
Crycoprecipitate		5-10mL/kg OR 1-2 units/10g	[4,6]

In all scenarios increased or decreased volumes may be indicated based on co-morbidities and clinical scenario. *Adapted with permission from Delaney, M., Wendel, S., Bercovitz, R. S., Cid, J., Cohn, C., Dunbar, N. M et al. (2016). Transfusion reactions: prevention, diagnosis, and treatment. Lancet, 388 (10061), 2825-2836 [122].

anemia can include apnea and necrotizing enterocolitis [9-11]. The ideal hemoglobin threshold at which to initiate transfusion therapy remains unclear. Two randomized controlled trials comparing a restrictive vs a liberal transfusion policy yielded contradictory results. In the study by Bell et al, 100 premature neonates with a birth weight of <1300 g were randomized to a restrictive threshold vs a liberal threshold (exact hemoglobin thresholds varied based on the level of respiratory support required) [12]. While the authors did find a reduction in the mean number of transfusions per patient using a restrictive threshold (5.2 vs 3.3, $P = .025$), infants in the restrictive group experienced a higher rate of intraparenchymal hemorrhage, periventricular leukomalacia, and episodes of apnea. However, on follow-up imaging, completed in nearly half of the original participants, there was a significant reduction in intracranial volume in the liberal group, and cognitive assessments completed over 8 to 15 years follow-up found lower scores on all measures of intelligence, achievement and neuropsychological functioning in children who had been in the liberal group [13,14]. The premature infants in need of transfusion (PINT) study by Kirpilani et al also randomized ELBW infants to either a restrictive or a liberal transfusion threshold, with specific thresholds chosen for the level of respiratory support required [15]. The short-term results found no statistically significant differences in their primary composite outcome of death or survival with retinopathy, bronchopulmonary dysplasia or brain injury (74% vs 69.7%, $P = .25$) [15]. However, post hoc follow-up at 18 to 21 months corrected gestational age found infants from the restricted group had an increased rate of death or neurodevelopmental impairment (cerebral palsy, cognitive delay or severe hearing/visual impairment), which approached significance (45.2% vs 38.5%, $P = 0.09$) [15,16]. In both studies, neonates in the restrictive group received fewer transfusions, though this did not appear to result in any cost savings [17].

Because the previously discussed investigations did not converge to similar findings, new studies that include long term neurodevelopmental outcomes were planned and are ongoing. The Effects of Transfusion Thresholds on Neurocognitive Outcome of ELBW Infants trial will attempt to resolve questions related to the preferred transfusion strategy in neonates by evaluating the long-term effect of a restrictive policy vs a liberal transfusion policy on neuro-developmental outcomes in ELBW infants (NCT 01393496) [18]. Another trial currently underway is the Transfusion of Prematures trial, which will randomize ELBW infants to restrictive vs liberal thresholds and evaluate both short-term (survival) and long-term (neurodevelopmental impairment) outcomes (NCT01702805). At this time, recommendations for transfusion thresholds remain driven by expert recommendation and are adjusted for postnatal age, respiratory status and other clinical features (Table 2) [4,19].

In older pediatric patients, the only large prospective randomized study to evaluate RBC transfusion thresholds is the TRIPICU study, which enrolled patients 3 days to 14 years of age admitted to the intensive care unit. Participants were randomized to a transfusion threshold of 7.0 g/dL vs 9.5 g/dL. There was no significant difference in new or progressive multiorgan-dysfunction syndrome (12% in both groups), death, nosocomial infection, mechanical ventilation or duration of ICU admission, indicating a restrictive threshold was safe in this population [20]. Several subgroup analyses later completed using this dataset also showed similar safety of a restrictive strategy in patients with sepsis, following cardiac surgery and following general surgery [21,22]. In patients who had undergone general surgery there was an increased length of stay in the liberal group [23]. A survey of North American and European pediatric intensivists continued to find high variability in the transfusion thresholds chosen by practitioners, though there was a trend towards a more restrictive strategy following publication of the TRIPICU results [24]. Guidelines published within the past year from the Pediatric Critical Care Transfusion and Anemia Expertise Initiative recommend critically ill but hemodynamically stable children should not receive RBC transfusions for a hemoglobin >7.0 g/dL [25].

Patients with malignancies and those with inherited RBC disorders represent another population with high RBC transfusion needs. The majority of available data is based upon studies in adult patients, which has led to significant variation in practice. Surveys of pediatric hematology and/or oncology physicians reveal that the median transfusion threshold used is 7.0 g/dL though more liberal thresholds are used in the setting of bleeding, neutropenic fevers, tachypnea, radiation therapy or patients with central nervous system tumors [26,27]. Pediatric bone marrow transplant (BMT) physicians also tend to employ higher transfusion thresholds [28]. Following publication of the TRIPICU study results, a group of transplant physicians published their experience using a more restrictive threshold: there were fewer RBC transfusions compared to historical controls without any difference in length of stay, time to engraftment or mortality [29]. In a randomized trial of pediatric patients undergoing allogeneic BMT, which compared the use of a higher hemoglobin threshold (12 g/dL) to a restrictive threshold (7g/dL), an excess number of patients developing veno-occlusive disease in the higher threshold arm, and the trial was closed early [30].

Transfusion requirements in patients with inherited RBC disorders are variable due to a wide spectrum in disease sever-

Table 2
Recommendations for transfusion threshold by transfusion indication, based on published studies.

Red blood cell transfusions		
Population	Transfusion threshold (g/dL)	Reference
Neonate:		
• Requires mechanical ventilation	<10.0-12.0	[4,118]
• Requires oxygen or noninvasive positive pressure ventilation	<8.5-12.0	
• Does not require respiratory support	<7.5-10.0	
Child/Adolescent:		
• Stable hemodynamic status, noncyanotic, respiratory failure without severe acute hypoxemia	<5.0-7.0	[4,25]
• Critically ill with acute brain injury	<7.0-10.0	[25]
• Critically ill, hemodynamically stable, with uncorrected congenital heart disease	<7.0-9.0	[25]
• Oncology/stem cell transplant		
• Sickle cell disease	<7.0-8.0	[4,25]
	*Consider transfusion based on baseline hemoglobin and overall clinical condition	[121]
• Thalassemia	<9.0-10.5 (trough Hb goal)	[32]
• Red cell aplasia	<8.0 (trough Hb goal)	[50]
Platelet transfusions		
Population	Transfusion Threshold ($x10^9$/l)	Reference
Neonate:		
• Stable full-term infant, no active bleeding, neonatal alloimmune thrombocytopenia (NAIT) without family history of intracranial hemorrhage (ICH)	<20-30	[4,6,58,71,118]
• Stable premature infant, moderate bleeding, NAIT with family history of ICH, personal history of ICH, coagulopathy, planned invasive procedure	<30-50	
• Ill premature infant, major active bleeding, planned major invasive procedure	<50-100	
Child/adolescent:		
• Bone marrow aplasia, myelodysplasia or chronic marrow failure not receiving active treatment, Immune Thrombocytopenic Purpura (ITP)	*May be observed without prophylactic transfusion	[62,71,120]
• Oncology, stem cell transplant, bone marrow aplasia or myelodysplasia receiving active treatment	<10	[62,71,120,4]
• Severe mucositis, sepsis, DIC without bleeding, receiving anticoagulation, high risk of bleeding from local tumor infiltration, undergoing insertion/removal of nontunneled central venous line, undergoing bone marrow biopsy or aspirate	<20	[4,62,120]
• Undergoing lumbar puncture	<40-50	[4,62,120]
• Moderate active bleeding, DIC with bleeding, prior to major surgery, epidural anesthesia, endoscopy with biopsy or liver biopsy	<50-100	[4,71,120]
• Major active bleeding, postoperative bleeding, prior to ocular surgery or neurosurgery	<75-100	[4,71,120]
• Multiple traumatic injuries, traumatic brain injury, spontaneous ICH	<100	[120]

In all scenarios transfusion threshold modifications may be necessary based on co-morbidities and clinical scenario. *Adapted with permission from Delaney, M., Wendel, S., Bercovitz, R. S., Cid, J., Cohn, C., Dunbar, N. M et al. (2016). Transfusion reactions: prevention, diagnosis, and treatment. Lancet, 388 (10061), 2825-2836 [122].

ity. The underlying defect in thalassemia is reduced or absent globin chain synthesis. Although all thalassemias result in ineffective hematopoiesis, hemolysis and anemia, the majority of patients with alpha thalassemia trait, alpha thalassemia minor and beta thalassemia intermedia are transfusion-independent and typically only require transfusions in the event of surgery, pregnancy or illness [31]. For the transfusion-dependent thalassemia disorders, including beta thalassemia major, alpha thalassemia major (often fatal even prior to birth) and hemoglobin H-constant spring, chronic transfusion is indicated for a persistent hemoglobin of <7.0 g/dL or for clinical symptoms including facial changes, growth failure, fractures or evidence of extramedullary hematopoiesis. Most transfusion programs will administer products every 2 to 5 weeks, with transfusion frequency titrated to maintain trough hemoglobin levels above 9 to 10.5 g/dL [32]. Up to 22.6% of transfusion-dependent thalassemia patients will develop RBC alloantibodies when matched only for ABO and RhD [33]. Therefore, patients should undergo extended red cell antigen typing (including to C, c, E, e, and Kell) and have a full crossmatch and screen for new antibodies completed prior to each transfusion. It is also strongly

recommended to administer blood products matched for C, E, and Kell antigens to avoid alloimmunization [32].

The underlying defect in patients with a hemoglobinopathy is a structural abnormality in the hemoglobin protein, the most common of which is sickle cell disease (SCD). Patients are often not transfusion dependent based upon hemoglobin values alone, but they may require transfusions for other indications, as for symptomatic anemia, acute splenic sequestration, transient aplastic crisis, acute sickle hepatopathy, multi-organ failure, and acute chest syndrome [34-36]. These indications are based on panel recommendations and low or moderate quality evidence. However, there is strong evidence that pre-operative transfusions decrease adverse peri-operative outcomes in patients with SCD. The TAPS trial demonstrated that pre-operative transfusion to a goal hemoglobin of 10.0 g/dL decreased the rate of clinically important complications, including acute chest syndrome, prior to low and medium-risk interventions (OR 3.8, $P = .027$) [37].

The primary indication for chronic transfusion in SCD is stroke prevention in patients with abnormal transcranial Doppler (TCD) ultrasonography. Both the stroke prevention trial in sickle cell anemia (STOP) and follow-up STOP II trials were closed prematurely due to the clear benefit of chronic transfusion. In the STOP trial, patients receiving chronic transfusion had a significantly decreased stroke risk compared to patients managed by standard care (1 event vs 11 event, $P < 0.001$). In the STOP II trial, there was a decreased risk of stroke or reversion to high-risk TCD values in patients receiving chronic transfusion compared to patients in whom chronic transfusions were discontinued (0 events vs 16 events, $p<0.001$) [38,39]. Recent evidence from the TCD with transfusions changing to hydroxyurea (TWiTCH) trial indicates that hydroxyurea therapy is an effective alternative to chronic transfusion for primary stroke prevention with comparable velocities on TCD (143 cm/s vs 138 cm/s) [40]. Exchange transfusion during an acute stoke, as well as continued chronic exchange transfusions following a stroke, have been associated with a reduced risk of recurrent strokes [41]. For this indication, hydroxyurea has not replaced the use of chronic transfusion for secondary stroke prevention. The stroke with transfusions changing to hydroxyurea (SWiTCH) trial was ultimately closed early for futility after it was found that discontinuing chronic transfusion in favor of hydroxyurea did not reduce iron overload [42]. Chronic transfusion has also been found to decrease the risk of stroke in patients with evidence of silent cerebral infarcts on MRI without a history of overt stroke (incidence rate ratio 0.41, $P = .04$) [43]. Secondary analyses of the results of several of the above trials have found that chronic transfusion is associated with a decreased incidence of acute chest syndrome and vasoocclusive pain episodes [44]. Blood transfusions administered during hospitalization for an acute pain crisis may also be associated with a decreased rate of readmission (33.3% vs 42.6%, $P < .001$) [45]. However, consensus guidelines recommend against the use of transfusion for an uncomplicated pain crisis [36].

Patients with SCD on chronic transfusion therapy are also at a high risk of alloimmunization, with 27% to 75% of patients who receive only ABO and RhD matched products developing alloantibodies [34]. Therefore, guidelines recommend transfusing patients with SCD with CcEe and K-matched red cell units [46]. Nevertheless, up to 58% of chronically transfused patients may become alloimmunized and 45% may become Rh-immunized, potentially due to variant alleles detected at the genotype level but not identified with routine serologic phenotyping [47]. The primary concern associated with alloimmunization is the risk of delayed hemolytic transfusion reaction and/or hyperhemolysis syndrome. This complication occurs when a patient, previously alloimmunized but now with antibody levels below detectable thresholds, is re-exposed to an antigen, triggering an anamnestic response and hemolysis. For such hemolytic transfusion reacts, a prevalence rate of 4% has been described in the adult population, but reactions have also been observed in pediatric patients with SCD as well [48].

Transfusions are less frequently utilized in patients with red cell membrane disorders, such as hereditary spherocytosis, elliptocytosis and stomatocytosis. These patients will often have increased transfusion requirements in the first year of life due to an inadequate EPO response to anemia, but following this period they require transfusions infrequently, often only with another illness. Transfusion based on hemoglobin value alone is not recommended [49]. For patients with RBC aplasia, chronic transfusion to maintain hemoglobin levels >8.0 g/dL is recommended to promote adequate growth [50].

Platelet transfusions

Like RBC products, platelet transfusions in pediatric patients are also administered using weight-based dosing (Table 1). Neonates are at a particularly high risk of thrombocytopenia. Up to 22% of infants admitted to the neonatal ICU are observed to have thrombocytopenia, and 12% of neonates will have platelet counts of $<100x10^9/L$ [51]. Severe thrombocytopenia (defined as a platelet count of $<60x10^9/L$) may be complicated by minor or major hemorrhagic events in 82% of neonates [52]. Thrombocytopenia is a risk factor for the development of intraventricular hemorrhage (IVH) and associated poor neurologic outcomes. However, several observational studies have found no correlation between the degree of thrombocytopenia and the risk of bleeding, complicating efforts to determine an acceptable threshold for prophylactic platelet transfusion [52-54]. A multicenter prospective trial in premature infants randomly assigned to prophylactic platelet transfusion thresholds of $<150x10^9/L$vs $<50x10^9/L$ found no significant difference in the overall incidence of IVH in patients, a result which has been supported by observational studies [55,56]. The Platelets for Neonatal Transfusion – Study 2 provided evidence that even lower platelet transfusion thresholds appear to be safe. Platelets for Neonatal Transfusion – Study 2 randomized premature infants to a platelet transfusion threshold of either $<50\ x10^9/L$ or $<25\ x10^9/L$. There was a significantly greater rate of death or major bleeding in the higher transfusion threshold group (26% v 19%, $P = .02$) in addition to increased transfusion utilization [57]. This suggests that higher transfusion thresholds in preterm low birth weight stable infants without recent IVH are not beneficial. However, higher transfusion thresholds may be required in the presence of active bleeding [19,58,59].

There are no randomized controlled trials evaluating safe thresholds for platelet transfusion in other groups of pediatric patients. Diedrech et al randomized both pediatric and adult patients undergoing BMT to a prophylactic platelet transfusion threshold of $<30\ x10^9/L$vs $<10\ x10^9/L$, and found no difference in bleeding incidence (18% vs 15%) or severity [60]. Likewise, in pediatric and adult BMT recipients randomized to a prophylactic platelet transfusion threshold of $<20\ x10^9/L$vs $<10\ x10^9/L$, Zumberg et al found no difference in bleeding incidence (17% vs 14%) [61]. Based on these trials, and studies in adult patients with hematologic malignancies, general practice guidelines from the American Society of Clinical Oncology recommend platelet transfusions at a threshold of $<10\ x10^9/L$ in patients receiving therapy for malignancies [62-65]. However, despite the common application of these findings to pediatric patients, children being treated for malignancies have been observed to have a significantly higher rate of bleeding (86%, 88%, 77%, and 67%, for ages 0-5, 6-12, 13-18, and $\geq$ 19 years, respectively; $P< .001$) compared to adult patients, suggesting that age impacts the risk of bleeding during periods of thrombocytopenia [66]. An increased threshold of at least $20\ x10^9/L$ for procedures such as bone marrow biopsy or insertion/removal of a cen-

tral venous catheter and 40 to $50x10^9/L$ for more invasive procedures is also recommended [62]. There have been no randomized trials to evaluate the safety of invasive procedures at lower transfusion thresholds, though several retrospective reviews of pediatric patients with acute lymphoblastic leukemia undergoing lumbar puncture (LP) reported that, while the risk of a traumatic or bloody LP may be increased in the presence of thrombocytopenia, the odds of a traumatic LP were not significantly different with varying degrees of thrombocytopenia. In addition, there was no increased risk of complication with lower platelet counts [67-70].

There is no prescribed transfusion threshold for patients with thrombocytopenia due to hypoproliferative conditions such as myelodysplastic syndrome, aplastic anemia, congenital or acquired platelet dysfunction or autoimmune thrombocytopenia. In the absence of bleeding, observation is usually recommended, although in the absence of high quality evidence, this is also based on expert opinion [62,71].

Granulocytes, plasma, and cryoprecipitate

While less commonly administered, granulocyte transfusions may be indicated in the treatment of proven, probable or presumed uncontrollable infection in patients with severe but reversible neutropenia [72]. Most commonly these are used in patients who have received a BMT or during therapy for leukemia. Several descriptions of clinical experience with granulocyte transfusions have reported tolerable adverse effects and favorable responses [73-76]. The single randomized trial of granulocyte transfusions included 10 pediatric patients and randomized participants to receive either standard antimicrobial therapy vs standard care plus granulocyte transfusions. The authors found no difference between groups in terms of survival or microbial response, but the study was under powered due to limited enrollment [77]. When physicians choose to administer granulocyte products, an ABO and Rh-matched donor should be selected due to the large number of RBCs contained within the product. In addition, irradiation is indicated due to the product's lymphocyte content [72].

Plasma transfusions are indicated in patients with coagulopathies such as active disseminated intravascular coagulation, with an acquired deficiency of multiple clotting factors if there is active bleeding or prior to invasive procedures, and in patients receiving treatment with Vitamin K antagonists who have major bleeding or insufficient time to reverse therapy [78]. Plasma is still used for correction of congenital factor deficiencies when specific concentrates are not available, such as in the case of protein C, protein S, factor II, factor V, factor X, and factor XI deficiency. Plasma is also used as a replacement fluid for apheresis in the treatment of thrombotic microangiopathies and in the treatment of hereditary angioedema when specific C1-esterase inhibitors are not available [71]. Plasma is most often administered to children under the age of 1 [79], related to the prolonged clotting times seen in neonates, even if these abnormalities have not been associated with an increased risk of bleeding [79,80]. The dosing for plasma is given in Table 1. Transfusion of plasma should result in a 15% to 20% increase in factor activity [4,6]. Of note, prothrombin complex concentrates may be more effective in normalizing markers of coagulation than is plasma in the management of intracranial hemorrhage related to vitamin K antagonists [81].

Cryoprecipitate is also widely used in children despite limited evidence to support efficacy, with up to 61% of cryoprecipitate orders in pediatric inpatients placed without an appropriate indication [82,83]. Guidelines recommend limiting use to the treatment of hypofibrinoginemia, dysfibrinogenemia and disseminated intravascular coagulation. Less frequently, cryoprecipitate can be used for factor XIII deficiency (when specific factor concentrates are not available), patients with hemophilia A when factor VIII concentrates are not available and patients with von Willebrand disease when desmopressin is contraindicated and factor VIII concentrates are not available [6,84]. Dosing is 1 to 2 units/10kg body weight or 5 to 10 mL/kg, which should result in an increase in fibrinogen of 60 to 100mg/dL [4,6].

Table 3
Indications for blood product irradiation for the prevention of transfusion-associated graft vs host disease.*

Indications for irradiation	Possible indications	Irradiation Not indicated
• Hematopoietic stem cell transplant patients • Congenital immunodeficiency affecting T cells • Hodgkin's Disease (continued for life) • Intrauterine transfusions (IUT) preterm low birth weight neonates • Neonatal exchange transfusions • High-dose chemotherapy or radiotherapy • Purine-analog drugs (eg, fludarabine, cladribine, pentostatin, bendamustine, clofarabine) • Alemtuzumab (CamPath) • Antithymoglobulin (ATG) • Granulocyte transfusions • Cellular components from first/second degree relatives • HLA-matched, HLA-selected or cross-matched platelet units	• Solid organ transplant patients • Infants up to 6 months • Healthy premature infants until 6-12 months of age	• HIV/AIDS patients • Acute or chronic leukemia • Aplastic anemia • Lymphoma other than Hodgkin's • Severe leukopenia • Autoimmune diseases • High-dose steroids • Azathiopurine • Cyclosporine • Mycophenolate Mofetil • Rituximab

* Adapted with permission from Delaney, M., Wendel, S., Bercovitz, R. S., Cid, J., Cohn, C., Dunbar, N. M et al. (2016). Transfusion reactions: prevention, diagnosis, and treatment. *Lancet, 388*(10061), 2825-2836 [122].

Blood product modification

Prior to administering blood products, physicians must consider if blood product modifications are needed. Modifications are generally aimed at reducing patient specific risks from blood product transfusion and include irradiation, leukoreduction, volume reduction and washing as well as other less common procedures [85].

Cellular blood products such as RBC, granulocytes and platelet products may be irradiated to prevent transfusion-associated graft vs host disease (TA-GVHD). TA-GVHD is a life-threatening, and often fatal, complication which occurs when donor lymphocytes mount an immune response against recipient tissues. Irradiation inactivates donor lymphocytes and prevents future mitosis, thereby preventing TA-GVHD. The main indications for blood product irradiation are congenital or acquired immunodeficiency states or when the blood donor and patient are blood relatives (Table 3). The neonatal population is one that deserves special consideration in the field of pediatrics. Neonates may be at an increased

risk of TA-GVHD as a result of their relative immune incompetence. While TA-GVHD is rare, several reports of its occurrence following intrauterine transfusion or exchange transfusion have led to the recommendation that all components administered by intrauterine transfusion be irradiated [86-88]. Other guidelines for the appropriate selection of blood product modifications have been published as well [86-88].

Leukoreduction is a filtration technique that leads to the removal of leukocytes from blood products and can be completed on RBC, platelet or plasma products. It has been shown to be effective in reducing the rate of febrile non-hemolytic transfusion reactions, platelet alloimmunization and refractoriness and cytomegalovirus (CMV) infection [89-91]. For these reasons, the majority of United States institutions now practice universal leukoreduction for RBCs and platelets. In hospitals where universal leukoreduction is not standard, leukoreduced products are generally used in patients considered to be at high-risk for these events, such as neonates and hematology/oncology patients [92,93].

RBC and platelet products can also be modified by washing, which replaces plasma supernatant with saline. Washing is effective in reducing the incidence of allergic transfusion reactions, and is therefore recommended for use in patients with a history of severe allergic reactions following transfusion. Washed products are also utilized in patients with IgA deficiency when products from an IgA-deficient donor (the first choice in this scenario) are not available [94,95]. A disadvantage of washing platelets is decreased platelet function, which may lessen the utility of the transfusion. Modification strategies which can provide blood products in patients who are sensitive to volume changes include splitting, which is the division or blood products into aliquots, and volume reduction, which is the removal of the supernatant solution to allow transfusion of primarily the cell fraction [85].

While not truly a blood product modification, another product characteristic that has been the topic of recent research is the storage age of the RBC administered. Only 1 randomized controlled trial has been conducted in pediatric patients to investigate the effects of storage. In the ARIPI trial fresh (mean age 5.1 days) vs standard-issue (mean age 14.6 days) RBC units were administered to premature infants. There was no significant difference between groups in terms of major complications or death (52.7% vs 52.9%) [96]. Though post hoc analysis of data from the TRIPICU study found an increased risk of new or progressive MOD in patients who received older blood products, the study was not set up to randomize RBC storage age [97]. The Age of Blood in Children in Pediatric Intensive Care Units study, currently enrolling, will prospectively assess the impact of RBC storage duration on outcomes (NCT01977547). Data published in the adult literature indicates that the duration of RBC storage does not have a significant impact on clinical outcomes [98,99].

Alternatives to blood products

Adjunct therapies may reduce the need for blood product transfusions and donor exposure. Adjunct therapies include antifibrinolytic agents, EPO and thrombopoeitin (TPO) receptor agonists. Antifibrinolytic agents are competitive inhibitors of plasminogen activation and inhibit fibrinolysis, stabilizing clots. Tranexamic acid (TXA) and aminocaproic acid have been used in the peri-operative setting, with resultant decreases observed in operative bleeding and blood product transfusion requirements [100-106]. The CRASH-2 (clinical randomisation of an antifibrinolytic in significant haemorrhage trial) (which enrolled patients as young as 16 years of age) found a reduced risk of death in bleeding trauma patients who received TXA [107]. Though studies in children have been less well-powered, TXA is now included in many trauma resuscitation protocols for pediatric patients [108].

EPO acts by stimulating endogenous RBC production, and has been heavily investigated in the neonatal ICU setting. Reviews of the use of EPO in preterm and low birth weight neonates found that EPO use is associated with a small reduction in the volume of RBC units transfused and number of donor exposures [109]. The use of EPO in older neonates (administered after 8 days of life) is also associated with a decrease in the number of RBC transfusions administered, though the total volume of blood transfused is not significantly different [110]. EPO has been investigated in several small studies of pediatric oncology patients, where it led to an improvement in mean baseline hemoglobin and decreased RBC and platelet transfusion requirements [111-113].

TPO receptor agonists stimulate endogenous platelet production. There is limited information at this time to guide the use of this medication in pediatric patients. Adult studies indicate that the use of TPO receptor agonists may reduce platelet transfusion requirements in patients with bone marrow failure disorders, though an associated decrease in the risk of bleeding events is not observed [114]. Their use in patients with hematologic malignancies and solid tumors has not led to a reduction in platelet transfusion requirements or bleeding events [115,116].

Conclusion

The information provided herein provides a basis to guide practitioners in their decision-making, while also highlighting the areas in which further research is needed. The importance of acquiring data specific to pediatric patients is increasingly recognized. In 2016 The National Heart, Lung and Blood Institute sponsored a meeting on Scientific Priorities in Pediatric Transfusion Medicine in order to identify key areas in pediatric transfusion medicine in which recognized gaps in knowledge exist and to promote their investigation [117]. The results of ongoing work will further shape the recommendations for pediatric transfusion practices in the years to come.

Conflicts of Interests

McCormick: None, Delaney: None related to this manuscript. Dr Delaney has received 1 time honoraria in 2018 from Grifols (topic unrelated to this paper) and has been an expert witness case review for Multicare.

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