Review Article

Intrauterine, neonatal and pediatric transfusion therapy

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Abstract: Transfusion practices for fetuses, neonates and children differ substantially from adults. These populations may be susceptible to adverse events due to their immature immune systems, decreased reserves to respond to stress and sensitivity to metabolic disturbances. Indications for intrauterine transfusions include hemolytic disease of the fetus and newborn, neonatal alloimmune thrombocytopenia and occasionally other immune or hematologic disorders. Neonates and children may require transfusions for diverse reasons including trauma, surgery, and severe medical conditions. Leukoreduction, donor selection criteria, and improved infectious disease screening have all contributed to a very safe blood supply. More recently, pathogen reduction has been implemented in many countries as a proactive protective approach for plasma and platelets, and has shown a good safety profile. Nevertheless, transfusions still carry infectious and non-infectious risks, and should therefore be administered carefully and judiciously. Excessive transfusions also consume blood products which may aid other patients. Fetuses, neonates and children are usually under-represented in trials because they constitute vulnerable populations. Thus, the transfusion literature is more limited than for older patients. Current neonatal and pediatric transfusion practices are guided by the age and clinical status of the patient but remain highly variable across institutions due to lack of evidence-based studies for many blood components. Recent clinical trials have contributed toward understanding of neonatal and pediatric transfusion triggers and clinical outcomes, but ongoing and future studies are needed for further clarification of these parameters as well as identification of viable alternatives to blood products.

Keywords: Intrauterine transfusion (IUT); neonatal transfusion; pediatric transfusion

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Introduction

Transfusion practices for fetuses, neonates and children differ substantially from adults. These populations may be susceptible to adverse events due to their immature immune systems, decreased reserves to respond to stress and sensitivity to metabolic disturbances. These patients are usually under-represented in trials because they constitute vulnerable populations. Thus, the transfusion literature is more limited than for older patients, but recent studies provide guidance about transfusion thresholds and indications.

Intrauterine transfusions

The possible utility of an intrauterine transfusion (IUT) in the management of the hemolytic disease of the fetus and newborn (HDFN), due to red cell alloimmunization, was first described by Dr. Liley in 1963 (1). While initially based on X-ray visualization of the fetus and fetal intraperitoneal cavity blood transfusions, the current practice involves either direct IUT into the umbilical vein, or into the intrahepatic portion of the umbilical vein, via ultrasound-guided cordocentesis (2). With the advancements in ultrasound imaging technologies, IUT is currently used

successfully in both immunologic and nonimmunologic indications. However, there is still potential risk for procedural and/or transfusion-related complications (2) and transfusion medicine service plays a crucial role in management of these patients.

Immunologic indications of intrauterine transfusion

While HDFN is the most common indication for IUT, where the transfused product consists of plasma-reduced red blood cells (RBC), neonatal alloimmune thrombocytopenia (NAIT) is the most common indication for a platelet IUT.

Hemolytic disease of the fetus and newborn

HDFN occurs due to the transplacental transport of IgG class antibodies targeting paternally inherited red cell and erythroid precursor antigens causing variable degrees of hemolysis, yielding a wide spectrum of outcomes ranging from serologic only findings to severe fetal anemia causing erythroblastosis fetalis and to hydrops fetalis. Sensitizing events include fetomaternal hemorrhage (FMH), transfusions and transplantations and, rarely, unknown stimuli.

Immunogenicity of red cell antigens play a key role since anti-D is one of the most potent immunogenic antigens (3) and globally the most common cause of HDFN with a 15.0% risk of Rh alloimmunization in pregnant women without prophylaxis. Of the pregnancies affected by Rh disease, 13.9% end in stillbirth and 7.2% survive with kernicterus (4). Some high-income nations have lowered the overall HDFN risk by providing routine Rh immunoprophylaxis to D-negative and variant D-positive females. ABO incompatibility has become a common cause of HDFN for such nations with a 1-4% incidence but is a significantly milder disease than anti-D related HDFN (4,5).

HDFN generally occurs after first pregnancy and at 18-20-week gestation but if maternal antibodies target erythroid precursors and cause erythropoietic suppression, then an earlier presentation may be seen. A classic example for such antibody is anti-K1 (6) but anti-Jr^a (7) and anti-Ge (8) were also reported in the literature. Since anti-I, -P1, Le^a and Le^b are not or poorly expressed on fetal red cells, they do not cause HDFN (9). Less commonly anti-E, -c, -C, -k, -Kp^a, -Kp^b, -Ku, -Js^a, -Js^b, -Jk^a, -Jk^b, -Fy^a, -Fy^b, -S, -s and -U antibodies were detected in HDFN patients (10,11).

Management of pregnancies complicated by maternal red cell alloimmunization includes monitoring maternal antibody titers and assessment of fetal wellbeing by ultrasound imaging which is generally done by fetal middle cerebral artery peak systolic velocity (MCA-PSV). If antibody titers are significantly elevated (e.g., anti-D >1:256) and/or severe anemia is detected by MCA-PSV, then treatment modalities include intravenous immunoglobulin (IVIG), plasmapheresis and IUT (12,13). The long-term outcomes of HDFN cases managed by IUT are good with an overall low incidence (4.8%) of neurodevelopmental impairment (14).

Neonatal alloimmune thrombocytopenia

The pathophysiology of NAIT closely resembles that of HDFN. IgG class maternal alloantibodies targeting human-platelet antigens (HPA) cross the placenta and cause immune-mediated thrombocytopenia. Almost all cases of NAIT are caused by antibodies against three antigens, HPA-1a affecting 80–90% of cases, and HPA-5b and HPA-3a for rest of the cases (15). Mothers who are HLA-DRB3*0101 positive have higher odds of developing HPA-1a alloimmunization (16). The mothers are asymptomatic and disease spectrum ranges from mild asymptomatic thrombocytopenia to intracranial hemorrhage (ICH) and even to extracranial hemorrhage, although the latter is very rare (17).

Overall, the incidence of NAIT is 0.3 to 1 in 1,000 pregnancies and can be detected in the first pregnancy, however, most cases are noticed after birth (18,19). Criteria for suspecting NAIT is the presence of fetal ICH or platelet count less than 100,000/μL at birth or within seven days after birth of the affected child (20).

The standard therapy for NAIT is IVIG and/or steroids (21). In very rare circumstances, fetal blood sampling may be performed to measure the platelet count and if it is found to be less than 50,000/μL then an IUT platelet transfusion could be performed (22).

Autoimmune thrombocytopenia

Compared to NAIT, transplacental transmission of autoantibodies causing immune thrombocytopenic purpura (ITP), systemic lupus erythematosus (SLE) and other autoimmune diseases with thrombocytopenia, are rare indications for IUT platelet transfusions and therapy is based on medical management (23,24).

Nonimmunologic indications of intrauterine transfusion

Fetal complications of maternal human parvovirus B19 infection are due to the inhibition of hematopoiesis and bone marrow failure and include fetal anemia, hyperdynamic circulation, cardiomegaly, non-severe to severe hydrops fetalis and fetal death (25). Although the fetal infection risk is low (1–2% of fetal infection in 30–50% of maternal infections), a timely IUT corrects anemia and improves the outcome. However, even with IUT there is a risk for neurological damage (2,25).

IUT can be performed in the management of FMH and twin-twin transfusion syndrome. In addition, literature also includes case reports/series of placental and fetal tumors, α- and β-thalassemia, elliptocytosis, Blackfan-Diamond anemia, hemochromatosis and cytomegalovirus infection managed with IUT with some success (2).

Unit requirements

Red blood cells

Per the AABB's Technical Manual, RBC units must be indirect antiglobulin test crossmatch compatible with the maternal plasma, irradiated to prevent transfusion-associated graft versus host disease (TA-GVHD), cytomegalovirus (CMV)-safe to prevent intrauterine CMV infection and hemoglobin S-negative to avoid sickling (9). In addition to the above mentioned restrictions, if possible, utilizing a 5–7-day old unit and washing RBCs to prevent hyperkalemia and also hemoconcentrating to 70–85% hematocrit to minimize the total volume of the IUT are recommended (26).

The RBC unit for IUT is generally group O D-negative, however, in some circumstances, such as need for a rare blood type unit then maternal or maternal sibling's RBCs could be used after following all allogeneic prerequisites (27) or if clinically safe, then non-group O or D-positive units could be used. However, meeting the donor hemoglobin requirements for mothers might be a challenge. The volume of RBCs to be transfused can be calculated by the below formula (28) and the usual post-IUT target hematocrit is 40–45% (9,26). The unit should be warmed to 37 ℃ before transfusion.

Platelets

Platelets for the IUT should be HPA-compatible with maternal alloantibody, irradiated and CMV-safe (9). In addition, some centers provide hyper-concentrated (>2,000×10^9/L) units for IUT (26) Advance notification of the transfusion service is required to prepare the product. The same formula used for calculating red cell volume (noted below) can be used for calculating the volume of platelet transfusion. The unit should be warmed to 37 ℃ before transfusion and infused slowly to prevent fetal stroke (26).

Formula for calculating volume of transfusion:

$$Volume\ to\ transfuse = \frac{Fetal\ weight \times 0.14 \times \left(C_{Desired} - C_{Pretransfusion}\right)}{C_{Unit}} \quad [1]$$

C: Hematocrit or platelet count

Neonatal transfusion practices

Neonates constitute one of the most heavily transfused patient groups in the hospital, with an incidence of 1.6% in a recent neonatal intensive care unit (NICU) study (29). Neonatal transfusion practices differ substantially from adult and pediatric transfusion practices because of unique physiology differences. Neonates have small blood volumes when compared with older children and adults but high blood volume per body weight. Their immature organ system function increases the risk of metabolic derangements from blood products and additive solutions, and to the infectious and immunomodulatory hazards of transfusion such as transfusion-transmitted CMV infection and TA-GVHD. Neonatal responses to stresses, including hypothermia, hypovolemia, hypoxia, and acidosis are dependent on gestational age, birth weight, and co-morbidities.

Blood products

Red blood cell transfusion

Most RBC transfusions in newborns are administered to either treat anemia of prematurity or replace blood loss, which can result from hemorrhage or phlebotomy. Iatrogenic losses from phlebotomy can be considerable, but can be minimized by judicious testing strategies, sampling from indwelling catheters, using microtainers for laboratory assays, and implementing point-of-care testing.

Recent neonatal and pediatric guidelines recommend transfusion at varying hemoglobin or hematocrit thresholds stratified by postnatal age and clinical condition or in circumstances where the amount of blood loss or removal exceeds 10% of a neonate's total blood volume (30,31). Infants with significant cardiac or respiratory disease generally receive more aggressive RBC transfusion

therapy. Villeneuve and colleagues recently summarized recommended guidelines from several countries for RBC transfusion therapy in neonates (32).

The literature supports the use of restrictive transfusion practices in neonates. Keir and colleagues recently performed a systematic review of primary and secondary adverse clinical outcomes in neonates exposed to liberal versus conservative transfusion strategies and found no statistically significant differences between the two groups across both randomized and non-randomized studies (33). Two clinical trials aimed at examining the short and long term outcomes in extremely low birth weight infants randomized to liberal or restrictive RBC transfusion thresholds recently reported results. The Effects of Transfusion Thresholds on Neurocognitive Outcome of Extremely Low Birth-Weight Infants (ETTNO) study randomized 1,013 infants weighing less than 1,000 grams at birth to a liberal (n=492) or restrictive (n=521) transfusion regimen (34). Hematocrit thresholds were based on postnatal age and whether the health state was critical or non-critical. The liberal transfusion approach did not reduce the likelihood of death or disability at 24 months of corrected age. Separately, the Transfusion of Prematures trial (TOP) enrolled 1,824 infants with a birth weight of 1,000 grams or less and randomized them to a high (n=845) or low (n=847) hemoglobin threshold for RBC transfusion. The higher threshold did not improve survival without neurodevelopmental impairment at 22 to 26 months of age (35).

Red blood cell dose and administration

A typical replacement transfusion is 10 to 15 mL of RBCs per kilogram. Because infants are so small, many pediatric transfusion centers dispense small aliquots from one RBC unit (300–350 mL) to one or several neonates who require multiple transfusions to decrease donor exposure and to conserve RBC inventory. This practice requires sterile connecting devices to assure that the original RBC unit remains a closed system and maintains its original shelf-life. Transfer packs or syringe sets permit multiple aliquots to be removed.

Several studies have investigated whether fresher RBCs decreased morbidity and mortality. In the Age of Red Blood Cells in Premature Infants (ARIPI) trial conducted in Canada, 188 very low birthweight (VLBW) infants provided with fresh RBC transfusions (mean age of transfused RBCs 5.1 days, SD 2.0 days) did not demonstrate an improvement in a composite outcome measure of major neonatal morbidities [NEC, IVH, bronchopulmonary dysplasia (BPD), and ROP] or death at 30 and 90 days compared with the 189 infants who received standard RBC products (mean age of transfused RBCs 14.6 days, SD 8.3 days) despite having 60% more donor exposures (36). Several other similarly-designed studies in older children and adults [ABLE (37), RECESS (38), TOTAL (39), and INFORM (40)] also did not identify a detrimental effect between fresh and standard age RBCs. Thus, guidelines for neonatal transfusion do not recommend limiting the age of transfused RBCs to <10 days (41).

Platelet transfusion

Indications

As with older children and adults, platelet transfusions are administered to neonates therapeutically or prophylactically to prevent the hemorrhagic complications of thrombocytopenia. Neonates have different risks of bleeding given the same degree of thrombocytopenia. Differences in platelet function or concurrent coagulopathy depending on the underlying disease are likely causes for these discrepancies (42).

Neonatal platelet transfusion threshold policies vary widely, both nationally and internationally (29). Because of the concern for IVH in the sick neonate, many physicians have traditionally adopted a fairly aggressive platelet threshold for transfusion (e.g., platelet count >100,000/μL in high-risk patients). However, in a cross-sectional observational study of neonatal outcomes with severe thrombocytopenia, Stanworth *et al.* failed to show a clear relationship between nadir platelet count/degree of thrombocytopenia and major hemorrhage (IVH, pulmonary, intra-abdominal, hematuria) (43,44). Retrospective studies have also failed to establish a link between the severity of thrombocytopenia and risk of IVH across both liberal and restrictive transfusion practices (45,46).

A historic randomized controlled trial addressing whether platelet transfusions reduce major bleeding in neonates found no benefit of maintaining a normal platelet count (platelets >150,000/μL) in preterm neonates compared with those maintained at greater than 50,000/μL. However, this study did not address bleeding risk or transfusion benefit for neonates with platelet counts less than 50,000/μL (47). More recently, Platelets for Neonatal Transfusion Study 2 (PlaNet 2), a randomized controlled trial in the UK, Ireland, and the Netherlands compared prophylactic platelet transfusion thresholds of 25,000/μL and 50,000/μL in terms of mortality and major bleeding complications in 660 premature infants (48). Surprisingly, a higher platelet transfusion threshold was associated with 7%

more deaths and/or major bleeding. A higher incidence of bronchopulmonary dysplasia was also noted but there were no differences for other complications such as retinopathy of prematurity and necrotizing enterocolitis. Another trial also showed adverse events with higher platelet transfusion thresholds (49). A significantly higher rate of IVH occurred in the higher threshold group. Possible reasons include the interaction between adult platelets with a neonatal coagulation system which is characterized by lower coagulation factors but higher von Willebrand factor levels and decreased levels of coagulation inhibitors (42).

Thus, a generally accepted transfusion trigger for platelet count less than 25,000/μL has been endorsed for healthy or stable term and preterm infants without other risk factors, whereas some experts propose a higher trigger (<30,000/μL–50,000/μL) for VLBW neonates within the first week of life, clinically unstable neonates, and neonates with NAIT (30,50).

Guidelines from the United Kingdom suggest the following thresholds:

- No bleeding, including NAIT without bleeding or family history of ICH: maintain platelet count above 25,000/μL.
- Bleeding, current coagulopathy, surgical prophylaxis, or NAIT with a family history of ICH in an affected sibling: maintain platelet count above 50,000/μL.
- Major bleeding or requiring major surgery (e.g., neurosurgery): maintain platelet count above 100,000/μL.

Platelet transfusions are also indicated to treat hemorrhage associated with acquired (i.e., ECMO, cardiopulmonary bypass, uremia) or congenital qualitative platelet abnormalities (i.e., Glanzmann thrombasthenia, Bernard-Soulier syndrome) even if the platelet count is normal.

Fresh frozen plasma transfusion

Plasma is used primarily to treat acquired coagulation factor deficiencies due to disseminated intravascular coagulation (DIC), liver failure, vitamin K deficiency from malabsorption, biliary disease, warfarin therapy, or dilutional coagulopathy from massive transfusion. It can also be used for specific factor replacement in congenital factor deficiencies (e.g., factor V, X, XI) when specific factor concentrates or recombinant products are not manufactured or unavailable (31,51). However, the optimal role of plasma in neonatal transfusion practice has not been established through evidence-based studies, and a majority of FFP transfusions in patients of all ages appear to be given for prophylactic purposes (52). Recent transfusion guidelines do not recommend routine use of plasma for correction of coagulopathy in neonates without clinically significant bleeds. In contrast, plasma may be of use in neonates with significant bleeding, including those requiring massive transfusion or at high risk for bleeding due to an invasive procedure or significant coagulopathy as evidenced by markedly prolonged PT or aPTT. Plasma is not indicated for volume expansion, enhancement of wound healing, or as first-line treatment for congenital factor deficiencies when either a virally-inactivated plasma derived factor concentrate or recombinant factor is available.

Cryoprecipitate transfusion

Cryoprecipitate is the cold-insoluble precipitate prepared from FFP that has been thawed slowly at 1 to 6 ℃ and refrozen at −18 ℃ after removal of the supernatant. It contains primarily fibrinogen, factor VIII, factor XIII and von Willebrand factor in a smaller volume than plasma (31). It may help neonates with specific coagulation factor needs who are volume restricted. Cryoprecipitate is indicated in the treatment of bleeding episodes associated with von Willebrand disease and/or hemophilia A only when FDA-licensed recombinant factor concentrates and/or viral-inactivated pooled plasma-derived factor concentrates are not available. Cryoprecipitate is the treatment of choice for factor XIII deficiency, congenital afibrinogenemia, dysfibrinogenemia, and severe hypofibrinogenemia (<150 mg/dL) associated with bleeding. In general, an infant should receive 1 bag of cryoprecipitate per 5 kg, which increases the total fibrinogen by about 100 mg/dL.

Non-infectious complications

Neonates, especially extremely premature infants, are more susceptible to metabolic alterations due to the immaturity of many of their organ systems. Glucose imbalances, hyperkalemia, and hypocalcemia are the most common metabolic derangements related to transfusion, owing to the inability of the infant to efficiently metabolize and/or excrete elements intrinsic to blood and blood components. TA-GVHD can occur if donor lymphocytes engraft in the recipient's bone marrow. Immune system immaturity is a risk factor. Although rare, TA-GVHD has a very high fatality rate (>90%). Non-infectious complications and mitigation approaches are summarized in *Table 1*.

Table 1 Non-infectious transfusion adverse events

Complication	Situation	Risk reduction
Hypoglycemia	Holding IV fluids/feeds during transfusion due to concerns about NEC. Anemia and immune dysregulation rather than RBC transfusion appear to increase risk of NEC	Continuing the infusion of maintenance fluids at a slower rate to maintain an adequate glucose infusion rate
		Close monitoring of blood glucose during transfusions
Hyperkalemia (risk of electrocardiac abnormalities and cardiac arrest)	K+ load in transfusions depends on RBC unit age, plasma volume, transfusion rate. Irradiation causes membrane damage and increased leakage of intracellular K+	Washing older RBCs is unnecessary for most small volume RBC transfusions (10–20 mL/kg)
	A recent study showed low prevalence in children, but the 1-day mortality rate was 20% (53)	Use fresh RBC units (<7–10 days) for large-volume RBC transfusions. If unavailable, volume-reduced or washed units can be considered. RBCs should be irradiated as close as possible to transfusion
Hypocalcemia	Blood products are stored in citrate anticoagulant solutions. Citrate chelates calcium	Recommend monitoring ionized calcium levels and/or QT intervals during exchange
	Complications are unlikely during a small-volume transfusion (10–20 mL/kg)	Minimize potentiating factors such as hypomagnesemia, hyperkalemia, alkalosis, and hypothermia
	However, exchange transfusion can lead to symptomatic hypocalcemia	Can consider prophylactic calcium infusion.
Hypothermia	RBCs are stored at 1–6 ℃. Hypothermia can develop with rapid large volume transfusions	Use inline blood warmers for massive transfusions or exchange transfusions
TA-GVHD	This complication may occur in patients with immature or impaired immune systems who receive cellular blood products (RBCs, platelets, granulocytes)	Irradiation prevents TA-GVHD
	Another risk factor is HLA similarity between blood donor and recipient (for example, directed donations from family members)	Some pediatric institutions have implemented universal irradiation of cellular blood products (54)

NEC, necrotizing enterocolitis; RBC, red blood cell; TA-GVHD, transfusion associated graft-versus-host disease; HLA, human leukocyte antigen.

Transfusion for pediatric patients

Introduction

Children require transfusion of blood components for a vast array of medical conditions, including acute hemorrhage, hematologic and non-hematologic malignancies, hemoglobinopathy, and allogeneic and autologous stem cell transplantation. Evidence-based literature on pediatric transfusion practices continues to be limited, particularly for non-red blood cell (RBC) products, and many recommendations are extrapolated from studies performed in adult populations.

Red blood cells

RBCs are indicated for treatment of blood loss and acute or chronic anemia in order to increase hemoglobin levels and restore adequate oxygen carrying capacity and tissue perfusion (55). While RBC transfusion is generally recommended for children experiencing acute blood loss exceeding 15–20% of their total blood volume (TBV) (56), the decision to transfuse is ultimately dependent upon individual patient characteristics, including age and physiology, hemoglobin/hematocrit levels or other laboratory values, clinical presentation, and underlying medical status. The therapeutic benefits of administering blood components must necessarily be weighed against the risks, including adverse events such as acute and delayed transfusion reactions, alloimmunization, physiologic derangements (e.g., hyperkalemia, hypothermia) and exposure to allogeneic blood.

Randomized controlled trials (RCTs) have aimed to elucidate the ideal hemoglobin trigger for RBC transfusion. Modeled after the Transfusion Requirements in Critical Care (TRICC) trial (57) in adults, the Transfusion Requirements in the Pediatric Intensive Care Unit (TRIPICU) study (58) compared restrictive (7 g/dL) *vs.* liberal (9.5 g/dL) transfusion thresholds in hemodynamically stable, critically ill children admitted to the pediatric intensive care unit (PICU). The investigators enrolled a total of 637 subjects, randomizing 320 to the restrictive strategy arm and 317 to the liberal strategy arm, and evaluated primary outcomes characterized by severity and/or progression of multi-organ dysfunction syndrome (MODS). They also looked at secondary outcomes such as 28-day mortality, length of stay, sepsis, transfusion reactions, and infection rates. No statistically significant differences were detected in the two groups for any of the outcomes, nor was there evidence of excess harm or adverse events occurring in patients in the restrictive arm. Unlike adults in the liberal study arm of the TRICC trial, patients in the TRIPICU liberal group did not have increased mortality or cardiopulmonary complications. The patients in the restrictive arm had a 96% reduction in any transfusion exposure and a 44% decrease in administered RBC transfusions compared to the liberal group. Subgroup analyses of patients with severe illness, sepsis, non-cyanotic cardiac disease or post cardiac surgery, respiratory dysfunction, acute lung injury, neurologic dysfunction, and severe trauma continued to support a restrictive transfusion threshold of 7 g/dL, although there was insufficient evidence for cyanotic patients (59). The results of a smaller RCT suggested that children with single ventricle physiology might benefit from a slightly higher restrictive threshold of 9 g/dL (compared with 13 g/dL for the liberal arm) (60). Hemoglobin thresholds are less useful in the setting of acute hemorrhage since significant losses can occur prior to detection via laboratory values, although nadir levels of 5 g/dL have been proposed as an absolute lower limit for critically ill patients (61). In the absence of prospective clinical trials studying clinically unstable children who are not in hemorrhagic or septic shock, general recommendations include reliance on clinical judgment or goal-directed therapy with physiologic targets (e.g., central venous O_2 saturation) (59).

In 2018, participants in the Pediatric Critical Care Transfusion and Anemia Expertise Initiative (TAXI) published RBC transfusion guidelines based on available evidence or expert consensus when evidence was lacking (62). In addition to recommendations aimed toward a general population of critically ill children (63), they provided separate recommendations for eight other diagnostic categories, including (I) acute respiratory failure (64), (II) non-hemorrhagic shock (65), (III) non-life threatening bleeding and hemorrhagic shock (66), (IV) acute brain injury (67), (V) acquired and congenital heart disease (68), (VI) sickle cell and oncologic disease (69), (VII) support from extracorporeal circuit membrane oxygenation (ECMO), ventricular assist devices (VADs), and renal replacement therapy (RRT) (70), and (VIII) use of alternative processing of blood products (71). The recommendations provided for the general population of critically ill children incorporated previously published guidelines by recommending 5 g/dL as the minimum and 7 g/dL as the maximum transfusion thresholds in hemodynamically stable patients (62,63). They were unable to provide specific recommendations when hemoglobin levels ranged from 5 to 7 g/dL and advocated for use of clinical judgement in such cases. For certain clinical subgroups, the authors recommended alternative hemoglobin thresholds such as 7–10 g/dL in the setting of acute brain injury (67), 7–8 g/dL for stem cell transplant and oncology patients (69), and 9 g/dL as a maximum threshold for those with uncorrected cardiac defect or single ventricle physiology (68). For patients with life-threatening bleeding, TAXI recommended empiric transfusions of RBCs, plasma, and platelets in a 1:1:1 or 2:1:1 ratio for resuscitation regardless of laboratory values (66).

Platelets

Platelet transfusions are indicated for restoring primary hemostasis during hemorrhage as well as prevention of bleeding in the presence of severe thrombocytopenia or acquired or congenital platelet dysfunction (55). The majority of transfusions are administered prophylactically to oncologic and hematopoietic stem cell transplant (HSCT) patients with hypoproliferative thrombocytopenia induced by chemotherapy, radiation, or myeloablation (72,73).

Platelet counts have historically been used as a surrogate marker for determining the likelihood of bleeding. As discussed earlier, recent studies in preterm neonates have suggested that restrictive prophylactic thresholds as low as 25,000/μL are safe and may actually be associated with a lower risk of major bleeding and mortality than more liberal thresholds of >50,000/μL (48,49). For pediatric patients, there are few platelet trigger RCTs available to formulate

evidence-based recommendations. The 2015 AABB clinical guidelines recommend a transfusion threshold of 10,000/μL to prevent spontaneous hemorrhage in adults with therapy-induced hypoproliferative thrombocytopenia; higher thresholds of 20,000/μL are recommended for those undergoing central venous catheter (CVC) placement and 50,000/μL for lumbar puncture (LP) or major non-CNS surgery (74). The extent to which these guidelines may be applied to children is controversial, especially considering evidence of poor correlation between platelet count and bleeding risk in children (75). Several pediatric clinical guidelines recommend a standard transfusion threshold of 5,000–10,000/μL for stable, non-bleeding children, excluding patients with immune-mediated thrombocytopenia or stable aplastic anemia (30,56). No definitive guidelines have been established for bleeding or unstable pediatric patients or those with qualitative platelet dysfunction, although higher values (e.g., 100,000/μL) or clinical evidence of hemostasis may be targeted in these situations (76).

The largest prospective randomized transfusion study to include a significant pediatric population is the Optimal Platelet Dose Strategy to Prevent Bleeding in Thrombocytopenia (PLADO) study, which examined the effect of different platelet doses on the incidence of bleeding in 1,272 patients with hypoproliferative thrombocytopenia (77). Patients were randomized to three different groups and received low ($1.1\times10^{11}/m^2$ of body surface area), medium ($2.2\times10^{11}/m^2$), or high ($4.4\times10^{11}/m^2$) platelet doses whenever their morning platelet counts were 10,000/μL or less. Subgroup analysis of the 200 children who received at least one platelet transfusion did not demonstrate an association between platelet dose and incidence of significant bleeding (75). However, pediatric patients (age 0-18 years), particularly those undergoing autologous or syngeneic stem cell transplantation, had a significantly higher risk (and increased frequency) of WHO grade 2 or higher bleeding compared to adults (age ≥19 years). This difference was observed regardless of pre-transfusion platelet count and suggests that other variables account for the higher incidence of bleeding in children compared to adults, possibly due to differences in endothelial structure or treatment chemotherapy dose/intensity (75,78).

Platelet transfusion thresholds for patients undergoing invasive procedures (79) or surgery (80) have also been the focus of multiple studies, although conclusive triggers have not been established in patients of any age. A retrospective review of 5,223 lumbar punctures performed on 958 children with acute lymphoblastic leukemia did not find increased rates of bleeding or other major adverse events in severely thrombocytopenic patients (742 LPs performed at platelet count of 21,000–50,000/μL, 170 at 11,000–20,000/μL, and 29 at ≤10,000/μL) (81). Based on these findings, the authors did not recommend prophylactic platelet transfusion prior to LP for patients with counts >10,000/μL, a far lower "safe" threshold than the 50,000/μL recommended by AABB for adults. AABB (74) and ASCO (82) guidelines recommend a transfusion threshold of 20,000/μL for minor invasive procedures such as bone marrow aspiration/biopsy and central venous catheter (CVC) insertion (83). For major, non-CNS surgery in patients without bleeding or coagulopathy, ASCO provides a range of 40,000–50,000/μL while AABB recommends a minimum count of 50,000/μL. British practice guidelines (30,76) have proposed 75,000–100,000/μL as targets for patients undergoing neuro- or ophthalmic surgery. ECMO patients are also heavily transfused since they are systemically heparinized and often experience rapid consumption and activation of circulating platelets by the extracorporeal circuit. Thus, they may require maintenance of counts at 100,000/μL or higher to prevent bleeding complications (56,72).

Plasma

Indications for plasma transfusion in children are similar to those described above for neonates. Although plasma transfusions are administered to nearly 3% of all pediatric inpatients in the United States (84) and 12–13% of all intensive care patients (85,86), multiple RCTs published since the 1970s have failed to demonstrate clear indications for plasma administration for either therapeutic or prophylactic purposes in adults and children (87). Expert consensus recommendations have specifically stated that prophylactic plasma transfusions should not be given solely for correction of mild to moderate coagulopathy without active bleeding or planned invasive procedures or surgery (30,76,88). Both adult (89) and pediatric (90) studies have found that over 65% of plasma transfusions in critically ill patients did not adhere to published guidelines, with approximately 34% of plasma orders being requested for non-bleeding patients without planned invasive procedures. These findings are highly concerning when considering transfusion-related risks and adverse events as evidenced by recent studies demonstrating increased organ dysfunction, nosocomial infections (91), hypercoagulability (92), and overall mortality associated with plasma transfusions in

critically ill children.

The studies referenced above also unveiled widely divergent INR thresholds used to guide transfusion decision-making (93,94). An international multicenter prospective study of critically ill pediatric patients examined incremental changes in coagulation parameters and found the differences between pre-transfusion and post-transfusion INR (median 1.5 *vs.* 1.4) and aPTT (median 48 *vs.* 41 sec) to be negligible regardless of dose except in cases of severe coagulopathy (INR >2.5 or aPTT >60 sec) (95). These observations are similar to those previously described in general populations (96,97) and confirm that traditional laboratory coagulation values are not sensitive biomarkers for evaluating response to plasma transfusion nor for predicting bleeding risks in children with mild coagulopathy (86). Hemorrhagic complications during invasive procedures, including pediatric liver biopsy (98) and central venous catheter placement (99), are rare in the setting of mild PT-INR abnormalities (range 1.5–2.0). A 2005 meta-analysis reviewed the safety profile of various invasive interventions, including bronchoscopy, central vein cannulation, femoral angiography, liver biopsy, kidney biopsy, and other minor procedures (100). The majority did not appear to be associated with increased bleeding, although there was insufficient data for particular procedures (kidney biopsy, lumbar puncture, and para- and thoracentesis), and the studies were of variable quality overall with inconsistent characterization of the degree of coagulopathy.

Cryoprecipitate

Cryoprecipitate is primarily used for fibrinogen replenishment in current clinical practice, primarily for hypofibrinogenemia or dysfibrinogenemia complicated by bleeding (e.g., DIC) or prophylaxis prior to invasive procedures or surgery (55). Human-derived (pathogen reduced) fibrinogen concentrate is approved for treatment of bleeding episodes in patients with congenital fibrinogen deficiency (i.e., afibrinogenemia or hypofibrinogenemia) (101), but is increasingly being used as an alternative to cryoprecipitate for acquired deficiencies. Several RCTs have found fibrinogen concentrate to be equally effective in treating hypofibrinogenemia-related bleeding following cardiac surgery in infants (102), children (103), and adults (104). Massive transfusion protocols have variably incorporated cryoprecipitate or fibrinogen concentrate, particularly for resuscitation in cases of postpartum hemorrhage (105). Similar to plasma, transfusion thresholds for cryoprecipitate remain controversial, although recommended fibrinogen levels range from 100 (traditionally indicated for congenital hypofibrinogenemia) up to 150–200 mg/dL for acquired deficiency secondary to trauma or cardiovascular surgery (106,107).

Ensuring infectious disease safety

Through the combination of the donor history questionnaire and improved infectious disease screening for HIV/AIDS, hepatitis B, hepatitis C and other pathogens, the blood supply has never been safer than it is now. However, donor testing does not cover all diseases and emerging pathogens continue to pose a risk.

Cytomegalovirus infection

The prevalence of CMV is 30% to 70% in blood donors, varies based on demographic differences within areas of the United States, and increases with age. This DNA virus remains latent within the leukocytes of immune persons and can be transmitted by transfusion of cellular blood components into seronegative recipients. Primary infection occurs in a seronegative recipient from a blood component from a donor who has either active or latent infection. There is wide variation in clinical sequelae from transfusion-transmitted CMV (TT-CMV), ranging from asymptomatic serological conversion, to significant morbidity and mortality from CMV-related pneumonia, cytopenias, and hepatic dysfunction. Premature, seronegative neonates less than 1,250 grams, fetuses receiving intrauterine transfusions, severely immunocompromised individuals, and recipients of hematopoietic stem cell and solid-organ transplants are recipient groups at increased risk for post-transfusion CMV-related morbidity and mortality (108).

In one study, equivalent rates of post-transfusion CMV infection in allogeneic HSCT patients occurred with CMV-seronegative units and leukoreduced units (1.4% *vs.* 2.4%, respectively) (109). These reports support considering leukoreduced blood products as "CMV safe" and some experts have argued that leukocyte reduction alone is sufficient to prevent TT-CMV (110). However, no formal consensus on the debate of equivalency has been developed (111), leading some to advise against the elimination of "dual inventories" of CMV-seronegative and seropositive blood products. Nonetheless, variable strategies

for preventing TT-CMV currently exist depending on the number of high-risk patients treated at a given center, the regional donor demographics, and product availability. A prospective multicenter birth cohort study revealed that acquisition of CMV in this patient population was primarily through maternal breast milk (112).

Pathogen reduction

Pathogen reduction (PR) is an all-encompassing term for a variety of methods (e.g., photochemical activation or solvent detergent treatment) that may be applied to blood following collection to confer broad protection against multiple infectious agents by countering proliferation and contamination (113). Many of these technologies target DNA or cell membranes and are effective across different classes of pathogens (e.g., viruses, bacteria, and parasites), offering the ability to interdict agents that are known to be transfusion-transmissible but also emerging pathogens that pose uncertain risks.

The appeal of pathogen reduction is that it is a pro-active approach to blood safety that inactivates pathogens instead of only screening for their presence. Although developed to complement current testing, PR could ultimately prove to be an alternative to testing. If widely effective, PR could reduce the number of donor deferrals due to disease risk factors. PR has been implemented for plasma and platelets. Its impact is limited by the absence of a suitable method that can be applied to RBCs, which are the most frequently transfused blood products. PR may provide additional benefits such as TA-GVHD prevention and alloimmunization reduction (114,115), but it is also associated with increased transfusion needs (due to decreased platelet corrected count increments) and potential detrimental effect on hemostatic properties of platelets and plasma (116).

Two different methodologies of photochemical activation have been more extensively studied. The only platform approved by the FDA at this time is the INTERCEPT® system (Cerus, Concord, CA, USA). This technique uses amotosalen, which can intercalate between DNA bases. In the presence of activation by UVA light, this molecule irreversibly cross-links with the DNA, thus preventing DNA transcription and cellular reproduction. After INTERCEPT® treatment, an adsorption step removes excess amotosalen; only a tiny quantity remains (117). The technology is effective against viruses, bacteria, and protozoans. However, breakthrough transmission has been reported with hepatitis A virus, hepatitis E virus, parvovirus B19, poliovirus, and certain spore-forming and/or fast-growing bacteria (118,119). There have also been cases of severe septic reactions with *Acetinobacter baumanii* complex and other bacteria due to processing or environmental contamination after INTERCEPT® treatment (120,121).

The Mirasol® (TerumoBCT, Lakewood, CO, USA) system uses riboflavin as a photosensitizer compound with UVB light. Riboflavin readily traverses lipid membranes and then intercalates non-specifically with nucleic acids. Upon exposure to UVB light, intercalated riboflavin modified guanine residues promote the generation of oxygen radicals (122,123). Since riboflavin and its by-products are naturally occurring, no additional steps for removal following treatment are believed to be necessary. Mirasol® has shown efficacy against a wide variety of pathogens (113,123,124).

There is relative paucity of neonatal and pediatric safety data. One study evaluated INTERCEPT platelets in 2,441 patients, including 46 neonates (<28 days of age) and 242 children (<18 years of age). Similar rates of adverse events occurred in children compared to adults. No events were reported in the neonates (125). In another study, Mirasol platelets were transfused to 2,458 patients, including 99 neonates (age range not specified) and 379 children (<15 years of age). Overall adverse event rate was similar in all patient groups, but neonates did have higher transfusion requirements when receiving PR platelets (126).

Summary and future directions

Current intrauterine, neonatal and pediatric transfusion practices are informed by a combination of evidence-based recommendations where they exist, expert consensus statements incorporating best practices, guidelines derived from adult populations, and historic precedents not supported by data. Practices can be highly variable between institutions. Cure and colleagues (127) recently identified several key areas requiring additional research, including ideal parameters for assessing the need for transfusion beyond cell counts as well as markers for assessing transfusion efficacy and long-term outcomes, methods of gathering and compiling epidemiologic data on neonatal transfusions, and blood management strategies for neonates. Studies in the last few years have provided more information about transfusion thresholds and the impact of growing pathogen-reduced product use (128). Nevertheless, the persistence of non-evidence-based approaches highlights the ongoing need for additional research targeted

toward these special populations.

Key points

- Indications for intrauterine transfusions include HDFN, NAIT and occasionally other immune or hematologic disorders.
- Current neonatal and pediatric transfusion practices are guided by the age and clinical status of the patient but remain highly variable across institutions due to lack of evidence-based studies for many blood components.
- Recent clinical trials have contributed toward understanding of neonatal and pediatric transfusion triggers and clinical outcomes, but ongoing and future studies are needed for further clarification of these parameters as well as identification of viable alternatives to blood products.
- Leukoreduction, donor selection criteria, and improved infectious disease screening have contributed to a very safe blood supply.
- Nevertheless, transfusions still carry infectious and non-infectious risks, and should therefore be administered carefully and judiciously. Rapid, large volume transfusions, in particular, can lead to metabolic derangements in smaller patients.
- Pathogen reduction is a proactive approach to blood safety and has shown a good safety profile.

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