REVIEW

Unique aspects of red blood cell transfusion in pediatric patients

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Abstract: Red blood cell transfusion plays an integral role in the management of the anemic child, and multiple factors must be considered when performing transfusions in children as compared with adults. The practitioner must be aware of the particular indication for transfusion, normal hemoglobin for age, and the need for special requirements based on the age and type of patient. Additionally, the practitioner must be aware of potential unique complications in the pediatric population and also ensure a system is in place in order to report and evaluate such potential adverse reactions. Here, we review the underlying physiological factors, symptomatology, transfusion guidelines, transfusion reactions, and potential side effects with an emphasis on those aspects that are unique to children with anemia. Many gaps remain in fully understanding pediatric red blood cell transfusion that should be addressed over time with continued research and hemovigilance.

Keywords: pediatrics, anemia, red blood cell transfusion, transfusion medicine, transfusion reaction

Introduction

Red blood cell (RBC) transfusion plays an integral role in the management of the anemic child, and multiple factors must be considered when performing transfusions in children as compared with adults. Pediatric patients require RBC transfusion for multiple presentations including 1) prematurity; 2) chronic diseases with underlying ineffective erythropoiesis such as β-thalassemia and sickle cell anemia (SSA); 3) congenital bone marrow failure syndromes such as Diamond-Blackfan anemia, Fanconi anemia, dyskeratosis congenita, and Schwachman-Diamond syndrome; 4) acquired bone marrow failure secondary to aplastic anemia, marrow infiltration as in hematologic malignancy, or chemotherapy-induced aplasia; 5) nutritional deficiencies, primarily iron deficiency but also folic acid or vitamin B12; 6) transient erythroblastopenia of childhood; 7) chronic disease resulting in decreased erythropoietin (EPO) production as well as macrophage trapping of iron and upregulation of hepcidin leading to decreased gastrointestinal iron absorption; 8) infection resulting in bone marrow suppression such as parvovirus B19; and 9) acute presentation of blood loss often secondary to underlying gastrointestinal pathophysiology such as milk protein allergy and Meckel diverticulum or dysfunctional uterine bleeding in the adolescent female. Here, we review the underlying physiological factors, symptomatology, transfusion guidelines, transfusion reactions, and potential side effects with an emphasis on those aspects that are unique to children with anemia.

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Age-dependent physiology of anemia

The neonatal, childhood, and adolescent periods have unique physiologic properties which affect the ability to tolerate anemia. In order to increase oxygen affinity in utero, 2,3-diphosphoglycerate (2,3-DPG) levels are decreased in the fetus. Additionally, fetal hemoglobin (Hb) does not interact with 2,3-DPG further increasing Hb oxygen affinity in a low oxygen tension environment.[1] After birth, levels of 2,3-DPG increase while fetal Hb decreases to <1% over a 6-month period in the infant with no underlying ineffective erythropoiesis. Due to the presence of fetal Hb at birth, tissue unloading of oxygen will be decreased, necessitating a higher baseline Hb concentration.[2] Fetal Hb is also less deformable, leading to increased blood viscosity.[2] Premature infants are at risk of anemia secondary to decreased endogenous EPO production and smaller total blood volume (TBV), leading to anemia from serial phlebotomy.[2–4] Decreased EPO leads to the physiologic nadir at 8–10 weeks of age, which is significantly more pronounced in premature infants.[3,4] Additionally, due to higher baseline heart rate, infants have a limited ability to increase myocardial contractility in response to hypovolemia.[2] Infants suffering from cyanotic congenital heart disease generally have polycythemia, which can also adversely affect blood viscosity.[2]

Infants, children, and adolescents have increased metabolic demand as compared with adult patients. This is especially important in considering a critically ill pediatric patient with increased metabolic needs secondary to sepsis or significant trauma.[2] Unlike younger children, adolescents may not tolerate the same level of anemia, such as during cancer therapy, and may require RBC transfusion to maintain higher Hb levels which can improve fatigue and quality of life.[5]

Age-dependent signs and symptoms of anemia

The presentation of anemia in children depends on 1) the severity of anemia, which determines the degree of reduction in oxygen carrying capacity; 2) the rapidity of onset of anemia, thus impacting the ability to compensate from a cardiovascular standpoint; 3) ongoing blood loss such as with bleeding or hemolysis; and 4) age of onset, as described earlier. Children generally have structurally intact cardiopulmonary systems allowing for compensation of severe anemia (ie, Hb <7.0 g/dL) with chronic onset, and can adapt without significant symptoms to an oxygen deficient state.[6] The acute symptoms of anemia unique to young patients include poor feeding, irritability, and lethargy, while older children may complain of loss of appetite, fatigue, headache, dizziness, and loss of concentration, and families may note a change in behavior and school performance. Signs of anemia are often related to severity and rapidity of onset and may include pallor, tachycardia, prominent arterial pulses, tachypnea, postural hypotension, cardiac murmurs, gallop rhythm, cardiac enlargement on chest X-ray, and evidence of congestive heart failure, presenting as hepatomegaly and periorbital edema rather than peripheral edema and increased jugular venous distension as in adults. Common signs such as tachypnea and tachycardia may not be present in premature infants and may not be impacted by transfusion.[7] Disease-specific signs include frontal bossing and prominent malar and maxillary bones with extramedullary hematopoiesis in thalassemia major, as well as radial limb dysplasia and thumb anomalies in Fanconi anemia. As with adult patients, dizziness and syncope can be seen with acute blood loss. Pica behavior is common in children with iron deficiency and lead toxicity and breath holding spells can be exacerbated by concomitant severe anemia.[8] Chronic anemia can adversely affect growth and development and potentially have long-term negative consequences on cognition.[5,9]

Normal Hb levels for age

The practitioner must be aware of normal Hb levels based on patient age which vary significantly over time. Jopling et al reported reference ranges for neonates and found that Hb concentration increased according to the formula

$$Hb = 9.92 + (GA \times 0.2087), \quad (1)$$

where GA is gestational age.[10] They additionally reported the expected drop in Hb over the first 28 days of life based on initial GA: infants born at 35–42 weeks began with a mean Hb of 18 g/dL (−2 standard deviation [SD] 14 g/dL), which fell to 13 g/dL (−2 SD 9.5 g/dL) at 28 days while Hb of those born at 29–34 weeks GA fell to 11 g/dL (−2 SD 7.8 g/dL). Infants born below 29 weeks invariably were transfused, making a calculation for this cohort impossible. Table 1 reports mean Hb and mean corpuscular volume values by age. Transfusion parameters must be implemented with consideration for normal Hb for age.

Hb threshold for transfusion

Different transfusion thresholds must be utilized in pediatric patients dependent on age. For anemia of prematurity, no consensus exists and practice is variable.[2,4,11] Strauss suggests very general transfusion guidelines which are presented in Table 2, but also emphasizes that the guidelines must be

Table 1 Red blood cell values at various ages

Age	Hemoglobin (g/dL)		MCV (fL)	
	Mean	−2 SD	Mean	−2 SD
Birth (cord blood)	16.5	13.5	108	98
1–3 days (capillary)	18.5	14.5	108	95
1 week	17.5	13.5	107	88
2 weeks	16.5	12.5	105	86
1 month	14.0	10.0	104	85
2 months	11.5	9.0	96	77
3–6 months	11.5	9.5	91	74
0.5–2 years	12.0	11.0	78	70
2–6 years	12.5	11.5	81	75
6–12 years	13.5	11.5	86	77
12–18 years; female	14.0	12.0	90	78
12–18 years; male	14.5	13.0	88	78
18–49 years; female	14.0	12.0	90	80
18–49 years; male	15.5	13.5	90	80

Note: Reproduced with permission from John Wiley & Sons. Hastings CA, Torkildson JC, Agrawal AK. *Handbook of Pediatric Hematology and Oncology: Children's Hospital and Research Center Oakland*. 2nd ed. © 2000 John Wiley & Sons, Ltd.[122]
Abbreviations: MCV, mean corpuscular volume; SD, standard deviation.

adjusted to local practice.[4] Use of a restrictive transfusion practice remains controversial in premature neonates as the methodological quality of the majority of randomized controlled trials (RCTs) trying to address this question is poor.[11,12] Two well-designed studies by Bell et al and Whyte et al have shown that a more liberal transfusion practice does not expose neonates to more donors and may have benefit in the rate of major adverse neurologic events as well as potential benefit in longer term neurodevelopmental outcome.[13,14] However, dos Santos et al reported that increased RBC transfusion was statistically associated with death in both univariate and multivariate analysis in very low birth weight (VLBW) premature infants, although, their results could have been confounded by the inclusion of sicker neonates who would have received more RBC transfusion.[15] Controversy remains and larger, well-designed multicenter studies are required to firmly address these questions.[11]

Less controversy exists with regard to the risk benefit ratio of transfusion in critically ill pediatric patients. The AABB

Table 2 Red blood cell transfusion guidelines for premature neonates

Consider transfusion to maintain hemoglobin (g/dL) threshold based on clinical scenario:

>11–15 for severe cardiopulmonary disease
>10 for moderate cardiopulmonary disease
>10 for major surgery
>7–9 for symptomatic anemia
>7 for asymptomatic anemia

Note: Adapted from Strauss RG. Anemia of prematurity: pathophysiology and treatment. *Blood Rev.* 2010;24(6):221–225, Copyright 2010, with permission from Elsevier.[4]

(formerly, the American Association of Blood Banks) recommends transfusion in both adult and pediatric intensive care units (PICUs) for Hb ≤7 g/dL as a high quality of evidence strong recommendation.[16] In a large multicenter RCT of PICUs, Lacroix et al showed that a restrictive transfusion strategy with Hb threshold of 7 g/dL, rather than a liberal threshold of 9.5 g/dL, in critically ill but hemodynamically stable children decreased transfusion requirements without impacting morbidity or mortality.[17] A subgroup analysis of PICU post-cardiac surgery patients similarly showed no difference in new or progressive multiple organ dysfunction, PICU length of stay or 28-day mortality between a restrictive and liberal transfusion strategy.[18] In addition, a retrospective study of 657 post-cardiac surgery pediatric patients showed no difference in mortality based on amount of RBC transfusions received.[19] Studies in infants undergoing cardiac surgery have shown similar results, with no benefit of a liberal transfusion practice in those with single-ventricle physiology post-cavopulmonary connection and blood transfusion being a statistically significant independent risk factor for prolonged duration of mechanical ventilation after reparative surgery.[20,21] Finally, a prospective observational multicenter study of PICUs reported an adjusted significantly increased number of days of mechanical ventilation and PICU stay, rate of cardiopulmonary dysfunction, nosocomial infection, and mortality in those children who were given RBC transfusion.[22]

Consensus guidelines are lacking for pediatric oncology patients, and it is therefore suggested to tailor transfusion to the individual patient's needs.[23,24] Considerations for transfusion must include the patient's clinical condition, anticipated procedures, presence of cardiopulmonary disease, and risk of bleeding. For young children, the effect of anemia on growth and development must be ascertained, while in adolescents, individual preference as well as the effect of anemia on fatigue and quality of life must be surmised.[25] As with neonates and critically ill patients, a restrictive transfusion strategy will safely limit transfusions. Suggested prophylactic RBC transfusion thresholds for pediatric oncology patients are presented in Table 3.

Transfusion is commonly utilized in pediatric patients with hemoglobinopathies. Patients with β-thalassemia major (β_0-thalassemia) and Eβ_0-thalassemia are transfusion dependent and require transfusion generally every 3 weeks with the goal of maintaining normal Hb levels and minimizing ineffective erythropoiesis.[26] Patients with β-thalassemia intermedia are often the most difficult to manage as they produce enough β-globin to not require chronic transfusion, but due

Table 3 Prophylactic red blood cell transfusion guidelines for children and adolescents with cancer

Clinical scenario	Signs/symptoms	Hemoglobin level to transfuse (g/dL)
Stable	Asymptomatic child, imminent hemoglobin and platelet recovery	<7
Vital sign changes	Tachycardia, tachypnea, hypotension	<8
Oxygen requirement	Pulmonary or cardiac comorbidities	8–10
Thrombocytopenia	History of prior hemorrhage and PRBC requirement	8–10
Procedure	Anticipation of blood loss	8–10
Fatigue	Negative effect on quality of life, especially in adolescents	8–10
Chronic anemia	Impact on development	8–10
Infants	Impact on growth or development	8–10
Radiation (controversial)		8–10

Note: Reprinted with permission from Agrawal AK, Hastings CH, Feusner J. Hematologic Supportive Care in Children With Cancer. In: Pizzo PA, Poplack DG, editors. *Principles and Practice of Pediatric Oncology.* 6th ed. Philadelphia: Lippincott Williams and Wilkins; 2011.[123]
Abbreviation: PRBC, packed red blood cell.

to phenotypic heterogeneity may develop signs of erythroid hyperplasia, including bony deformities as well as significant impact on growth and development.[27,28] Some experts suggest that patients with β-thalassemia intermedia also be chronically transfused to avoid these potential complications.[27] If the in utero diagnosis of α-thalassemia major is made based on family history and prenatal findings of anemia, cardiomegaly, and hydrops, fetal transfusion can be commenced and continued after birth until the infant is old enough for curative hematopoietic stem cell transplantation (HSCT).[29]

Transfusion in SSA has widespread benefit and is generally underutilized. The Stroke Prevention Trial (STOP) for Sickle Cell Anemia Study showed that chronic transfusion (ie, transfusion every 3–5 weeks with goal HbS <30%) can prevent first stroke in pediatric patients with an abnormal transcranial Doppler ultrasound and secondarily showed improved growth and development and decreased acute chest syndrome and pain episodes in those children randomized to receive regular transfusions.[30–33] Erythrocytapheresis is the ideal way to transfuse normal HbA while removing HbS and minimizing transfusional iron burden, but does expose the patient to more RBC units.[34] Patients with SSA should be chronically transfused for primary stroke prevention in case of abnormal transcranial Doppler ultrasound, for secondary stroke prevention (ideally with erythrocytapheresis), and during the second and third trimester of pregnancy; acute

transfusion should be performed in case of severe acute chest syndrome, acute stroke (ideally with erythrocytapheresis), during splenic sequestration, with episodes of RBC aplasia from infections such as parvovirus B19, and prior to surgery to obtain an Hb of 10 g/dL.[34,35] Further data are required to fully support the decision to chronically transfuse during pregnancy.[36] Whether early transfusion during a vaso-occlusive event mitigates symptoms is yet to be fully elucidated.[37] Overtransfusion should be avoided due to risk of hyperviscosity and potentiating stroke.[38]

RBC transfusion in fetal medicine and premature neonates
Intrauterine transfusion (IUT) for RBC alloimmunization

The passage of fetal RBCs across the placenta can lead to the development of red cell antibodies, which can subsequently cause significant fetal anemia due to suppressed erythropoiesis and extravascular hemolysis. IUT has been shown to be beneficial and safe at experienced centers in cases of maternal RBC IgG alloantibodies as well as RBC aplasia from parvovirus infection.[39] Utilization of IUT may lead to additional RBC alloantibodies; thus, it is important to provide phenotypically matched RBCs between donor and mother.[40,41]

Autologous/placental RBC transfusion

Although technically feasible, placental RBC extraction for autologous transfusion continues to have limited applicability.[42] In small pilot studies, there has been no benefit in autologous transfusion in neonates as compared with standard allogeneic transfusion.[42,43] Additionally, there is limited benefit due to low volume of collection in extremely low birth weight infants.[42,44–46] The shelf-life of umbilical cord blood autologous product is also shorter at 14–21 days.[47] In addition to these concerns, bacterial contamination and high cost continue to hamper clinical usage.[42,44]

RBC transfusion and intraventricular hemorrhage (IVH)

Reports from one main group have shown potential correlation between RBC transfusion and either risk of developing or propagation of existing IVH in premature neonates. Baer et al first reported that RBC transfusion was the most significant contributor to increased odds of extending a Grade 1 IVH to a Grade 3–4 IVH, though it remained unclear if this was secondary to underlying baseline risk in the infant or due

to transfusion.[48] A follow-up study by the same group was more conclusive showing that IVH Grade 3–4 cases were significantly more likely to have received RBC transfusion than matched controls, and each subsequent RBC transfusion doubled the risk of severe IVH.[49] After reducing RBC transfusion from 58% to 25% in the first week of life over a 9-year period, the same group was able to show a relatively correlated decrease in IVH from 17% to 8%.[50] This reduction was accomplished by delaying umbilical cord clamping, milking or striping the cord, and minimizing phlebotomy as well as drawing neonatal ICU admission labs from the placenta.[51] IVH occurred in the first week in 27% of those receiving RBC transfusion and in only 2% of those not being transfused ($P<0.001$).[50] Causation is uncertain, and it remains unclear if the increased IVH risk is due to biomechanical properties related to the need for RBC transfusion or due to RBC transfusion itself or potentially secondary to inflammatory upregulation with transfusion.[50]

Transfusion associated necrotizing enterocolitis (TA-NEC)

An association between transfusion and necrotizing enterocolitis (NEC) in premature neonates has been reported in the literature but it remains unclear if TA-NEC is a true entity. Multiple conflicting reports have been published; a meta-analysis by Mohamed and Shah was unable to conclusively determine correlation.[52] TA-NEC appears related to late-onset NEC (~ 31 weeks GA) with no difference in the prevalence of NEC based on the RBC preservative or age of stored RBCs.[52] Withholding feeds during RBC transfusion may potentially decrease TA-NEC.[52,53] Multiple etiological factors are proposed including impaired splanchnic blood flow before or after transfusion, inflammatory cytokines from RBC transfusion, ischemia/reperfusion injury, or underlying impaired intestinal angiogenesis.[51,52] Data are lacking to make firm conclusions regarding either causation or etiology and further prospective multicenter studies are required.

EPO to minimize premature neonatal RBC transfusion

The conclusion of multiple studies and meta-analyses is that EPO does not play a significant role in reducing exposure to RBC transfusion whether given early after birth (ie, in the first 2 weeks) or later.[54–57] In addition, correlation between risk of retinopathy of prematurity and early utilization of EPO in meta-analyses highlights the need to consider alternative methodologies to reduce the need for early transfusion.[54,56] Although late EPO administration has been shown to

fractionally decrease the number of RBC transfusions (<1 transfusion per infant), the clinical significance of this decrement is questionable.[55]

RBC storage lesion

Various changes occur to RBCs during storage including decreased 2,3-DPG, ATP depletion, membrane vesiculation, passive leakage of potassium out of RBCs, and loss of RBC deformability. Collectively, these changes are known as the RBC storage lesion and have been reviewed by Tinmouth et al.[58] While the biochemical and morphological changes have been well documented for decades, the clinical impacts of these changes remain unclear. Multiple observational studies reviewed by Lacroix et al have reported that prolonged RBC storage (ie, >7–14 days) may impact RBC function resulting in harm to vulnerable patients.[59] Hod et al showed in a murine model that transfusion of stored RBCs initiates inflammation through upregulation of non-transferrin bound iron, which subsequently leads to iron tissue deposition and enhanced bacterial growth.[60] The transfusion of fresh RBCs, on the other hand, did not lead to this inflammatory cascade.[60] A meta-analysis including 21 adult studies, found that older blood was statistically correlated with increased risk of death, unrelated to type of patient or amount of RBCs transfused.[61]

In critically ill pediatric patients, Gauvin et al reported a significant independent increased risk of multiple organ dysfunction syndrome (MODS) in patients who received RBC transfusion >14 days old and increased risk of mortality if >21 days old.[62] The significant increased risk of MODS was also demonstrated by Karam et al in addition to prolonged PICU stay for those receiving RBC transfusion ≥14 days old but with no effect on mortality.[63] However, these and other observational studies have many potential pitfalls as reviewed by Tinmouth et al as well as Zimrin and Hess.[58,64,65] Three large multicenter RCTs have failed to show harm from older RBCs.[66–68] In the Age of Blood Evaluation (ABLE) trial, Lacroix et al studied critically ill adults who received RBCs either an average of 6.1 versus 22.0 days old and showed no difference in 90-day mortality or any secondary outcome.[66] Steiner et al recently reported the results of the Red-Cell Storage Duration Study (RECESS), a study of patients ≥12 years of age undergoing cardiac surgery, and found no difference in the rate of MODS comparing RBC storage duration ≤10 versus ≥21 days.[67] And finally, the Age of Red Blood Cells in Premature Infants (ARIPI) trial at six Canadian tertiary neonatal ICUs comparing RBCs stored <7 days versus standard transfusion showed no difference

in any of the major neonatal morbidities, mortality or rate of nosocomial infection.[68]

Multiple studies have shown the safety of older blood in premature neonates, especially in order to prevent exposure to multiple donors.[4,57] Although concerns have been raised regarding the increase in cellular potassium and decrease in 2,3-DPG with age of the RBC unit, it is considered safe to transfuse an adenine saline (AS) unit up to the 42-day shelf-life, when given as small aliquots.[4,57] Transfusion of CPDA-1 (citrate–phosphate–dextrose–adenine) stored RBCs up to 28 days old has been shown safe in VLBW premature infants with no clinical or biochemical changes in potassium level, even with increased potassium concentration in the transfused product.[69]

Pediatric cardiac surgery

In high-risk pediatric cardiac surgery it remains controversial whether RBC storage duration impacts outcomes. In a retrospective study, Manlhiot et al reported that in those patients who required a significant amount of RBC transfusions (>4 units or >150 mL/kg) for complex surgical cases, longer storage duration by day was statistically correlated to increased in-hospital mortality, and effect on post operative bleeding was greatest for storage duration >14 days.[70] Contradictory reports are available on the effect of RBC storage duration of the priming solution before and during cardiopulmonary bypass in children, with one report showing no difference, one in favor of shorter RBC storage duration, and the third in favor of older blood.[71–73] Finally, Cholette et al observed that washing RBCs in pediatric cardiac surgery reduced inflammatory markers post operatively with a trend toward decreased total transfusion and mortality in those receiving washed products.[74] A follow-up study by the same group reported a significantly higher infection rate in those children receiving the oldest blood, especially if those RBCs were washed.[75] No data are available regarding the age of RBCs in priming for extracorporeal membrane oxygenation, though it is suggested to use the freshest blood and, if required, to irradiate immediately before issuing the product.[76]

Guidelines for pediatric RBC transfusions
RBC component therapy and dosing

Multiple anticoagulant-preservative solutions (outlined in Table 4) can be added to RBCs to allow for a longer storage period by maintaining pH and preventing coagulation including CPDA (35-day storage) or extended storage solutions AS-1 (Adsol, Baxter International Inc., Deerfield, IL, USA), AS-3 (Nutricel, MedSep Corporation, Covina, CA, USA), and AS-5

Table 4 Formulation of anticoagulant-additive solutions in blood collection sets

Constituent	CPDA-1	AS-1	AS-3	AS-5
Volume (mL)	63	100	100	100
Hematocrit (%)	70–80	55–60	55–60	55–60
Sodium chloride (mg)	None	900	410	877
Dextrose (mg)	2,000	2,200	1,100	900
Adenine (mg)	17.3	27	30	30
Mannitol (mg)	None	750	None	525
Trisodium citrate (mg)	1,660	None	588	None
Citric acid (mg)	206	None	42	None
Sodium phosphate (monobasic) (mg)	140	None	276	None

Note: Reproduced with permission from John Wiley & Sons. Strauss RG. Data-driven blood banking practices for neonatal RBC transfusions. *Transfusion.* 2000;40(12):1528–1540. © 2000 John Wiley & Sons, Ltd.[124]
Abbreviations: AS, adenine saline; CPDA, citrate–phosphate–dextrose–adenine.

(Optisol, Terumo Medical Corporation, Somerset, NJ, USA) (42-day storage).[4,57] Preterm neonate and pediatric RBC dosing is generally 10–20 mL/kg aliquots transfused at a maximum of 5 mL/kg/hour. RBC units can be sterilely aliquoted in order to prevent exposure to multiple donors in those patients expected to require multiple RBC transfusions such as the premature neonate.[2,4,57] A study comparing CPDA-1 with AS-1 in VLBW infants showed no difference in Hb increase when correcting for Hb concentration differences between products.[77] The RBC unit should be warmed for premature neonates and if the volume of transfusion will exceed >20% of TBV (with TBV approximated as 80 mL/kg to a maximum of 6 L).[2]

Concerns regarding the age of transfused RBCs and increase in potassium concentration are important with massive transfusion. Lee et al reviewed pediatric cases of transfusion-associated hyperkalemic cardiac arrest and observed risk factors including 1) infancy, 2) age of RBCs, 3) rate of transfusion more so than the total RBCs transfused, and 4) comorbidities, especially electrolyte derangements and hypotension.[78] Massive transfusion was considered if >35 mL/kg were given over 3 hours or if >70 mL/kg were given over 24 hours.[78] Suggestions to reduce risk of transfusion-associated hyperkalemic cardiac arrest include 1) use of fresher RBCs, 2) minimizing time between irradiation and transfusion, 3) washing older irradiated RBC products, and 4) use of a peripheral intravenous catheter to decrease rate of transfusion.[78] Of note, hypokalemia can also occur with massive transfusion as metabolism of citrate leads to metabolic alkalosis and an intracellular shift of potassium in addition to dilutional effects with concomitant administration of large amounts of potassium-poor solutions such as crystalloids.[77,78] Citrate can additionally lead to ionized hypocalcemia, especially with massive transfusion in infants.[77,79]

The practitioner should determine the expected rate of Hb increase based on transfusion volume in order to prevent hypervolemia; for an AS unit with a hematocrit of 55%–60% without active blood loss, Hb should increase by 2 g/dL for each 10 mL/kg of transfused blood (ie, a transfusion factor of approximately 5).[80] Additionally, anecdotal teaching that a period of "re-equilibration" after RBC transfusion is required before obtaining an accurate Hb measurement has been disproven in both neonatal and pediatric patients.[80,81]

Leukoreduction and irradiation

Based on adult studies, leukoreduction has been reported to significantly reduce febrile nonhemolytic transfusion reactions (FNHTRs) and cytomegalovirus (CMV) transmission and may be effective in reducing transmission of additional infectious agents as well as attenuating transfusion-related immunomodulation.[82] Universal leukoreduction of RBCs for premature neonates has been shown to improve outcomes, though did not impact bacteremia from transfusion or overall mortality.[83] A retrospective study of line infections in adult and pediatric patients reported a significant decrease in infection rate after implementation of universal leukoreduction.[84] In order to prevent transfusion-associated graft-versus-host disease, immunocompromised pediatric patients including premature infants as well as those with immunodeficiencies or undergoing chemotherapy or HSCT should receive irradiated RBCs.[85]

CMV seronegative RBC transfusion

Risk of CMV transmission remains a concern in immunocompromised CMV-seronegative pediatric patients including premature neonates and those undergoing chemotherapy, HSCT, and solid organ transplantation.[86] Although leukoreduction reduces risk of transmission to the same order of magnitude as CMV-seronegative blood products, controversy remains that the risk of transmission remains significantly higher with leukoreduction alone.[86–88] Leukoreduction significantly reduces viral burden but does not completely remove CMV from blood components.[89] Therefore, consensus guidelines continue to recommend CMV-seronegative, leukoreduced RBCs for the highest-risk pediatric populations, namely, premature infants born to CMV-negative (or CMV-unknown) mothers, those with potential immunodeficiencies, and those receiving HSCT.[90,91]

Special considerations in pediatric patients
Severe chronic anemia
Generally, due to normal underlying cardiopulmonary status, pediatric patients can adapt to severe anemia of slow onset by increasing plasma volume to near normal levels. Given this underlying physiology, concern exists for the development of transfusion-associated circulatory overload with cardiogenic pulmonary edema and cardiac decompensation with rapid transfusion in such patients (ie, Hb $\leq$5 g/dL). Although slow transfusion is often recommended, data to support this are lacking, and two studies have shown the safety of transfusion of at least 2 mL/kg/hour in patients without signs of cardiac failure or circulatory overload.[92,93]

Hyperleukocytosis
Pediatric patients with acute myelogenous and acute lymphoblastic leukemias can present with hyperleukocytosis or white blood cell counts $\geq$100$\times$10^9/L with resultant risk of leukostasis. In order to maintain a stable cytocrit, the body will compensate by reducing the erythrocrit, and anemia is common secondary to this compensation as well as due to underlying bone marrow dysfunction.[94] RBC transfusion should be used judiciously in such cases in order to not increase the cytocrit and worsen leukostasis; Hb levels >10 g/dL should be avoided.[95]

Radiation therapy
Although tumor hypoxia may play a role in the efficacy of radiation therapy, it remains unclear if treatment of anemia improves tissue hypoxia and thereby improves outcomes in oncology patients.[96–98] Although many pediatric oncologists will transfuse to Hb levels $\geq$9 g/dL during radiation therapy, data supporting the efficacy of such a practice are lacking.[24]

Jehovah's Witness
Families that are Jehovah's Witness must balance the tenets of their belief system that preclude the use of blood or blood products in any form with the potential needs of their child. Although adult patients may refuse transfusion, the rights of parents to make this decision for their child have been refuted by the legal system.[99–101] Whenever possible, alternative methods for augmentation of Hb, such as through utilization of EPO, should be employed, and hospitals should have policies in place for "bloodless" surgeries to minimize blood loss and need for transfusion in such circumstances.[102] If necessary, a court order can be obtained to allow for RBC transfusion, a practice that most Jehovah's Witness families find acceptable in emergent situations.[101]

Directed donation
Many families will inquire about direct donation given the presumed risk of infection from RBC transfusion, although

data supporting directed donor blood being safer than the screened donor pool are lacking and there is also a high wastage rate.[103,104] For patients potentially undergoing HSCT, the risk of directed donor RBC transfusion from a biological parent includes development of significant RBC alloantibodies. Given these risks and potential lack of benefit, there remain scenarios where directed donation can be considered and should be discussed with the family. Strauss et al observed that biological parents can feasibly serve as blood donors for their premature neonate in a safe fashion and limit donor exposure.[105]

Transfusion complications unique to pediatric patients

Transfusion complications that are generally common between adult and pediatric patients include acute hemolytic transfusion reactions, FNHTRs, allergic transfusion reactions, delayed hemolytic transfusion reactions, transfusion-related acute lung injury, transfusion-associated graft-versus-host disease, and infectious complications. Oakley et al compared adult and pediatric transfusion reactions and found a significantly increased incidence in the pediatric population (6.2 reactions per 1,000 transfusions versus 2.4 reactions per 1,000 in adults), including, specifically, FNHTRs, allergic transfusion reactions, and hypotensive reactions.[106] A similar review of transfusion-related acute lung injury reported to the Canadian Blood Service showed an incidence of 5.58 for children and 3.75 for adults per 100,000 RBC transfusions, with the majority of pediatric cases in infants and teenagers and with no differences in presentation or outcome compared with adults.[107] Lavoie observed an increased risk of adverse events in children (18 per 100,000 RBC units issued) and neonates (37 per 100,000) as compared with adults (13 per 100,000) in large part due to poor understanding of the special requirements for neonates and through overtransfusion.[108] The risk of transfusion-associated circulatory overload is poorly defined in the pediatric population, with premature neonates and those with poor cardiac function at theoretically greater risk.

Chronically transfused pediatric populations, such as those with underlying hemoglobinopathies or congenital bone marrow failure syndromes, are at risk of RBC alloimmunization with subsequent delayed hemolytic transfusion reactions, as well as iron overload. Patients with SSA are at highest risk of alloimmunization due to the mismatch with the largely Caucasian RBC donor pool.[109] Rate of pediatric alloimmunization in SSA is reported to be ~30%, which is significantly higher than other frequently transfused groups.[109,110] Although there are concerns about cost-effectiveness, given the high rate of pediatric SSA alloimmunization, most tertiary SSA centers would initially match RBCs for at least minor antigens Rh, C, E and Kell in addition to ABO.[111,112]

To prevent long-term complications of iron overload, chronically transfused pediatric populations must be monitored closely through measurement of ferritin levels as well as non invasive testing such as with T2*/R2* magnetic resonance imaging or a superconducting quantum interference device given the risk of free iron deposition in the liver, heart, pancreas, and endocrine tissues with the commencement of chelation therapy as indicated.[113–115] Iron overload may also be a risk factor in late effects for long-term survivors of pediatric cancer who have a high transfusion burden, such as patients with acute myelogenous leukemia and those requiring HSCT.[116,117]

Hemovigilance

Hemovigilance, or the reporting of adverse events related to RBC transfusion, is a vital component to ensure continued safety for pediatric patients.[118] Hospitals are required to have policies for reporting, documenting, and evaluating the potential adverse events as well as routine assessment of the appropriateness of transfusions.[118] Yet, given these requirements, pediatric transfusion remains under researched, and reports have shown significant variation in practice between children's hospitals in the USA and Canada.[118,119] Surveys in the UK of transfusion practice in pediatric patients, as well as competency of junior physicians, have both shown variation in practice and potential areas of improvement, especially given the higher rate of adverse events in neonatal and pediatric patients as compared with adults.[120,121]

Summary

Pediatric patients have multiple unique aspects that the practitioner must consider in the process of prescribing RBC transfusions. The practitioner must be aware of the particular indication for transfusion, normal Hb for age, and the need for special requirements based on the age and type of patient. Finally, the practitioner must be aware of potential unique complications in the pediatric population and also ensure a system is in place in order to report and evaluate such potential adverse reactions. Many gaps remain in fully understanding pediatric RBC transfusion that should be addressed over time with continued research and hemovigilance.

Disclosure

The authors report no conflicts of interest in this work.

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