Epidemiology of Necrotizing Enterocolitis

New Considerations Regarding the Influence of Red Blood Cell Transfusions and Anemia

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KEYWORDS

• Infant • Neonate • Preterm • Blood • Oxygenation • Morbidity

KEY POINTS

- The optimal hemoglobin thresholds to administer red blood cell (RBC) transfusion are currently uncertain.
- Results of ongoing randomized trials are likely to provide important new evidence to guide RBC transfusion.
- Until new trial data are available, it is advisable to avoid using routine RBC transfusion thresholds above the liberal arm or below the conservative arm of thresholds studied in trials to date in preterm infants, as the safety of such approaches is uncertain.
- Practices to minimize RBC transfusion and anemia, such as placental transfusion by delayed cord clamping, have important benefits but it is unclear if these practices reduce NEC.

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INTRODUCTION

Necrotizing enterocolitis (NEC) is major contributor to morbidity and mortality in infants, accounting for 10% of deaths in the neonatal intensive care unit.[1,2] Recent data suggest the incidence of NEC is decreasing in the United States[3]; however, the reported incidence of NEC is highly variable among high-income countries.[4] The pathogenesis of NEC is multifactorial and includes innate, maternal, and postnatal risk factors. Multiple observational studies have demonstrated an association between NEC and the potentially modifiable risk factors of anemia and red blood cell (RBC) transfusion. Some investigators have proposed that the occurrence of NEC in temporal association with an RBC transfusion is a distinct clinical entity, separate from non–transfusion-associated NEC.[5] This review appraises data on the epidemiology of NEC with a focus on the potential role of RBC transfusion and anemia.

OVERVIEW OF TRANSFUSION PRACTICES

Neonatal hemoglobin (Hb) levels decline in the days and weeks after birth.[6] Preterm infants, in comparison with term infants, have a relatively lower Hb level at birth[7] and experience a greater Hb decline during the neonatal period.[8] This decline in Hb often leads to treatment with an RBC transfusion. The ideal threshold for administering an RBC transfusion is currently not known. Clinicians often consider the Hb level along with the postnatal age of the infant and need for cardiorespiratory support to guide their decision for when to administer an RBC transfusion. Studies of direct comparisons of restrictive (low Hb threshold) versus liberal (high Hb threshold) strategies are limited to 3 randomized controlled trials[9–11] and 2 ongoing trials.[12,13] The Hb transfusion thresholds in the restrictive and liberal arms of these trials are summarized in **Table 1**.

Temporal trends suggest increasingly restrictive RBC transfusion practices, with acceptance of a lower concentration of Hb before an RBC transfusion.[14–16] In the absence of a clear advantage of either approach, the optimal Hb transfusion threshold remains uncertain with a recent Cochrane review justifying clinical equipoise.[17]

DATA ON RED BLOOD CELL TRANSFUSION AND NECROTIZING ENTEROCOLITIS

Since the publication of several initial reports of a temporal association between RBC transfusion and NEC,[18–20] multiple subsequent observational studies[21–36] have reported on the association between RBC transfusion and NEC. Most of these observational studies report on NEC occurring within 48 hours of an RBC transfusion, although the 48-hour cutoff is arbitrary.

Several systematic reviews and meta-analyses have summarized and evaluated the potential association between RBC transfusion and NEC (**Table 2**). Two meta-analyses of observational studies[37,38] were published in 2017. A meta-analysis by Garg and colleagues[37] of 17 observational studies reported no evidence of an association between exposure to RBC transfusion and the risk of NEC (odds ratio [OR] 0.96, 95% confidence interval [CI] 0.53–1.71, $P = .88$) with high study heterogeneity ($I^2 = 93\%$). In addition, the investigators performed subgroup analyses and found heterogeneity in results by study type (cohort studies and case-control studies). Analysis of data from 4 cohort studies showed a significant association between RBC transfusion and a lower risk of NEC (OR 0.51, 95% CI 0.34–0.75, $P = <.01$) with low statistical heterogeneity ($I^2 = 28\%$). By comparison, subgroup analysis of 13 case-control studies showed no difference in odds for NEC with RBC transfusion (OR 1.20, 95% CI 0.58–2.47, $P = .63$) with high heterogeneity ($I^2 = 93\%$). Another meta-analysis by

Table 1
Hemoglobin transfusion thresholds used in clinical trials

Study	Postnatal Age, d	Clinical Status	Restrictive Hb Threshold, g/dL[a]	Liberal Hb Threshold, g/dL[a]
PINT trial,[10] 2005	1–7	Any respiratory support (capillary/central sample)	11.5/10.4	13.5/12.2
		No respiratory support (capillary/central sample)	10.0/9.0	12.0/10.9
	8–14	Any respiratory support (capillary/central sample)	10.0/9.0	12.0/10.9
		No respiratory support (capillary/central sample)	8.5/7.7	10.0/9.0
	≥15	Any respiratory support (capillary/central sample)	8.5/7.7	10.0/9.0
		No respiratory support (capillary/central sample)	7.5/6.8	8.5/7.7
Bell et al,[9] 2005		Ventilated	11.3	15.3
		CPAP or oxygen	9.3	12.7
		No respiratory support	7.3	10.0
Chen et al,[11] 2009		Ventilated	11.7	15.0
		CPAP	10.0	13.3
		Spontaneous breathing	7.3	10.0
TOP trial[12]	Week 1	Any respiratory support	11.0	13.0
		No respiratory support	10.0	12.0
	Week 2	Any respiratory support	10.0	12.5
		No respiratory support	8.5	11.0
	Week 3	Any respiratory support	8.5	11.0
		No respiratory support	7.0	10.0
ETTNO trial[13]	3–7	Critical[b]	11.3	13.6
		Noncritical	9.3	11.7
	8–21	Critical[b]	10.0	12.3
		Noncritical	8.0	10.3
	>21	Critical[b]	9.0	11.3
		Noncritical	7.0	9.3

Abbreviations: CPAP, continuous positive airway pressure; ETTNO, Effects of Transfusion Thresholds on Neurocognitive Outcome of Extremely Low Birth Weight Infants; Hb, hemoglobin; PINT, Premature Infants in Need of Transfusion; TOP, Transfusion of Prematurity.

[a] If hematocrit was reported, the Hb threshold was approximated by dividing by 3.

[b] Critical defined as any of the following: (1) requirement of mechanical ventilation, (2) requirement of CPAP with FiO_2 greater than 0.25 for more than 12 hours per 24 hours, (3) patent ductus arteriosus requiring therapy, (4) more than 6 apneas that require stimulation per 24 hours, or more than 4 desaturations to SpO_2 less than 60% per 24 hours despite methylxanthines and CPAP, and (5) acute sepsis or acute necrotizing enterocolitis requiring inotropic or vasopressor support.

Table 2
Meta-analyses of observational studies reporting on RBC transfusion and NEC

Study Author, Year	Number of Studies	Study Types	NEC Events Related to RBC Transfusion/Total	NEC Events Unrelated to RBC Transfusion/Total	I^2, %	Summary Odds Ratio (95% CI)
Kirpalani & Zupancic,[40] 2012	6	Cohort studies	150/2940	192/19,215	98	7.48 (5.87–9.53)
	4	Case-control studies	129/186	129/381	92	2.19 (1.52–3.17)
Mohamed & Shah,[39] 2012	5	All observational studies reporting unadjusted estimates	N/A	N/A	58	3.91 (2.97–5.14)
	4	All observational studies reporting adjusted estimates	N/A	N/A	91	2.01 (1.61–2.50)
Garg et al,[37] 2017	17	All observational studies	N/A	N/A	93	0.96 (0.53–1.71)
	4	Cohort studies	N/A	N/A	28	0.51 (0.34–0.75)
	13	Case-control studies (3 unmatched, 10 matched)	N/A	N/A	93	1.20 (0.58–2.47)
Hay et al,[38] 2017	13	All observational studies reporting on NEC within 48 h of transfusion	479/4498	1242/7104	93	1.13 (0.99–1.29)
	9	All observational studies reporting on NEC at any time after transfusion	334/2380	256/2541	86	1.95 (1.60–2.38)

Abbreviations: CI, confidence interval; N/A, not available; NEC, necrotizing enterocolitis; RBC, red blood cell.

Hay and colleagues[38] of 13 observational studies found no evidence of an association between RBC transfusion and NEC occurring within 48 hours of transfusion (OR 1.13, 95% CI 0.99–1.29) with high statistical heterogeneity among studies (I^2 = 93%). The investigators concluded that there was a very low confidence of a true relationship between RBC transfusion and NEC, based on the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system.

These results from more recent meta-analyses are in contrast to results of 2 previous meta-analyses of observational studies in 2012 by Mohamed and Shah[39] and by Kirpalani and Zupancic[40] that reported an increased risk of NEC within 48 hours after receiving an RBC transfusion. The meta-analysis by Mohamed and Shah[39] of 4 studies reported a pooled adjusted OR for NEC of 2.01 (95% CI 1.61–2.50, I^2 = 91%) among RBC-exposed infants. Kirpalani and Zupancic[40] included only full-length publications and excluded data from abstracts and reported an increased risk for NEC with blood transfusion in 6 cohort studies (unadjusted OR 7.48, CI 5.87–9.53) and in 4 case-control studies (OR 2.19, CI 1.52–3.17).

The differences in the results of meta-analyses from 2012 and 2017 may be from publication bias, as noted by Hay and colleagues,[38] with earlier studies predominantly reporting positive associations between RBC transfusion and NEC and more recent studies reporting no association and some suggesting RBC transfusion may be protective toward NEC. In addition, a meta-analysis of randomized trials[40] comparing restrictive and liberal transfusion strategies in preterm infants found no effect of more restrictive thresholds (leading to fewer RBC transfusions), compared with liberal RBC transfusion thresholds (leading to more RBC transfusions) on the risk of NEC (OR 1.67, 95% CI 0.82–3.38). Notably, the estimates are heavily weighted by a single trial (PINT trial)[10] with weight of 89% (**Table 3**). In addition, these trials did not report on a temporal relationship between RBC transfusion and NEC. In the absence of higher-quality data, the question of does RBC transfusion cause NEC remains unresolved.

DATA ON ANEMIA AND NECROTIZING ENTEROCOLITIS

Several observational studies that reported on an association between RBC transfusion and NEC did not report a significant effect of anemia as an independent risk for NEC.[23,24,29,41] However, in a case-control study, Singh and colleagues[30] identified 111 preterm (≤32 weeks) infants with NEC and 222 matched controls and reported that, after controlling for other factors, each 1-point decrease in the nadir hematocrit was associated with a 10% increase in odds for NEC (OR 1.10, 95% CI 1.02–1.18). Patel and colleagues,[42] in a prospective multicenter study, reported that in a given week, severe anemia, defined as Hb level of 8.0 g/dL or less, was associated with a higher adjusted risk for NEC (adjusted cause-specific hazard ratio 5.99, 95% CI

Table 3
Meta-analyses of randomized trials reporting on RBC transfusion and NEC

Study Author, Year	Number of Trials	NEC Events with Restrictive RBC Transfusion Threshold	NEC Events with Liberal RBC Transfusion Threshold	I^2	Odd Ratio of NEC (95% CI), Restrictive vs Liberal RBC Transfusion Threshold
Kirpalani & Zupancic,[40] 2012	3	21/292	13/298	0%	1.67 (0.82–3.38)

Note: Estimates similar to meta-analyses by Whyte and Kirpalani[17] and, therefore, not repeated.
Abbreviations: CI, confidence interval; NEC, necrotizing enterocolitis; RBC, red blood cell.

2.00–18.0, $P = .001$); however, the study did not evaluate the interaction between severe anemia and RBC transfusion. A recent case-crossover study by Le and colleagues,[43] designed to identify an association of NEC with RBC transfusion, feed advances, or fortification, found no evidence of an association between RBC transfusion and NEC (OR 1.80, 95% CI 0.60–5.37). A subgroup analysis showed that among anemic infants (Hb $\leq$9.3 g/dL), the risk of RBC transfusion on NEC was higher (OR 6; 95% CI 0.72–49.8) compared with those without anemia (OR 1, 95% CI 0.20–4.95), but the difference in effect estimates among subgroups was not statistically significant.

It is plausible that the occurrence of NEC after an RBC transfusion is the result of interaction between the effect of anemia and the effect of RBC transfusion. Evaluating such an interplay between the contribution of anemia and RBC transfusion is challenging in clinical studies, as assessing interaction between 2 exposures (anemia and RBC transfusion) typically requires a much larger sample size than assessing the effect of a single exposure (anemia or RBC transfusion). In addition, lower Hb oxygen saturation targeting, an important determinant of oxygenation that increases the risk of NEC,[44] has not been measured, controlled, or reported in observational studies of RBC transfusion-associated NEC, limiting the understanding of the interaction between Hb saturation and anemia. Preclinical studies offer an opportunity to assess the biologic plausibility of such an interaction and may provide data on the potential of such an interaction that is challenging to assess without very large, adequately powered randomized trials. Two ongoing, large randomized trials[12,13] comparing liberal and restrictive transfusion thresholds are designed to assess the effect of high versus low transfusion thresholds on survival and long-term neurocognitive outcomes; however, with NEC as a secondary outcome measure, these trials may contribute important data on the effect of both RBC transfusion and anemia (by comparing high and low Hb transfusion thresholds) on NEC when these results are considered alongside those of prior trials.

POTENTIAL MECHANISMS UNDERLYING THE ASSOCIATIONS

The development of NEC in an infant is considered the final common endpoint of a multitude of etiologic pathways[45] that result in disruption of mucosal integrity and inflammation from responses to intraluminal pathogenic organisms. Several mechanisms for intestinal injury in response to RBC transfusion, with or without the presence of anemia, have been proposed (**Fig. 1**) and are discussed in additional detail in the following section.

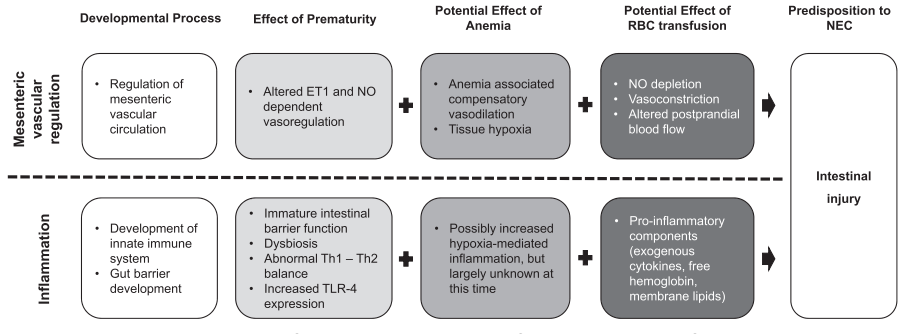

Fig. 1. Potential mechanisms for the pathogenesis of intestinal injury from anemia and RBC transfusion. ET1, endothelin 1; NO, nitric oxide; Th, T helper cell; TLR-4, toll-like receptor 4.

Hypoxemia and Dysregulation of Mesenteric Blood Flow

Reversible binding of oxygen to Hb accounts for more than 98% of oxygen carriage by blood. At physiologic partial pressure of oxygen, 100 mL of plasma contains 0.3 mL of oxygen. In comparison, each gram of Hb can combine with 1.34 mL of oxygen.[46] A decrease in blood Hb concentration leads to circulatory adjustments, such as increases in capillary perfusion and increased oxygen extraction by tissues.[46,47] However, worsening anemia may overwhelm the compensatory mechanisms and significantly impair the ability of blood to meet oxygen demands of the tissues causing hypoxia,[48] which may be worsened in the setting of lower oxygen saturation targets.[44] Molecular compensatory mechanisms exist to maintain the gut barrier in the setting of hypoxia[49,50]; however, it has been proposed that progressive hypoxia may reach a critical imbalance in oxygen delivery as compared with consumption, leading to mucosal barrier injury[51] and poor mucosal healing,[52] predisposing the neonate to development of NEC.[5]

In a growing neonate, the intestines proliferate as the gut elongates and the mucosa grows. Active expression of angiogenic factors in the metabolically active and rapidly proliferating gut mucosa ensures concomitant development of vascular structures in the intestine.[53] It has been proposed that the developing thin arterioles may be structurally weak, and on exposure to an RBC transfusion and associated alterations in oxygen availability, blood pressure, flow, or viscosity, these arterioles are prone to injury, precipitating ischemic injury to the gut mucosa.[5,54] However, experimental evidence is needed to confirm the proposed mechanisms.

Mesenteric or splanchnic blood flow is determined by a dynamic balance between vasoconstrictive and vasodilatory inputs by mediators such as endothelin-1 (ET-1) and nitric oxide (NO).[54] Ontogeny of the regulatory mechanisms of the mesenteric vascular tone during the neonatal period demonstrates distinct responses to autonomic, humoral, and paracrine factors as compared with a mature infant.[55,56] In the newborn, the balance is favored toward NO-mediated vasodilation.[55,57] In addition, as compared with older subjects, NO inhibition leads to a greater increase in vascular resistance in newborn animal models.[58–60] RBC transfusion leads to an alteration in postprandial response to mesenteric blood flow as evident from a clinical study by Krimmel and colleagues.[61] Analysis of preprandial and postprandial mesenteric blood flow in 22 infants (mean gestational age, 27.3 weeks, mean postmenstrual age, 31.8 weeks) demonstrated that anemia was associated with increased flow in the superior mesenteric artery following feeding, which was evident pre-transfusion and absent in the immediate post-transfusion state. One potential mechanism for this decreased blood flow is by RBC transfusion–associated depletion of intravascular NO.[62] This may be secondary to depletion of NO in RBCs during storage, consumption of NO through binding to free Hb released from hemolysis, or from release of arginase from RBCs, which depletes the NO precursor arginine.[62] The transient anemia-associated hypoxia followed by reperfusion after RBC transfusion and associated dysregulation of blood flow may have a cumulative and/or interactive role in pathogenesis of disease.[63]

Role of Inflammation

The occurrence of NEC in response to RBC transfusion or anemia has been proposed to be the outcome of a 2-hit mechanism,[5] similar to the proposed mechanisms for transfusion-related acute lung injury (TRALI), a condition that can occur following transfusion of any blood component. In TRALI, underlying clinical conditions lead to endothelial activation in the host (first hit), which in the presence of a blood product

transfusion and associated exposure to mediators, such as donor HLA antibodies, biologically active lipids, free Hb, red cell membrane fragments, and inflammatory cytokines (second hit), leads to a severe inflammatory response and associated lung injury.

It has been proposed that the immature neonatal gut is in a heightened state of immune activation and prone to inflammation. Multiple factors, such as mucosal exposure to substrates, hypoxia, and changes in the gut microbiome associated with the use of antibiotics and formula feeds,[5,16,64–66] have been proposed to contribute to inflammation and associated phenotypic shift of T helper (T_H) cells from T_H2 to T_H1.[67] Upregulation of Toll-Like Receptors (TLRs), particularly TLR-4,[68] is a significant contributor to intestinal inflammation.[68,69]

In such a background, RBC transfusion can potentially introduce biological response modifiers such as donor antibodies,[70] cytokines in stored blood,[71] free Hb,[72] lipids from RBC membranes, and white cells generating an exaggerated systemic immune response that may cause gut mucosal inflammation and injury. Dani and colleagues[73] demonstrated serum cytokine changes after an RBC transfusion event in 20 infants of less than 32 weeks' gestational age. The study identified significant increases in interferon-gamma, monocyte chemoattractant protein-1, intracellular adhesion molecule-1, and interleukin (IL)-1β, IL-8, and IL-17 after an RBC transfusion. Ho and colleagues[74] measured fecal calprotectin (FC) before and after 46 RBC transfusion events in 26 very low birthweight (VLBW) infants, and showed that FC was higher than baseline after RBC transfusion and was higher in multiply-transfused infants. Notably, FC was the highest in infants with the lowest pretransfusion hematocrits and in those who received RBCs that had been stored for more than 21 days.

In a background of constitutive vasodilation and increased reactivity in the neonatal gut vasculature, despite compensatory hemodynamic and molecular changes, progressive anemia may reach a critical level leading to hypoxia. RBC transfusion in such a state may lead to depletion of NO and loss of vasodilation along with abnormal regulation of mesenteric blood flow leading to tissue ischemic injury. Multiple factors associated with prematurity such as dysbiosis and increased TLR-4 expression cause a state of inflammation in the intestinal mucosa that can potentially increase with hypoxia. Introduction of exogenous biological response modifiers in transfused products may lead to heightened immune responses leading to damage to the intestinal mucosa. However, additional data are needed from both human and preclinical studies to better understand the mechanisms that may underlie the possible adverse effects of both RBC transfusion and anemia on the neonatal intestine.

INFLUENCE OF CLINICAL STRATEGIES TO PREVENT ANEMIA AND RED BLOOD CELL TRANSFUSION

Iatrogenic phlebotomy loss, a result of intensive clinical monitoring in critically ill newborns, is a major cause of neonatal anemia and driver of RBC transfusion.[75] The common strategies to minimize blood sampling in the neonatal intensive care unit include the use of noninvasive monitoring and point of care testing[76] and use of umbilical cord blood for admission blood tests for VLBW preterm neonates.[77] With a combination of several approaches and ongoing vigilance, studies have shown a significant effect in preventing anemia and decreasing RBC transfusion.[78]

Placental transfusion achieved by delayed clamping of the umbilical cord after birth or by milking of the umbilical cord before clamping is now recommended as standard care for neonatal resuscitation of preterm infants.[79–81] A 2012 Cochrane review of 15

randomized controlled trials, 5 of which reported NEC as an outcome measure, indicated a decreased risk for NEC in infants receiving delayed cord clamping, compared with immediate cord clamping (n = 241, RR 0.62, 95% CI 0.43–0.9).[82] However, a more recent meta-analysis, including 12 studies that reported on NEC, found that delayed cord clamping was not associated with a decreased risk for NEC for all infants less than 37 weeks' gestation at birth (n = 2397, RR 0.88, CI 0.65–1.18) and for infants born <28 weeks' gestation (4 studies, n = 977, RR 0.87, CI 0.61–1.24).[83] The quality of evidence was determined as low using the GRADE criteria. Notably, the findings of this recent meta-analysis were weighted heavily by the Australian Placental Transfusion Study of 1566 infants born at less than 30 weeks' gestation, randomized to placental transfusion by delayed cord clamping or early clamping.[84] In this trial 44 (6.2%) of 712 infants randomized to delayed cord clamping developed NEC, as compared with 41 infants (5.6%) of 734 randomized to early clamping. Importantly, the effect of delayed cord clamping on Hb nadir and RBC transfusion requirements is likely to depend on postnatal RBC transfusion approaches.

Apart from its role in prompting erythropoiesis and decreasing need for RBC transfusion, erythropoietin (EPO), which is also present in breast milk,[85] may play a role in intestinal development, cellular repair,[86] and inhibition of NO formation.[87] Ledbetter and Juul[88] first reported an association of recombinant human erythropoietin (rEPO) administration in infants $\leq$1250 g and a decreased incidence of NEC (4.6% in the rEPO group as compared with 10% in controls). A recent Cochrane meta-analysis of a randomized controlled trial of early (age <8 days) administration of erythropoiesis-stimulating agents (ESAs) (EPO or darbepoetin) versus placebo or no intervention included 15 studies (n = 2639).[89] The analysis demonstrated a significantly reduced risk for NEC (any stage) in the ESA group compared with the placebo group (RR 0.69, 95% CI 0.52–0.91, I^2 = 0%). The quality of the evidence was deemed moderate.[89,90] Previous concerns regarding the increased risk for retinopathy of prematurity (all stages) with EPO administration[91] were not demonstrated in this meta-analysis (11 studies, n = 2185, RR 0.92, 95% CI 0.79–1.08; I^2 = 0%).[89,91] A Cochrane meta-analysis of late EPO administration (8–28 days) in extremely low birthweight infants (6 studies, n = 656) did not demonstrate any difference in the risk for NEC with EPO as compared with placebo or no intervention (RR 0.88, 95% CI 0.46–1.69, I^2 = 0%).[90] Late EPO was associated with a nonsignificant trend toward an increased risk for retinopathy of prematurity (ROP) (stage $\geq$3, 3 studies, n = 442) with an RR 1.73 (95% CI 0.92–3.24, I^2 = 18%) and for all ROP stages (3 studies, n = 404) with an RR 1.27 (95% CI 0.99–1.64, I^2 = 83%). Two ongoing large randomized trials of EPO administration in preterm infants, Preterm Erythropoietin Neuroprotection Trial (PENUT Trial, NCT01378273)[92] and Erythropoietin in Premature Infants to Prevent Encephalopathy (NCT02550054), include NEC as a secondary outcome and will provide additional evidence regarding the effect of EPO on the risk of NEC and the safety of EPO administration in different populations.

ROLE OF FEEDING DURING RED BLOOD CELL TRANSFUSION

With the recognition of a potential association between RBC transfusion and development of NEC, there has been interest in withholding feeding during RBC transfusion. In prospective observational studies, feeding immediately after RBC transfusion has been associated with an attenuation of the postprandial increase in superior mesenteric artery blood flow velocity as compared with the pretransfusion measurements made using pulse Doppler ultrasound.[61,93] However, a prospective observational comparison of infants less than 33 weeks at birth who were fed (n = 9) or not fed

(n = 8) during RBC transfusion demonstrated that mesenteric tissue oxygenation, as measured by using near-infrared spectroscopy (NIRS), was not influenced by feeding.[94]

A systematic review of 7 observational studies reported that withholding feeds during RBC transfusion was associated with lower risk of NEC associated with transfusion (n = 7492, RR 0.47, 95% CI 0.28–0.80, I^2 = 11%).[95] Although biologically plausible, the results from these observational studies remain vulnerable to bias and confounding. A large randomized controlled trial, Withholding Enteral Feeds Around Transfusion (WHEAT) trial is currently under way[96] and will hopefully provide evidence to answer the clinically relevant question of whether feeding during an RBC transfusion causes NEC.

ROLE OF NEAR-INFRARED SPECTROSCOPY

NIRS is a noninvasive technique for monitoring regional tissue oxygenation in real time. NIRS measures the difference between oxyHb and deoxyHb, which reflects oxygen uptake in the specific tissue bed measured.[97] This measurement, which is reported as the regional oxygen saturation (rSO_2), reflects the balance of oxygen that is delivered minus what is extracted at the tissue level.[97] A decreasing NIRS rSO_2 reading indicates either increasing oxygen extraction at the tissue level or decreasing oxygen delivery to tissues in the region measured.

With its ability to monitor mesenteric tissue oxygenation,[98] use of NIRS to monitor intestinal oxygenation in preterm infants has been studied.[99] Bailey and colleagues[100] demonstrated large variability of mesenteric oxygenation during RBC transfusion in preterm neonates. Marin and colleagues[101] compared NIRS measurements in 4 patients with NEC associated with RBC transfusion with 4 controls who received RBC transfusion but did not develop NEC. This study demonstrated wide fluctuation and decreases in mesenteric oxygenation patterns that were more pronounced in infants who developed NEC with RBC transfusion as compared with non-NEC infants. In a pilot study, Sood and colleagues[102] compared the mesenteric and cerebral rSO_2 patterns of infants who did not develop NEC within 7 days of RBC transfusion (n = 120), infants who developed NEC within 7 days before RBC transfusion (n = 20), and infants who developed NEC within 7 days after an RBC transfusion (n = 8). The study reported decreases in mesenteric rSO_2 during and after an RBC transfusion in infants who went on to develop NEC within 7 days as compared with the other 2 groups that had an increase in rSO_2.

Although promising, there is currently no evidence to support the use of NIRS monitoring to guide RBC transfusion approaches to prevent NEC. Two prospective trials registered at clinicaltrials.gov, Transfusion of Prematurity (TOP trial) NCT01702805 and Combining Restrictive Guidelines and an NIRS SCORE to Decrease RBC Transfusions, include NIRS monitoring at different thresholds for RBC transfusion. The data from these trials may provide more insight into the utility of this technique into identifying the need for RBC transfusion and allow for a better understanding of the effects of RBC transfusion and anemia on intestinal oxygenation and NEC.

SUMMARY

Observational studies have provided conflicting evidence regarding the effect of RBC transfusion and anemia on NEC. It is possible that anemia and/or RBC transfusion may lead to tissue hypoxia, dysregulation of mesenteric vascular regulation, or inflammation. Such mechanisms may act independently or in combination to lead to intestinal injury and, potentially, the development of NEC. Placental transfusion and the use of

ESA have a role in decreasing RBC transfusion and anemia, although it is unclear if these treatments reduce NEC. Ongoing RBC transfusion trials have the potential to provide additional evidence to improve our understanding of transfusion strategies to decrease the risk for NEC.

Best practices

What is the current practice?

Currently, there is uncertainty regarding the optimal Hb thresholds to transfuse RBCs into preterm infants.

What changes in current practice are likely to improve outcomes?

The following practices are suggested:

1. Provide placental transfusion, when feasible.
2. Minimize unnecessary phlebotomy-related blood losses.
3. Avoid using routine RBC transfusion thresholds above the liberal Hb level or below the conservative Hb level of thresholds studied to date, as the safety of such approaches is uncertain.

Summary Statement

Results of data from 2 multicenter randomized trials of high versus low transfusion thresholds (TOP, ETTNO) are likely to provide important new evidence to guide RBC transfusion. Until these data are available, no confident conclusions regarding the effects of RBC transfusion or anemia on NEC can currently be provided.

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