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

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Abstract

This review summarizes available evidence on the relationship between red blood cell transfusion, anemia and necrotizing enterocolitis (NEC). We review recent studies that highlight the uncertainty of the effect of red blood cell transfusion on NEC and the potential role of anemia. We also discuss potential pathophysiologic effects of both red blood cell transfusion and anemia and highlight strategies to prevent anemia and red blood cell transfusion. We also discuss ongoing randomized trials that are likely to provide important new evidence to guide red blood cell transfusion practices.

Keywords

Infant; neonate; preterm; blood; oxygenation; morbidity

Introduction

Necrotizing enterocolitis (NEC) is major contributor to morbidity and mortality in infants, accounting for 10% of deaths in the NICU [1,2]. Recent data suggest the incidence of NEC is decreasing in the US [3]. However, the reported incidence of NEC is highly variable among high-income countries [4]. The pathogenesis of NEC is multifactorial and includes innate,

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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 authors 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 will appraise 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 to 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 a 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 control trials [9–11] and two 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 a 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 RBC transfusion and NEC

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 cut-off is arbitrary.

Several systematic reviews and meta-analyses have summarized and evaluated the potential association between RBC transfusion and NEC reported in the studies (Table 2). Two meta-analysis of observational studies [37,38] were published in 2017. A meta- analysis by Garg et. al. of 17 observational studies reported no evidence of an association between exposure to RBC transfusion and the risk of NEC (OR 0.96, 95% CI: 0.53-1.71, P=0.88) with high study heterogeneity (I^2 = 93%) [37]. In addition, the authors 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 = <0.01) 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 = 0.63) with high heterogeneity (I^2 = 93%). Another meta-analysis by Hay et al. 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%) [38]. The authors 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 from results of two 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 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 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 et al. [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 towards 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 to 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 NEC

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 et al. identified 111 preterm (≤ 32 weeks) infants with NEC and 222 matched controls and reported that, after controlling for other factors, each one 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 et al [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: 2.00-18.0, P = 0.001). However, the study did not evaluate the interaction between severe anemia and RBC transfusion. A recent case-crossover study by Le et al. [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 ≤ 9.3 g/dL), the risk of RBC transfusion on NEC was higher (OR: 6; 95% CI: 0.72-49.8), compared to 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 two exposures (anemia and RBC transfusion) typically requires a much larger sample size than assessing the effect of a single exposure (anemia or RBC transfusion). Additionally, 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. Pre-clinical studies offer an opportunity to assess the biologic plausibility of such an interaction and may provide data on the plausibility 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 vs. 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 end-point 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 (Figure 1) and are discussed in additional detail below.

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 saturations 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 to 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 upon

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 [554]. 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 to a mature infant [55,56]. In the newborn, the balance is favored towards NO-mediated vasodilation [55,57]. In addition, as compared to 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 post-prandial response to mesenteric blood flow as evident from a clinical study by Krimmel et al. [61]. Analysis of pre- and post-prandial 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 two-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) lead 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, 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 from T_H2 to T_H1 [67]. Upregulation of Toll Like Receptors (TLR), 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 et al [73] demonstrated serum cytokine

changes after an RBC transfusion event in 20 infants less than 32 weeks gestational age. The study identified significant increases in interferon-gamma, monocyte chemoattractant protein-1, intracellular adhesion molecule-1 (ICAM-1), and interleukins (IL) IL-1β, IL-8 and IL-17 after an RBC transfusion. Ho et al. [74] measured fecal calprotectin (FC) before and after 46 RBC transfusion events in 26 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 pre-transfusion hematocrits and in those who received RBCs that had been stored for >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 RBC 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 includes 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 to 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 < 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 (APTS) trial of 1566 infants born < 30 weeks gestation, randomized to placental transfusion by delayed cord clamping or early clamping [84]. In this trial 44/712 (6.2%) infants randomized to delayed cord clamping developed NEC,

as compared to 41/734 infants (5.6%) 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 et al. first reported an association of rEPO administration in infants ≤ 1250 g and a decreased incidence of NEC (4.6% in rEPO group as compared to 10% in controls) [88]. A recent Cochrane meta-analysis of RCT of early (< 8d age) administration of erythropoiesis stimulating agents (ESA, 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 [8990]. 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%) [8991]. A Cochrane meta-analysis of late EPO administration (8-28 d) in ELBW infants (6 studies, n= 656) did not demonstrate any difference in the risk for NEC with EPO as compared to placebo or no intervention (RR = 0.88, 95% CI 0.46-1.69, I^2 = 0%) [90]. Late EPO was associated with a non-significant trend towards an increased risk for ROP (Stage≥ 3, 3 studies, n=442) with a RR 1.73 (95% CI 0.92-3.24, I^2 = 18%) and for all ROP stages (3 studies, n=404) with a 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) [92], 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 RBC 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 to the pre-transfusion measurements made using pulse Doppler ultrasound [61,93]. However, a prospective observational comparison of infants <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

underway [96] and will hopefully provide evidence to answer the clinically relevant question of whether feeding during an RBC transfusion causes NEC.

Role of NIRS

NIRS is a non-invasive 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 babies has been studied [99]. Bailey et al. demonstrated large variability of mesenteric oxygenation during RBC transfusion in preterm neonates [100]. Marin et al. compared NIRS measurements in 4 patients with NEC associated with RBC transfusion with 4 controls who received RBC transfusion but did not develop NEC [101]. 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 to non-NEC infants. In a pilot study, Sood et al. 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 prior to RBC transfusion (n=20) and infants that developed NEC within 7 days after an RBC transfusion (n=8) [102]. 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 to the other two groups who had an increase in rSO_2.

While 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 a NIRS SCORE to Decrease RBC Transfusions (NCT02535208), include arms with 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.

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Abbreviations:

NEC	necrotizing enterocolitis
RBC	red blood cell
Hb	hemoglobin
OR	odds ratio
CI	confidence interval
NIRS	near-infrared spectroscopy
NO	nitric oxide
TRALI	transfusion-related acute lung injury
TLR	Toll-like receptor
FC	fecal calprotectin
VLBW	very low birth weight
EPO	erythropoietin
rSO_2	regional oxygen saturation

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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.

Best Practices Box

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 two multicenter randomized trials of high- vs. 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.

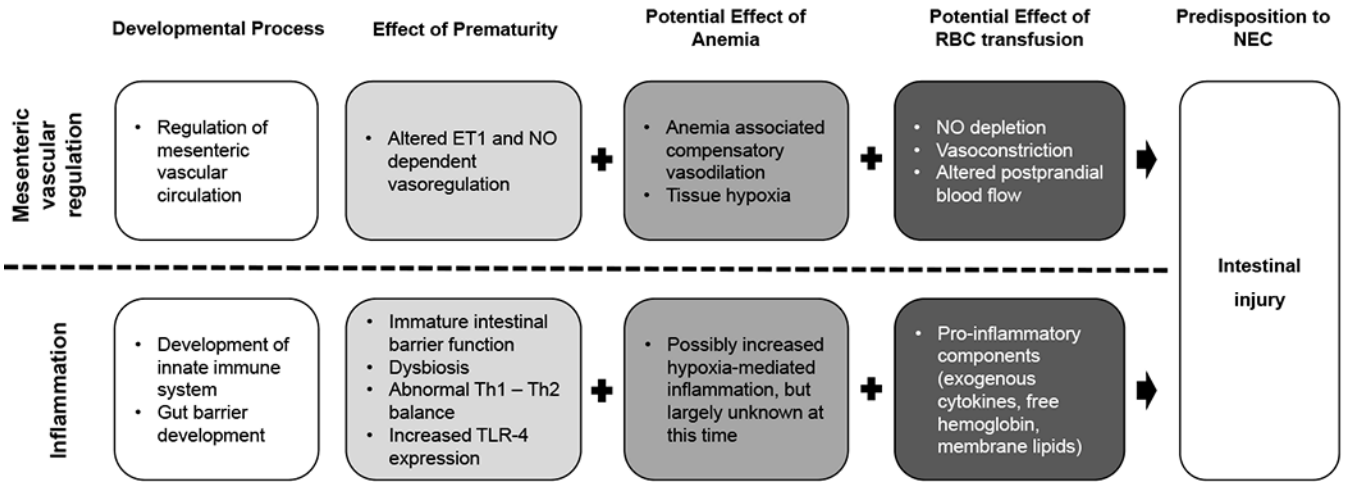

Figure 1.

Potential mechanisms for the pathogenesis of intestinal injury from anemia and RBC transfusion.

Abbreviations: NEC, Necrotizing Enterocolitis; ET1, Endothelin 1; NO, Nitric Oxide; TLR-4, Toll-like receptor 4; Th, T helper cell

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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, 2005[10]	1-7d	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 d	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, 2005 [9]		Ventilated	11.3	15.3
		CPAP or Oxygen	9.3	12.7
		No respiratory support	7.3	10.0
Chen, 2009 [11]		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 d	Critical[b]	11.3	13.6
		Non critical	9.3	11.7
	8-21d	Critical[b]	10.0	12.3
		Non critical	8.0	10.3
	>21 d	Critical[b]	9.0	11.3
		Non critical	7.0	9.3

[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 >0.25 for >12 h per 24 h, (3) patent ductus arteriosus requiring therapy, (4) more than 6 apneas that require stimulation per 24 h, or more than 4 desaturations to SpO_2 <60% per 24 h despite methylxanthines and CPAP and (5) acute sepsis or acute NEC requiring inotropic or vasopressor support.

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

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, 2012 [40]	6	Cohort studies	150/2940	192/19215	98%	7.48 (5.87-9.53)
	4	Case Control studies	129/186	129/381	92%	2.19 (1.52-3.17)
Mohamed, 2012 [39]	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, 2017 [37]	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, 2017 [38]	13	All observational studies reporting on NEC within 48 hours of transfusion	479/4498	1242/7104	93%	1.13 (0.99-1.29)
	9	All observational studies reporting on NEC at anytime after transfusion	334/2380	256/2541	86%	1.95 (1.60-2.38)

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, 2012 [40]	3	21/292	13/298	0%	1.67 (0.82-3.38)

Note: Estimates similar to meta-analyses by Whyte and Kirpalani. *Cochrane Database Syst Rev. 2011 Nov 9;(11):CD000512* and, therefore, not repeated.