Feeding Practices and Effects on Transfusion-Associated Necrotizing Enterocolitis in Premature Neonates

Emma Killion, MSN, NNP-BC

ABSTRACT

Background: Red blood cell (RBC) transfusions have been implicated in the development of necrotizing enterocolitis (NEC) in premature infants. Some evidence exists to support that withholding feedings during transfusion reduces the risk of subsequent NEC development.

Purpose: To review the most recent literature on this topic to determine best evidence-based practice regarding withholding or not withholding feedings during RBC transfusions.

Methods/Search Strategy: Four databases were searched using keywords and MeSH terms including “necrotizing enterocolitis,” “NEC,” “NPO,” and “transfusion,” with specifications limiting the search to articles published in the last 10 years and limiting the population to neonates.

Findings: Four studies did not demonstrate a reduction in transfusion-associated necrotizing enterocolitis (TANEC) with the implementation of feeding protocols during packed red blood cell (PRBC) transfusions. One study concluded that it could not confirm the benefit of withholding feedings during transfusion to reduce the risk of TANEC. A 2020 randomized controlled trial (RCT) found no difference in splanchnic oxygenation when enteral feeds are withheld, continued, or restricted during a PRBC transfusion. Holding feedings during PRBC transfusions did not result in adverse nutritional outcomes.

Implications for Practice: To determine best evidence-based practice surrounding feeding protocols during RBC transfusions in very low-birth-weight and premature infants less than 37 weeks’ gestation.

Implications for Research: It is recommended that large, multicentered, adequately powered RCTs be conducted in this area. Individual institutions should standardize their practice to improve quality, safety, and patient outcomes.

Key Words: anemia, blood transfusion, feeding, necrotizing enterocolitis, neonatal, nil per os, prematurity, very low-birth-weight infant

Transfusion-associated necrotizing enterocolitis (TANEC) is defined as the development of necrotizing enterocolitis (NEC) within 48 to 72 hours following a blood transfusion.1 TANEC has demonstrated adverse clinical outcomes of greater severity, with increased morbidity and mortality as compared with NEC cases that are not associated with a preceding administration of packed red blood cells (PRBCs).2 Although the exact mechanism that causes damage to the premature infant gut is not understood, many hypotheses exist. Among these hypotheses is the theory that the immature intestinal tract of premature infants is susceptible to damage related to reperfusion of previously hypoxic tissue following red blood cell (RBC) transfusion.2 This theory stems from an understanding that the preterm infant has an immature gastrointestinal tract, which is composed of poorly expressed tight junction proteins, leading to a weakened epithelial barrier.3 A weakened epithelial barrier, immature gut motility, and inadequate quantities of digestive enzymes and hormones that normally aid digestive processes together contribute to intestinal stasis. Physiologic immaturities such as bacterial overgrowth and immature host defenses subsequently enable the survival of pathogenic microorganisms in the gut.3

For many years, the development of NEC has been associated with feeding practices surrounding the administration of PRBC transfusions.1 The literature supports that certain populations of infants are at increased risk for the development of NEC.4-17 High-risk infants include very low-birth-weight (VLBW) infants (<1500 g),4-11 infants with severe anemia (defined as hemoglobin ≤ to 8 g/dL or hematocrit ≤25%)18 who receive RBC transfusions,4-16 and infants born less than or equal to 32 weeks’ gestation.9,14,16,17 One controversy in literature and clinical practice is whether continuing to feed during the administration of PRBC transfusions increases the risk of developing TANEC among premature infants. While some studies support the theory that feeding

Author Affiliation: University of Pennsylvania, Philadelphia.
The author declares no conflict of interest.
Correspondence: Emma Killion, MSN, NNP-BC, 2610 South St, Apt #2, Philadelphia, PA 19146 (emma.killion@gmail.com).
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practices around the administration of PRBC transfusions are associated with TANEC, especially in preterm and low-birth-weight infants, conflicting literature cites that there is no correlation between feeding during blood transfusions and the incidence of TANEC.1,2,4,6,9,11,17,19

Currently, clinical practice regarding feeding versus withholding feedings during PRBC transfusion varies from setting to setting and, at times, from provider to provider within the same setting. At this time, there is no evidence-based guideline for managing feeds during PRBC transfusion in premature infants, nor is there a widely accepted consensus as to best practice. It is important to evaluate the benefits and risks of feeding management during PRBC transfusions to establish a standard of practice. The aim of this article is to evaluate the most recent literature related to risk factors for NEC/TANEC in VLBW and/or preterm infants less than 37 weeks gestation, with dedicated interest regarding the risk factor of feeding during blood transfusion. The secondary goal of this article is to establish evidence-based recommendations for clinical practice.

METHODS

Four databases were searched using keywords and MeSH terms “necrotizing enterocolitis,” “NEC,” “NPO,” and “transfusion.” Limitations included results published in a journal within the last 10 years, written in the English language, and limited to the neonatal population. PubMed search yielded 115 results, 5 of which were applicable, and 2 that qualified as original research studies. Embase search yielded 110 results, 12 of which were applicable, and 5 of which were original research studies. CINHAL search yielded 14 results, 0 of which were applicable. Scopus search yielded 157 results, 51 of which were applicable, and 19 of which were original research studies. After removal of duplicates, there were 21 original research articles that were reviewed for inclusion in this article. Of these articles, 6 specifically evaluated the influence of feeding practices during RBC transfusion. In revision of this literature review, 1 article was eliminated for being outdated and 1 additional article fitting inclusion criteria was subsequently added, having been published after completion of the first draft of this review (July 2020). Refer to Figure 1 for overview.

Pathophysiology of the Preterm Gut and NEC

To date, there is no known proven cause of NEC.1-27 The literature recognizes NEC as a multifactorial disease process of etiologic mechanisms including ischemia, infection, mechanical injury, iatrogenic factors, and immunologic barrier dysfunction.19-22 Ranges of symptoms involved in NEC are often nonspecific and closely resemble sepsis; symptoms include, but are not limited to, apnea with or without bradycardia, temperature instability, and lethargy.20,22 Diagnosis of NEC is based on symptomatology and radiographic findings, and severity is classified according to the modified Bell’s criteria (see Table 1). Classification of stage II or greater constitutes a diagnosis of definite NEC, and development of NEC within 48 to 72 hours of completing a PRBC transfusion constitutes TANEC.

Prematurity is the most consistently recognized risk factor for NEC, demonstrating an inverse relationship; lower birth weight further increases this risk.20 Other proposed risks include lack of exposure to antenatal steroids, lower 5-minute Apgar score when compared with control groups, mechanical ventilation more than 1 week, prolonged use of antibiotics within the first 10 days of life, feeding practices, and PRBC transfusions.2,6,14,15,19,20,22,23

Premature infants with TANEC are more likely to require surgical intervention and are at increased risk of mortality.20,23 TANEC, like NEC, is thought to be multifactorial. It has been proposed to result from severe anemia (hemoglobin of ≤8 g/dL or hematocrit ≤25%),18 leading to impaired oxygenation of the gut tissue and intestinal injury; immunologic reactions resulting from exposure of the premature gastrointestinal tract to biologically active mediators such as free hemoglobin, cytokines, or broken RBC fragments in RBC transfusions; ischemia and reperfusion injury; altered intestinal angiogenesis; release of cytokines triggered by transfused RBCs due to leukocyte depletion; and prolonged storage of transfused blood leading to reduced stability, increased adhesion, and lower nitric oxide content or adjuvant added to transfused blood.21 Some researchers propose that the increased oxygen content of intestinal blood following PRBC transfusion is toxic to the immature intestinal vasculature, inducing “reperfusion injury” and setting the stage for the development of TANEC.16,21

Association of TANEC With Packed Red Blood Cell Transfusions

There are many risks associated with the development of NEC. As previously stated, an important and controversial risk factor among VLBW and premature infants is PRBC transfusions.7 Premature infants are highly susceptible to anemia, which is exacerbated by innate factors including inadequate production of RBCs, shorter life span of fetal hemoglobin, and lower stores of iron, as well as external factors such as repeated blood sampling.18 Between 50% and 90% of VLBW infants receive at least one blood transfusion throughout their neonatal intensive care unit (NICU) course.23,24 Neonatal transfusion standards are subjective, without clear thresholds for transfusion of PRBCs in premature infants.18
In addition to unclear transfusion thresholds, research evaluating the impact of PRBC transfusion on the hemodynamic status of premature infants is limited. One recent study utilizing cardiac output monitor and cerebral/somatic oximeter revealed significant differences in multiple hemodynamic measurements between transfused infants and nontransfused infants. These physiologic findings among the transfused group included increased pretransfusion heart rate and respiratory rate, lower pretransfusion $\text{SpO}_2$, upward trend in systolic blood pressure and mean cardiac output over the course of transfusion, reduced trend in respiratory rate throughout transfusion, and decreased heart rate complexity post-transfusion. These pretransfusion findings may reflect the state of decreased tissue oxygenation of premature infants prior to PRBC transfusion, and trends throughout PRBC administration might suggest correction of anemic state.

Other new studies challenge the theory of ischemia-reperfusion damage as the causative agent of TANEC, suggesting that PRBC transfusions serve as incidental markers for clinically significant anemia among infants already in the early stages of undiagnosed NEC. "Two separate retrospective cohort studies demonstrated that PRBC transfusions did not increase the risk of NEC, and furthermore supported a protective benefit of PRBC transfusion against NEC in premature and VLBW infants." Instead of the PRBC transfusion as the culprit, other processes have been proposed as the causative agents responsible for the development of TANEC, among which include the degree of anemia prior to transfusion, feeding practices during transfusion, and characteristics of stored blood. The methodological concern in studies that address the association of PRBC transfusion with the development of NEC is the observational nature of these studies and the potential for confounders, biases, and the inherent inability of the study design to conclude causation.

**Transfusion-Associated NEC**

**Demographics**

Baseline differences exist between infants who developed TANEC compared with those who developed NEC. Infants who developed TANEC were often of younger gestational age at birth, lower birth weight, were more likely to have a patent ductus arteriosus (PDA), be receiving mechanical ventilation at time of diagnosis, and have lower Apgar scores at 1 and 5 minutes of life, compared with study controls who do not develop TANEC. TANEC typically occurred at later postnatal age (3-5 weeks) than the early-onset incidence of NEC (<=1 week postnatal age). Preterm infants of older postnatal age are more likely to have prolonged exposure to proposed risk factors of NEC, including ventilator days exceeding 1 week, central venous access, and greater lengths of antibiotic treatment. While the overall incidences of NEC and TANEC are inversely proportional to gestational age and birth weight, it also cannot be overlooked that infants born at a younger gestational age and smaller birth weight are disproportionately at increased risk for morbidity and mortality as a direct result of prematurity and size. Infants with a PDA preferentially shunt blood away from mesenteric circulation to the lungs.
increases the risk for intestinal tissue hypoxia, thereby also putting this group of infants at increased risk for NEC and TANEC. A 2018 retrospective analysis of 3 prospective cohort studies utilized near-infrared spectroscopy (NIRS) to evaluate intestinal and cerebral regional organ tissue oxygenation ($r_{so2}$ and $r_{SO2}$, respectively) among preterm infants receiving PRBC transfusions. This study found that lower $r_{SO2}$ values during and after PRBC transfusions were associated with TANEC, regardless of pre- and posttransfusion hemoglobin levels. These findings suggest reduced adaptability of the premature intestinal vasculature to oxygen supply and reflect the overall compromised circulatory status and fragility of this population. However, these findings should be interpreted cautiously, as this study defined TANEC as the development of NEC within 6 to 48 hours of PRBC transfusion instead of the standard 0 to 48 to 72 hours. Additionally, this study did not withhold enteral feeds during transfusion.

**Feeding Practices, Risks, and Benefits**

The consequence of withholding feedings in VLBW and premature infants is argued as rationale not to withhold feedings during RBC transfusions. Those who support this argument cite potential harm as rationale for continuing to feed through transfusions; concerns include disruption of optimal nutrition, metabolic instability, changes in electrolytes and osmotic load, delay in attainment of goal feeds, and an increase in central line days. However, a 2015 intervention-based study investigating the nutritional outcomes of infants made nil per os (NPO) during PRBC transfusion found that implementing NPO feeding guidelines during PRBC transfusion did not result in adverse nutritional outcomes and instead had the beneficial outcome of allowing for standardization of practice, which contributes to a decreased risk of NEC and TANEC. In non-NICU healthcare settings, the standardization of practice has demonstrated increased quality and safety; examples include the reduction of hospital-acquired central line infections, improved safety among medication administration practices, and increased safety throughout surgical settings. Doing the same by standardizing unit feeding practices during PRBC transfusion stands to reduce variability and ultimately lessen the risk for NEC in preterm and VLBW infants.

In the 6 studies that evaluated feeding practices during PRBC transfusion in relation to the risk of TANEC, 3 had specific protocols for holding the feeds and 3 evaluated infants who were NPO during transfusion (due to illness severity, feeding intolerance, provider preference, or randomization of study) versus those who were fed. (See Table 2 for an overview of results from the studies included in this literature review.) Four studies did not demonstrate a reduction in TANEC with the implementation of feeding protocols during PRBC transfusions. One study concluded that it could not confirm the benefit of withholding feeds during transfusion to reduce the risk of TANEC. Of the studies reviewed, those that did not find a benefit to withholding feeds during PRBC transfusion to decrease the risk of NEC or TANEC were inadequately powered and had a lower incidence of NEC at baseline, when compared with rates of NEC in other studies.  

### TABLE 1. Modified Bell’s Staging Criteria for NEC

<table>
<thead>
<tr>
<th>Stage</th>
<th>Systemic Signs</th>
<th>Abdominal Signs</th>
<th>Radiographic Findings</th>
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<tbody>
<tr>
<td>IA (suspected NEC)</td>
<td>Temperature instability, apnea, bradycardia lethargy</td>
<td>Gastric retention, abdominal distention, emesis, heme-positive stool</td>
<td>Normal or intestinal dilation, mild ileus</td>
</tr>
<tr>
<td>IB (suspected NEC)</td>
<td>Same as above</td>
<td>Grossly bloody stool</td>
<td>Same as above</td>
</tr>
<tr>
<td>IIA (definite NEC, mildly ill)</td>
<td>Same as above</td>
<td>Same as above, + absent bowel sounds, + abdominal tenderness</td>
<td>Intestinal dilation, ileus, pneumatisis intestinalis</td>
</tr>
<tr>
<td>IIB (definite NEC, moderately ill)</td>
<td>Same as above, + mild metabolic acidosis and thrombocytopenia</td>
<td>Same as above, + absent bound sounds, definite tenderness, + abdominal cellulitis, ± right lower quadrant mass</td>
<td>Same as IIA, + ascites</td>
</tr>
<tr>
<td>IIA (advanced, NEC severely ill, intact bowel)</td>
<td>Same as IIB, + hypotension, bradycardia, severe apnea, combined respiratory and metabolic acidosis, DIC, and neutropenia</td>
<td>Same as above, + signs of peritonitis, marked tenderness, and abdominal distention</td>
<td>Same as IIA, + ascites</td>
</tr>
<tr>
<td>IIB (advanced NEC, severely ill, perforated bowel)</td>
<td>Same as IIA</td>
<td>Same as IIA</td>
<td>Same as above, + pneumoperitoneum</td>
</tr>
</tbody>
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**Abbreviations:** DIC, disseminated intravascular coagulopathy; NEC, necrotizing enterocolitis.
<table>
<thead>
<tr>
<th>Source</th>
<th>Study Design/Sample</th>
<th>Methods</th>
<th>Results/Findings</th>
<th>Limitations</th>
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<tbody>
<tr>
<td>Clarke-Pounder et al(^{12})</td>
<td>Prospective, pre-/postintervention study Infants (\leq 32) wk Total 145 infants</td>
<td>Pre-/post data collection during same 6 mo (December 31 to July 1) in 2 separate years. Intervention: holding feeds during the immediate time of transfusion (2-4 h) and restarting at full volume immediately post-transfusion.</td>
<td>Cases of NEC 11/145 (6 pre; 5 post) Cases of NEC 9/82 (5 pre; 4 post) 2/145 TANEC (1 infant already NPO prior to transfusion and the second infant was in postintervention group and had feedings held during transfusion) Time to full feedings was shorter in the postintervention group for all infants (6.6 d less, (P = .008)) and those infants feeding prior to transfusion (9.8 days less, (P &lt; .001)). No difference in need for additional IV fluid or extra IV placements. No significant difference of hypoglycemia rates, though more hypoglycemia was observed in the postintervention group (3% pre vs 7% post).</td>
<td>Study was not powered to find a difference in NEC rates, as primary interest was focused on nutritional outcomes. Variation in provider practice (some providers holding feeds before, providers not compliant with standardization, etc)</td>
</tr>
<tr>
<td>DeRienzo et al(^{6})</td>
<td>Single-center, retrospective cohort study VLBW infants Total 1380 infants</td>
<td>Compared incidence of TANEC pre- and post-implementation of peritransfusion feeding protocol. Protocol = NPO 4 h before, during, and after transfusion. Restart feeds at 50% (\times) 12 h, then advance to full volume.</td>
<td>NEC 148/1380 (10.7%) Peritransfusion feeding protocol: cases of NEC before/after 126/939 (12%) to 22/293 (7%); TANEC before/after 51/126 (41%) vs 9/22 (41%). TANEC infants were smaller, more likely to develop surgical NEC, had lower mean pretransfusion hcts prior to TANEC transfusions compared to all other transfusions before their NEC episode (hct 28% vs hct 33%). Risk of TANEC inversely related to pretransfusion hct: odds ratio 0.87 (0.79-0.95)</td>
<td>Single-center study. Potential for missing data. Population was underpowered to detect the 2% drop in overall incidence of TANEC between pre- and postfeeding protocol groups. Cannot separate risk of NEC stemming from anemia from risk originating from transfusion due to nature of the study.</td>
</tr>
<tr>
<td>Doty et al(^{11})</td>
<td>Retrospective chart review VLBW infants with GA &lt;36 wk Total 387 infants 180 infants received transfusion (64 NPO; 116 fed)</td>
<td>Chart review VLBW infants who received transfusion prior to 36 wk</td>
<td>NEC 30/387 (78%) NPO group: 5/64 w/NEC (7.8%) FED group: 16/116 w/NEC (13.8%) Not statistically significant ((P = .33)), but perhaps clinically important. 11/21 cases of TANEC (52.3%) 5/11 cases TANEC resulted in mortality (45%) 6/11 cases TANEC were fed (55%)</td>
<td>Retrospective nature limits to concluding associations rather than true causality. Inadequately powered. Relatively low incidence of NEC.</td>
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<td>Bajaj et al(^2)</td>
<td>Single-center, retrospective chart review Birth weight (&lt;1250) g Total 125 infants</td>
<td>Evaluation over 2-y period before and after institution of standardized feeding regimen (withholding feeds for (\geq 12) h with transfusion).</td>
<td>19 cases of NEC TANEC in 6/19 (31.6%); rate of 4.8% overall NEC rates (15.8 vs 14.7%) and proportions of TANEC (22.2 vs 40%) in 2 periods were not significantly different.</td>
<td>Single-center retrospective study. Not powered to confirm noninferiority of approaches between 2 periods.</td>
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<tr>
<td>Sahin et al(^10)</td>
<td>Pilot study; single-center, prospective randomized controlled trial VLBW infants with GA (\leq 32) wk Total 110 infants</td>
<td>Random assignment to NPO or continued feeding (FED) group during RBC transfusion. NPO group: feedings held for 8-12 h (1-2 feedings before, during transfusion, and 1-2 feedings after); (-120) mL/kg/d dextrose/saline provided IV. Feeding intolerance: &gt;2 episodes of gastric residual &gt;50% of previous feed volume, bilious residuals, vomiting, hematochezia, or 2-cm increase in girth</td>
<td>2/80 in FED developed TANEC 0/74 NPO developed NEC 4/80 FED with feeding intolerance 1/74 NPO with feeding intolerance No relationship between the pretransfusion hematocrit value and development of NEC or feeding intolerance.</td>
<td>Lack of analysis of markers of intestinal perfusion (NIRS) or mucosal injury (occult blood testing or intestinal fatty acid binding protein). Lower incidence of TANEC compared with other studies.</td>
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<tr>
<td>Schindler et al(^27)</td>
<td>Open, multiarm, parallel-group, single-center RCT Infants with GA (&lt;35) wk and receiving PRBC transfusion</td>
<td>Randomized to 1 of 3 enteral feeding regimens: (1) No feeds: withholding enteral feedings for 12 h from start of transfusion (2) Full feeds: continuing enteral feeds (3) Restricted feeds: restriction of enteral feeds to 120 mL/kg/d (maximum 20 kcal/30 mL) for 12 h</td>
<td>0 episode of TANEC Prior to transfusion: Mean SCOR no feeds 0.97 ± 0.10 vs full feeds 0.97 ± 0.09 vs restricted feeds 0.98 ± 0.07 ([P = .72]) Mean FOE no feeds 0.25 ± 0.07 vs full feeds 0.22 ± 0.07 vs restricted feeds 0.20 ± 0.07 ([P = .72]) End of transfusion: Mean SCOR no feeds 0.99 ± 0.09 vs full feeds 0.98 ± 0.07 vs restricted feeds 1.02 ± 0.07 ([P = .20]) Mean FOE no feeds 0.19 ± 0.06 vs full feeds 0.18 ± 0.06 vs restricted feeds 0.16 ± 0.05 ([P = .16]) 12 h post-transfusion: Mean SCOR no feeds 0.99 ± 0.09 vs full feeds 0.99 ± 0.12 vs restricted feeds 0.99 ± 0.08 ([P = .10]) Mean FOE no feeds 0.21 ± 0.07 vs full feeds 0.19 ± 0.09 vs restricted feeds 0.20 ± 0.07 ([P = .83])</td>
<td>Absence of TANEC. Lack of standardization processing and interpreting data from NIRS technology. Splanchnic NIRS measurements have not been validated in the same way as cerebral NIRS measurements. Study design limits ability to interpret secondary clinical outcomes.</td>
</tr>
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**Abbreviations:** FOE, fractional oxygen extraction; GA, gestational age; hct, hematocrit; IV, intravenous; NEC, necrotizing enterocolitis; NIRS, near-infrared spectroscopy; NPO, nil per os; PRBC, packed red blood cell; RCT, randomized controlled trial; SCOR, splanchnic-cerebral oxygenation ratio; TANEC, transfusion-associated necrotizing enterocolitis; VLBW, very-low birth weight.
DeRienzo et al’s study published in 2014 demonstrated a reduction in cases of medical and surgical NEC from 12% to 7% following implementation of a transfusion-related feeding protocol, but no reduction when evaluating only those cases that qualified as TANEC (ie, cases of NEC occurring within 48 hours of PRBC transfusion). This study, however, was underpowered to detect the 2% drop in overall incidence in TANEC between the preimplementation and postimplementation of feeding protocol groups; therefore, these findings must be interpreted cautiously. Among the most recent randomized controlled trial (RCT), preterm infants were randomized to 1 of 3 enteral feeding regimens where feedings were withheld, continued, or restricted throughout PRBC transfusion and for a period of 12 hours afterward. NIRS measurements were collected to measure splanchnic cerebral oxygenation ratio and cerebral and splanchnic fractional oxygen extraction (cerebral FOE and splanchnic FOE). Findings from this RCT found that there was no difference in splanchnic oxygenation when enteral feeds were withheld, continued, or restricted during a PRBC transfusion.

The protocols for holding feedings among the other studies were varied; DeRienzo et al’s protocol called for infants to be NPO for 4 hours before, during, and after transfusion for a total of 12 hours without feeds; following this period, feeds were restarted at 50% of original volume for 12 hours, then advanced to full volume. Clarke-Pounder et al’s intervention called for holding feeds during the immediate time of transfusion, a period ranging from 2 to 4 hours, and then restarting feedings at full volume immediately posttransfusion. Still another study evaluated infants NPO for 8 to 12 hours (1-2 feedings before, during, and after transfusion) and another study for 12 to 24 hours during and after blood transfusion.

As these variations suggest, there is no consensus for what constitutes an adequate period for premature infants to be maintained NPO in an attempt to reduce the risk of TANEC. Intestinal transit times are considered to be 4 times longer in premature infants compared with term infants. It must be considered whether holding feeds for 4 hours prior to or during transfusion is time enough to allow for complete gut clearance or could significantly influence rates of TANEC. Clarke-Pounder et al’s study, which kept infants NPO for a maximum of 4 hours, was not powered specifically for the purpose of detecting differences in rates of NEC, as the primary interest of this study was to evaluate nutritional outcomes of infants kept NPO during PRBC transfusions. This factor must be taken into consideration when evaluating study outcomes.

LIMITATIONS
These studies are limited by their designs, as observational case control studies tend to overestimate risk and association. The retrospective nature of many of the studies additionally limits the ability to draw conclusions based on association rather than true causality. Confounding factors such as changes in clinical practice and incorporation of new protocols over the study periods were unable to be controlled for in these retrospective study designs. To establish a cause-and-effect relationship between PRBC transfusions and NEC, well-designed prospective RCTs are needed. The small incidence of NEC in these studies further limits the ability to draw strong conclusions, as does the inadequately powered nature of all of the studies reviewed here.

RECOMMENDATIONS FOR PRACTICE AND RESEARCH
It is recommended that large, multicenter RCTs be conducted evaluating interventions such as establishing transfusion threshold protocols and implementing peritransfusion feeding protocols. Adequately powered RCTs are essential to make practice recommendations with confidence, yet interventional studies of this nature present an ethical dilemma given the danger of NEC. In designing RCTs of this nature, ethical considerations would be of the utmost importance. Informed parental consent, strict exclusion criteria of the most at-risk infants (eg, <28 weeks’ corrected gestational age, growth restriction less than third percentile, those with major congenital anomalies, known malformations, or diseases of the gastrointestinal tract), and adequate sample size to account for infants needing to discontinue inclusion in the study due to compromised clinical state would all be important variables to consider.

Preterm neonates are among the most highly transfused patient populations. Although accompanied by life-saving benefits, PRBC transfusions are not without risk in this vulnerable population. Future research should explore the appropriate threshold for transfusing preterm infants, as clinical practice is currently varied and nonstandardized. Institutions, and even clinical practice within the same institution, transfuse below certain levels of hematocrit, while others rely on symptomatology such as increasing respiratory support, apnea, bradycardias, and/or desaturation episodes, increasing FiO₂, or lethargy. Debate often arises over transfusing older preterm infants for symptomatic anemia; given this, it would also be important to assess how the transfusion threshold in preterm infants changes with increasing postnatal age.
Summary of Recommendations for Practice and Research

What we know:
- The etiologies of NEC and TANEC remain unknown; at best, we understand their development as multifactorial.
- NEC most commonly affects VLBW infants (<1500 g) and is inversely proportional to gestational age and birth weight.
- A significant proportion of NEC cases occur within 48 hours of PRBC transfusion, particularly in preterm neonates of older postnatal age.
- The risk for TANEC is greatest within the first 48 hours of transfusion.
- The risk for TANEC is greatest within the first 48 hours of transfusion.

What needs to be studied:
- Appropriate threshold for administering PRBC transfusions to preterm neonates.
- Impact of withholding enteral feeds on the risk of TANEC, including determination of the most desirable length of time before, during, and after transfusion for which feeds should be withheld.
- RCTs to delineate causation versus association between PRBC transfusion and development of NEC and to investigate other risk factors, such as degree of pretransfusion anemia.

What we can do today:
- Develop standardized feeding practices within individual institutions.
- Identify infants at greatest risk for developing TANEC: earlier birth gestational age, lower birth weight, presence of PDA, on mechanical ventilation, and lower Apgar scores at 1 and 5 minutes of life.
- Frequently perform thorough assessments prior to, during, and after transusions to identify subtle changes in clinical status, with careful attention to apnea, bradycardia, temperature instability, hypotension, abdominal distention, abdominal discolouration, emesis, and bloody stools.

References


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