Influences of Feeding on Necrotizing Enterocolitis

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Education Gap

Despite the recognition that enteral feeding and some clinical conditions encountered during the management of prematurity may affect the development of necrotizing enterocolitis (NEC) in premature neonates, there is still significant variation in practice. Clinicians should be aware of the current evidence regarding feeding and the development of NEC in premature neonates, specifically relating to the use of breast milk, feeding when a patent ductus arteriosus is present and during its treatment, as well as the potential association of NEC with anemia and red blood cell transfusions.

Abstract

Necrotizing enterocolitis (NEC) remains one of the leading complications of prematurity with an incidence of 5% to 13% and a mortality of up to 30%. Its occurrence is inversely related to gestational age, with the most premature neonates being at highest risk. Despite numerous studies assessing risk factors, the most commonly observed associations remain prematurity and enteral feeding. Furthermore, studies have pointed to receipt of breast milk as a protective factor in decreasing the risk of NEC and formula feeding as potentially increasing the risk. Other potential risk factors and associations in the premature infant include lack of antenatal steroids, receipt of prolonged courses of postnatal antibiotics, presence of anemia, receipt of packed red blood cell transfusions, and presence of a patent ductus arteriosus. Despite the recognition that NEC remains a serious complication of prematurity, there is still no specific prescription for its prevention. Given that enteral feeding is one of the most commonly observed risk factors for the development of NEC, wide variation exists in the enteral feeding recommendations and practices for premature infants. Feeding practices that may contribute to NEC, which remain variable in practice, include feeding strategies used in the presence of a hemodynamically significant patent ductus arteriosus and feeding during packed red blood cell transfusions. Use of breast milk (mother's own milk or donor milk) is recognized as one of the mainstays of NEC prevention. This article explores multiple influences of feeding on the development of NEC.

Objectives After completing this article, readers should be able to:

1. Recognize the impact of breast milk on the occurrence of necrotizing enterocolitis (NEC).

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ABBREVIATIONS

CI	confidence interval
GI	gastrointestinal
NEC	necrotizing enterocolitis
NIRS	near-infrared spectroscopy
NPO	nil per os
OR	odds ratio
PDA	patent ductus arteriosus
PRBC	packed red blood cell
RCT	randomized controlled trial
RR	risk ratio
SMA	superior mesenteric artery
TANEC	transfusion-associated NEC
VLBW	very low birthweight

2. Describe the association between a patent ductus arteriosus, its pharmacologic treatment, and the development of NEC.
3. Explain the possible contribution of anemia, receipt of red blood cell transfusion, and the impact of feeding on NEC.

INTRODUCTION

Necrotizing enterocolitis (NEC) remains one of the leading complications of prematurity, affecting between 5% and 13% of premature infants and is the most common gastrointestinal (GI) emergency in this population. Its occurrence is inversely related to gestational age with the most premature neonates being at highest risk. (1) The most commonly found associations remain prematurity and enteral feeding. Breast milk appears to confer protection from NEC and formula feeding potentially increases the risk. Other potential risk factors and associations include lack of antenatal steroids, receipt of prolonged courses of postnatal antibiotics without bacteremia, presence of anemia, receipt of packed red blood cell (PRBC) transfusions, and presence of a patent ductus arteriosus (PDA). (2)(3)(4)(5)(6)(7)(8)(9)

NEC remains a serious complication of prematurity; however, there is still no specific prescription for its prevention. Although enteral feeding is one of the most commonly observed risk factors for the development of NEC, wide variation still exists in the enteral feeding recommendations and practices for premature infants. This article briefly discusses the pathogenesis of NEC and explores the evidence behind the influences of feeding on the development of NEC.

PATHOGENESIS

The origin of NEC is multifactorial, with intestinal immaturity at its center and genetic susceptibility, inflammation, the altered microbiome of the premature gut, and hemodynamic instability being additional contributory factors. (10) While the pathogenesis of NEC is still being explored, at its core, it is thought to arise from the premature state of the gut. Prematurity portends an impairment of intestinal repair mechanisms, limited mucin production, and other forms of gut protection, leading to a more porous intestinal epithelium. (11) Activation of toll-like receptor 4 and impaired innate immunity lead to a proinflammatory state. These immune factors are genetically determined and may increase or decrease the risk of NEC. (12) A lack of microbial diversity and colonization with predominantly pathogenic bacteria are also established in infants at higher risk of NEC especially when enteral feedings using formula are introduced. (13)(14) The effects of low blood flow states and transient hypoxemia likely cause ischemic injury to an already predisposed gut. Impaired gut motility leads to bacterial stasis, with subsequent bacterial translocation across a leaky, inflamed, and ischemic intestinal epithelium contributing to the pathogenesis of the disorder. (10)(15)

The most commonly described risk factors for NEC are extreme prematurity and enteral feeding. Numerous studies have pointed to the receipt of breast milk as a protective factor in decreasing the risk of NEC. (16) Other potential risk factors and associations include lack of antenatal steroids, receipt of prolonged antibiotics, presence of anemia, receipt of PRBC transfusions, presence of a hemodynamically significant PDA and enteral feeding during its treatment, and other low blood flow states. (2)(3)(4)(5)(6)(7)(8)(9)

DIAGNOSIS AND MANAGEMENT

Symptoms in patients with NEC may include nonspecific metabolic derangements or symptoms specific to the GI tract. GI signs and symptoms may include bilious emesis, hematochezia, abdominal distention, abdominal tenderness, and discolored abdomen. Other signs and symptoms may include lethargy or irritability, cardiorespiratory derangements (apnea, bradycardic episodes, oxygen desaturation, need for increased respiratory support, respiratory acidosis, hypotension), hematologic abnormalities (thrombocytopenia, disseminated intravascular coagulopathy, low or elevated white blood cell count), renal failure (associated electrolyte abnormalities such as hyponatremia, hyperkalemia), metabolic acidosis, bacteremia, and sepsis syndrome.

The hallmark of diagnosis is clinical symptoms coupled with the presence of pneumatosis on abdominal radiography. Abdominal distention, presence of a sentinel intestinal loop, portal venous gas, a paucity of gas, gasless abdomen, and the presence of pneumoperitoneum may also be observed radiographically. The modified Bell staging criteria are used to delineate 3 stages of NEC and the associated signs and symptoms. (17) Because symptoms of stage I NEC can be nonspecific and short-lived, many studies use NEC stage II or higher as their definition of the disorder.

Management includes bowel rest with intestinal decompression, broad-spectrum antibiotics, and supportive care for multisystem organ failure as needed. Serial radiographs are used to monitor for progression of disease. Surgical treatment is warranted in case of a worsening clinical picture or if pneumoperitoneum is noted on abdominal radiography. Approximately 30% of affected neonates require surgical management. NEC has a mortality of up to 30%, with the highest mortality seen in infants who receive surgical management. (15) Short gut, cholestatic liver failure, prolonged hospital stays with increased medical costs, and more significant neurodevelopmental impairment are additional concerning outcomes. (18)(19)

IMPACT OF GENERAL FEEDING PRACTICES ON THE DEVELOPMENT OF NEC

Though enteral feeding is one of the most commonly observed risk factors for the development of NEC, wide variation exists in enteral feeding recommendations and practices for premature infants. (20)(21) Once relative stability has been achieved after the birth of a premature infant, enteral feedings are initiated. Availability and use of an institutional feeding protocol addressing timing of initiation of enteral feedings, use of trophic feedings, use of breast milk versus preterm formula, fortification of feedings, use of continuous versus bolus feedings, and the pace of feeding advancement are some of the variations in practice that are observed and whose evidence is examined further in this article.

Standardized Feeding Protocols

Studies have shown a reduction in NEC rates with the use of institution-specific standardized feeding regimens. A 2017 meta-analysis by Jasani and Patole (22) evaluated 15 observational studies spanning the years 1978 to 2016 and involved 18,160 premature neonates of less than 37 weeks' gestational age. A 78% reduction in NEC stage II or higher was observed with the use of a standardized feeding regimen (risk ratio [RR] 0.22; P=.0001; 95% confidence interval [CI] 0.13-0.36). (22) To account for possible practice changes over time, 2 different epochs were compared, 1978 to 2004 and 2004 to 2016. The results were still significant in both periods, indicating that the use of standardized feeding regimens decreased NEC rates.

Trophic Feedings/Minimal Enteral Nutrition

It was hypothesized that using a strategy of minimal enteral nutrition or trophic feedings for the first few days of enteral feeding shortly after birth for premature infants, compared with keeping the infant nil per os (NPO) would allow the premature gut to be "primed," promoting intestinal maturation and hence a reduction in the incidence of NEC. A Cochrane review in 2013 analyzed 9 trials with 754 study subjects in which trophic feedings with milk volumes up to 24 mL/kg per day were initiated before 96 hours' postnatal age and continued until at least 1 week after birth. (23) There was no statistically significant effect on the incidence of NEC (RR 1.07; 95% CI 0.67-1.70). (23) It is possible that, despite the lack of a statistical effect indicating a decreased incidence of NEC when studies were pooled, there may be sicker, more premature, and more vulnerable populations of premature infants who may benefit from the use of trophic feedings or minimal enteral nutrition.

Delayed versus Early Advancement of Enteral Feedings

It has been postulated that delaying the progressive advancement of feedings for some days after initiation of enteral feedings could reduce the likelihood of NEC. A Cochrane review in 2014 addressed this question, seeking to compare infants who had early (days 1-4 after birth) versus delayed (days 5-7 after birth) advancements of their enteral feedings. (24) Overall, 9 studies were included in the meta-analysis, with 1,106 subjects who were very preterm (<32 weeks' gestational age at birth) or very low birthweight (VLBW; <1,500 g). The NEC analysis included 8 trials with 1,092 subjects. A statistically significant effect on the risk of NEC was not found (RR 0.93; 95% CI 0.64-1.34). This would suggest that it is not beneficial to delay advancement of enteral feedings past 4 days after birth, because it does not portend a reduction in NEC risk. It was noted that most of the study subjects were not extremely premature (few were born at <28 weeks' gestational age); hence, it is unclear that these results are generalizable to this cohort of premature infants who would have the highest risk of NEC. (24)

Slow versus Fast Feeding Advancement

It is hypothesized that advancing enteral feedings in premature neonates at a pace greater than that considered trophic, that is, greater than 20 mL/kg per day, may increase the risk of NEC in premature neonates. In a 2017 Cochrane review, slow (<24 mL/kg per day) versus faster (30-40 mL/kg per day) enteral feeding advancement rate did not result in a statistically significant difference in NEC for very preterm or very low birthweight infants. (25) Included in the meta-analyses were 10 randomized controlled trials (RCTs) with 3,753 subjects (NEC RR 1.07; 95% CI 0.83-1.39). In this meta-analysis, approximately one-third of subjects were extremely premature or extremely low birthweight (<1,000 g), potentially limiting the generalizability of the results to this population subset at the highest risk of NEC. (25)

Breast Milk (Mother's Own Milk and Donor Milk) versus Formula

The benefits of breast milk for premature infants are many and include a reduction in the incidence of NEC, lower rates of retinopathy of prematurity, reduced episodes of late-onset sepsis, improved neurodevelopmental outcomes, and fewer hospital readmission rates during the year after discharge from the NICU. (26)(27)(28)(29)(30) Reduction in rates of bronchopulmonary dysplasia has been demonstrated less consistently. (26)(27)(28)(29)(30) These benefits are observed even with nonexclusive breast milk use. Breast milk contains many protective factors, including bactericidal, immunologic, antioxidant, and anti-inflammatory properties. (31) Maternal white blood cells, lysozymes, secretory immunoglobulin A, various growth factors, lactoferrin, oligosaccharides, and commensal bacteria are among its protective factors. (32)(33)

Although breast milk use has multiple desirable benefits, including reduction in some of the catastrophic comorbidities experienced with prematurity, without fortification, it can be suboptimal for growth and nutritional balance for the rapidly growing premature infant. There are no studies that directly compare, in randomized fashion, mother's own milk to formula. However, one study evaluating a prospective cohort of premature infants grouped by those who received more than 50% of breast milk in the first 14 days of age versus those who received less than 50% of breast milk showed a reduction in NEC. In the high proportion of breast milk (>50%), NEC occurred at a rate of 3.2% versus 10.6% in the low proportion of breast milk (odd ratio [OR] 0.17; 95% CI 0.04-0.68). (34) In an analysis of 1,272 infants enrolled in the National Institute of Child Health and Human Development glutamine study, increasing human milk intake was associated with a decreasing risk of NEC. Of these infants, 13.6% developed NEC after 14 days of age. (35) For each 10% increase in the amount of milk received, risk for NEC (or death) decreased by 0.83 (95% CI 0.72-0.96). (35) It is still unclear, however, what the threshold is for volume or proportion of milk to which a premature neonate would need to be exposed in order to benefit from its use, if that infant is unable to be exclusively fed breast milk.

When exclusive breast milk use is desired and mother's own milk is unavailable, a donor milk option is available, albeit at a significant expense. The processing of donor milk may reduce some of the protective properties. In addition, donor milk is typically pooled from mothers of larger or full-term infants whose milk composition is different from that of the mother of a premature infant. (27) It is, however, recognized that the use of donor milk also reduces the risk of NEC when compared with formula. In a 2014 Cochrane review comparing donor milk to formula, 9 trials were included, with 1,070 subjects. (16) A significant increase was noted in the risk of NEC in infants receiving formula (OR 2.77; 95% CI 1.40-5.46). (16) In a 2016 study by Chowning et al, a retrospective chart review was undertaken of 550 VLBW infants who received some proportion of mother's own milk and donor milk. (36) The results indicated that receipt of human milk, mother's own or donor, for more than or equal to 50% of hospital days was associated with a statistically significant reduction in NEC, from 13.5% to 3.4% ($P<.001$). (36) While donor milk presents a significant opportunity for reduction in rates of NEC, concern exists regarding suboptimal growth. Hence, attention to optimal fortification is warranted. (27)

Fortification

Although breast milk is seen as the most optimal nutrition for premature neonates and is associated with reduced rates of NEC, to meet the needs of the growing premature infant, fortification with protein or fat as well as micronutrients is needed. This need is even more pressing when donor milk is used. (27) It was thought that with the addition of fortification products and other medications to breast milk, there is an increase in osmolality that may warrant caution. On average, the osmolality of fortified breast milk (without protein additive) is similar to that of preterm formula. (37) It is common practice to wait for establishment of at least half of the daily enteral breast milk volume before fortifying. However, given the link between achieving normal or close to normal growth patterns and improved outcomes related to prematurity, it may be beneficial to fortify breast milk feedings earlier. Tillman and colleagues performed a retrospective pre-post study comparing 53 premature infants of less than 31 weeks' gestational age whose feedings were fortified at first feed and 42 others fortified between 50 and 100 mL/kg per day of breast milk feedings. (38) There was no observed effect on NEC incidence. (38) Shah and colleagues performed a randomized study assessing whether early (20 mL/kg per day) versus delayed (100 mL/kg per day) fortification affected feeding tolerance and time to full feedings; NEC was not noted to be different between the 2 groups. (39)

Bovine versus Human Milk Fortifiers

Despite the reduction in NEC that breast milk offers, its use alone may lead to lower postnatal growth rates compared with preterm cow milk formula of equivalent caloric density, necessitating the use of fortifier products. (27) There has

been increased emphasis on minimizing cow milk in the diet of premature infants when possible, including the products available for fortification. An all-human milk diet, including fortifier products, is associated with the lowest risk of NEC. In a study by Sullivan et al, 207 premature infants fed human milk were randomized to 3 groups: 2 groups received pasteurized donor human milk-based human milk fortifier when mother's own milk or donor milk feedings reached 100 and 40 mL/kg per day, respectively, and the third group received bovine-based human milk fortifier and preterm formula if mother's milk was unavailable. (40) They found the groups that received exclusive human milk diets including fortification had significantly lower rates of NEC (P=.02), and "surgical NEC" (P=.007). (40) Other studies have supported this conclusion as well. (30)(41)(42) There is also a suggestion that nonacidified liquid human milk fortifier added to human milk may offer the greatest reduction in NEC. (43)

Continuous versus Bolus Feedings

It has been purported that feedings may be better tolerated by premature infants if administered in a continuous fashion. However, a Cochrane review in 2011, evaluating 7 trials with 511 VLBW subjects, showed no difference in NEC when continuous oro- or nasogastric feedings were compared with bolus feedings given every 2 or 3 hours. (44)

THE INFLUENCE OF A PATENT DUCTUS ARTERIOSUS ON NEC

In utero, a PDA is responsible for the shunting of oxygenated blood into the systemic circulation. Postnatally, for approximately 30% of preterm infants (higher rates with earlier gestational age) there is delayed spontaneous closure of this shunt, leading to increased pulmonary blood flow after pulmonary pressures drop, and "ductal steal" with decreased systemic blood flow. (8) This phenomenon can lead to impaired perfusion of distal organs, including the gut, which has been purported to cause feeding intolerance and possibly NEC. (45)(46)(47) The effects of a hemodynamically significant PDA on superior mesenteric artery (SMA) blood flow have been examined, with some correlation seen in Doppler blood flow velocity parameters. (47)(48) SMA blood flow response has been noted to be blunted in the presence of a PDA in baboons and human infants. (49)(50)

Increasingly conservative management is being practiced for stable premature infants. (51) In cases of a symptomatic PDA, treatment options for closure include cyclooxygenase inhibitors indomethacin and ibuprofen, and more recently, acetaminophen, as well as surgical ligation for symptomatic persistent PDAs. (52)(53)(54) Indomethacin has been associated with vasoconstrictive phenomena affecting distal organs and causing spontaneous intestinal perforation, and in some cases, increased risk of NEC as well as renal insufficiency. (52)

In a large systematic review published in 2018, Mitra et al compared various pharmacologic treatments for PDA closure. (55) They evaluated 68 randomized clinical trials with 4,802 premature and/or low-birthweight subjects. Although the PDA closure rate was 67.4% and was highest with high-dose oral ibuprofen, in a comparison of placebo with all other medical treatment, no differences in NEC were observed. (55)

Indomethacin can be administered via a prolonged or shorter course. However, based on a systematic review done in 2007 evaluating 5 studies with 431 study subjects, the prolonged course (>4 doses) of indomethacin was associated with increased NEC risk (RR 1.87; 95% CI 1.07-3.27). (56) Ibuprofen is associated with less vasoconstrictive effects with a better GI and renal side effect profile, yet has comparable PDA closure rates. (52) A Cochrane review done in 2015 evaluating 33 studies with 2,290 subjects compared treatment of PDA in premature, low-birthweight neonates using indomethacin, ibuprofen, placebo, or no treatment. (57) Results indicated that ibuprofen was just as effective as indomethacin for PDA closure. However, the risk of developing NEC was reduced for ibuprofen (16 studies, 948 infants; RR 0.64; 95% CI 0.45-0.93). (57) In addition, Doppler blood flow studies show less vasoconstrictive effects on mesenteric and renal artery with ibuprofen compared with indomethacin. (58) Acetaminophen has been studied as a relatively newer therapy for PDA closure. In a Cochrane review of 8 randomized studies including 916 infants, acetaminophen was found to be as effective as ibuprofen, but the evidence was considered to be of low quality to assess the effectiveness in comparison with indomethacin. (54) However, concern exists for neurodevelopment impairment, with autism or autism spectrum disorders suggested with pre- and postnatal exposure to the drug. (54) Additional studies with long-term follow-up are ongoing.

FEEDING IN THE PRESENCE OF A PERSISTENT PDA AND ITS PHARMACOLOGIC TREATMENT

Because of the vasoconstrictive effects of pharmacologic treatment of a PDA and its potential increased risk of

NEC, clinicians sometimes reduce or terminate enteral feedings when a hemodynamically significant PDA is discovered; this practice may vary regionally. (59) Jhaveri et al reported a survey on US- and non-US-based neonatologists regarding their beliefs about whether feedings should be withheld when a persistent PDA is suspected. (59) Results indicated that if neonatologists felt that they had to stop feedings, then they would ligate a PDA irrespective of the need for respiratory support. Of the US neonatologists surveyed, 70% believed that enteral feedings need to be stopped in the presence of a hemodynamically significant PDA. (59) Meanwhile, 70% of non-US neonatologists believed that enteral feedings should continue in the presence of a hemodynamically significant PDA. (59) There are few randomized studies to guide practice.

Bellander et al performed a retrospective review to address whether feeding with breast milk within a few hours after birth in neonates who were less than or equal to 29 weeks' gestational age at birth and ultimately received indomethacin treatment for a PDA led to increased GI risks. (60) There was no difference in the outcome of NEC between the 2 groups. Clyman et al assessed enteral feeding during indomethacin and ibuprofen treatment of a PDA. (61) One hundred seventy-seven preterm infants of more than 31 weeks' gestational age at birth were randomized to trophic feedings versus NPO. The results indicated that the time to achievement of 120 mL/kg per day feedings was less in the trophic feeding group and there was no increase in NEC. (61) A retrospective cohort study by Louis et al in 2016 assessed the risk of NEC when neonates were divided into 3 feeding groups: (NPO [n=229], <60 mL/kg per day [n=142], and >60 mL/kg per day [n=44]) and who received indomethacin for PDA treatment. (62) No difference in the primary outcome of NEC was observed. (62)

TRANSFUSION-ASSOCIATED NEC

Recently, clinicians have expressed concern about transfusion-associated NEC (TANEC), also called *transfusion-related acute gut injury* or *transfusion-related NEC*. This condition is most commonly defined as NEC occurring within 48 hours of receiving a PRBC transfusion. (4)(63)(64) Its etiology has been said to be multifactorial and may relate to an increase in proinflammatory cytokines seen after PRBC transfusion in neonates, alterations in vascular adaptability after transfusion (seen on near-infrared spectroscopy [NIRS] as higher intestinal tissue oxygen saturation as well as altered blood flow velocity noted on Doppler studies) and reperfusion injury related to sudden correction of anemia in poorly perfused and oxygenated intestinal tissues. (65)(66)(67)(68) Singh et al, in their retrospective case-control study, found that both a lower hematocrit and PRBC transfusion increased the likelihood of NEC. (3)

Despite the presence of observational studies linking the temporal receipt of PRBC to the development of NEC, there is still strong debate about whether TANEC is an actual pathologic entity, that is, is the receipt of PRBCs simply an association or is it causative in some cases of NEC? Included in this debate are theories as to whether the degree of anemia before transfusion is the factor that predisposes patients to TANEC. (5)(63)(69) Hay et al (70) performed a systematic review and graded the quality of the available evidence around the TANEC phenomenon. Most of the studies evaluated were observational (n=23) with only 3 randomized studies addressing the allocation of PRBC transfusions. When the definition of NEC occurring within 48 hours of PRBC transfusion was used, the results did not show a statistically significant association of NEC with PRBC transfusion. (70) Similarly, Garg et al performed a meta-analysis of 17 observational studies and did not find an independent association between PRBC transfusion and NEC. (71)

FEEDING DURING PRBC TRANSFUSION

Because of the possible association of PRBC transfusion and development of NEC, some neonatal units have developed transfusion guidelines based on consensus within their unit regarding whether to feed during PRBC transfusions, and for how long a duration to maintain NPO, as well as changes in volume of feedings upon reinitiation. Withholding feedings during PRBC transfusion for the smallest and youngest premature infants may mean need for intravenous access, initiation of intravenous fluids, and possible prolongation of the time to acquire full enteral feedings. Despite the adoption of peritransfusion feeding cessation guidelines by many centers in varying forms, there is limited evidence from randomized trials to guide hemoglobin or hematocrit cutoffs as well as the duration of time for which to withhold enteral feedings to protect from TANEC.

In 2014, DeRienzo and colleagues published a retrospective cohort study of VLBW infants comparing outcomes before and after institution of a peritransfusion feeding protocol. (69) The incidence of NEC decreased from 12% to 7% in the pre- to postprotocol interval (P=.01). However, the incidence of TANEC (NEC within 48 hours of a PRBC transfusion) remained the same in both intervals, 41% of the total number of NEC cases. The risk of TANEC was higher with lower pretransfusion hematocrit (OR 0.87; 95% CI 0.79-0.95). (69)

Marin and colleagues published a study in 2014 in which they assessed mesenteric tissue oxygenation measured by NIRS in preterm infants less than 33 weeks' gestation at birth, categorized into 2 groups: those who were fed (n=9) during PRBC transfusion and those not fed (n=8). (72) Mesenteric oxygenation was assessed for up to 48 hours after PRBC transfusion. Upon resuming feedings, they found lower postprandial mesenteric oxygenation trends in infants fed during transfusions, compared with positive trends in those who were not fed during the transfusion interval. This could indicate a risk of mesenteric ischemia that may potentiate the development of TANEC in infants fed during PRBC transfusions. (72)

Pitzele and colleagues explored whether postprandial SMA blood flow velocity would be affected in neonates who were all fed during PRBC transfusion. (73) Infants were VLBW preterm infants, older than 14 days, who received transfusions while being bolus fed every 3 hours. Pre- and postprandial SMA blood flow velocity was assessed, as well as immediately before and after transfusion and at 24 and 48 hours after transfusion. They found that SMA blood flow velocities were blunted immediately after the transfusion and then normalized at 24 hours after transfusion, suggesting that there may be a period of increased risk of ischemia after PRBC transfusion that may potentiate the risk of TANEC. (73) Importantly, they observed normal postprandial responses in the anemia, in the pretransfusion period. (73)

A systematic review undertaken by Jasani et al in 2017 sought to review the effect of withholding feedings during PRBC transfusion on TANEC. (74) In this review, TANEC was defined as NEC stage II or higher occurring within 48 to 72 hours after a PRBC transfusion. No RCTs were available for inclusion in the review; 7 nonrandomized studies with 7,492 study subjects were included. The results indicated that the practice of withholding feedings during PRBC transfusion significantly reduced the incidence of TANEC (RR 0.47; *P*=.005; 95% CI 0.28-0.80). Of note, the feeding protocols used in the included study varied in the amount of time feedings were withheld before transfusion, the total NPO duration, when feedings were restarted, and if feedings were restarted at lower than prior volumes, how fast they were advanced. (74)

DISCUSSION

A 2006 survey assessing nutrition practices in the NICU for 3 different birthweight categories was undertaken by Hans et al to determine how current nutrition practice intentions for preterm infants compare with published recommendations and previous feeding practices. Of the invited participants, 23% responded (N=176). (21) Breast milk was the most common first enteral feeding in all birthweight categories. Enteral feedings were initiated earlier and advanced faster than in the past, especially for infants weighing less than 1,000 g at birth. Even though data support the safety of more rapid feeding advancement, more than 80% of surveyed NICUs had slow feeding advancements of 10 to 20 mL/kg per day across all weight categories. (21) This study highlights that evidence and practice sometimes are not concordant. Those charged with the care of premature infants often do not have strong experimental evidence from RCTs by which to guide management, and instead have to weigh and interpret observational or retrospective data to inform our practice. As such, this leads to significant variability in management for common complications of prematurity. One such common issue faced by premature infants is NEC, the most common GI illness in this population. Although prematurity and enteral feeding are the most common risk factors for NEC, the use of breast milk, even if not exclusive and including donor milk, is highly associated with conferring protection from NEC. However, a host of other variables that may influence the risk of NEC come into play, including the timing of initiation of feedings, use of trophic feedings or minimal enteral nutrition, pace and rate of progressive feed advancement, timing of initiation of enteral feed fortification, and continuous versus bolus feedings. Another clinical issue affecting premature neonates is the presence of a PDA which, if hemodynamically significant, is purported to be a risk factor for NEC. While the trend is toward more conservative management for patients with a PDA, challenges for some still include whether to feed with a PDA. In addition, if a PDA is being treated with cyclooxygenase inhibitors, given their vasoconstrictive properties and effect on mesenteric vessels, is there risk of NEC if feeding occurs during treatment? Another common condition encountered is anemia of prematurity. Its treatment with a PRBC transfusion has been noted as associated with the development of NEC. This has prompted many NICUs to use feed withholding strategies during transfusion to prevent TANEC, despite the evidence of direct causality being marginal.

The influences of certain aspects of feeding on the development of NEC are supported by observational evidence in many cases. (20)(75) The Table provides a summary of the evidence regarding influences of the discussed feeding factors on NEC. The lack of high-quality evidence still leaves wide variation in feeding practices that may affect NEC, with the exception of strong recommendations for the use of breast milk and standardized feeding regimens. No RCTs have been performed to date to assess the practice of withholding feedings during PRBC transfusion. Although

TABLE. **Influence of Feeding Factors on NEC: Summary of the Evidence**

FEEDING FACTOR	DECREASES NEC	INCREASES NEC	NO/MINIMAL IMPACT ON NEC	UNCLEAR
Standardized feeding regimen	+ (meta-analysis - 15 observational studies)			
Trophic feedings/minimal enteral nutrition			+ (meta-analysis – 9 RCTs)[a]	
Delayed vs early advancement of enteral feedings (5-7 d vs 1-4 d)			+ (meta-analysis - 9 RCTs)[a]	
Slow versus fast feeding advancement <24 mL/kg per day vs 30-40 mL/kg per day)			+ (meta-analysis - 10 RCTs)[a]	
Breast milk (mother's own milk and donor milk)	+ (meta-analysis – 9 RCTs)			
Formula		+ (mix of study types)		
Fortification				
Osmolality			+	
Timing of initiation			+ (mix of study types)	
Human milk-based human milk fortifier vs bovine fortifier	+ (mix of study types)			
Continuous vs bolus feedings			+ (meta-analysis - 7 RCTs)	
PDA				
Feeding with a PDA				+ (regional variation in feeding practices; epidemiologic association from observational data and suggestion of risk by SMA blood flow studies)
Feeding during pharmacologic treatment of a PDA			+ (retrospective studies × 2 and 1 RCT; trophic/ minimal enteral feedings; oral ibuprofen associated with less NEC)	
TANEC				
Anemia		+ (observational)		
PRBC transfusion			+ (meta-analysis - 40 observational, 3 RCTs)	
Withholding feedings during PRBC transfusion	+ (meta-analysis - 7 nonrandomized studies)			

NEC=necrotizing enterocolitis; PDA=patent ductus arteriosus; PRBC=packed red blood cells; RCT=randomized controlled trial; SMA=superior mesenteric artery; TANEC=transfusion-associated NEC.

[a]*Overall low proportion of extremely low-birthweight study subjects.*

the available observational data point toward the positive benefit of this practice, this should not yet be considered standard of care. Moreover, the American Academy of Pediatrics has issued no statements or recommendations concerning the practice.

CONCLUSION

Given that enteral feeding is one of the consistently observed risk factors for NEC, neonatologists need to pay close attention to the varying aspects of feeding and how they influence the incidence of the disease. These observations may translate into practice changes despite lack of high-quality experimental evidence to protect the most vulnerable of our pediatric patient population. Of the feeding-related factors that may influence NEC, the evidence regarding the protection that breast milk confers is the most consistently observed along with the use of standardized feeding regimens. We strongly support the future performance of one or more sufficiently powered RCTs to adequately assess whether withholding feedings during PRBC transfusion makes a difference in the incidence of NEC.

American Board of Pediatrics Neonatal-Perinatal Content Specifications

- Know the immunologic and anti-infective constituents in human milk and their physiologic effects.
- Know the pathophysiology of NEC.

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