An update on necrotizing enterocolitis: pathogenesis and preventive strategies

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Abstract

Necrotizing enterocolitis (NEC) is one of the most critical morbidities in preterm infants. The incidence of NEC is 7% in very-low-birth-weight infants, and its mortality is 15 to 30%. Infants who survive NEC have various complications, such as nosocomial infection, malnutrition, growth failure, bronchopulmonary dysplasia, retinopathy of prematurity, and neurodevelopmental delays. The most important etiology in the pathogenesis of NEC is structural and immunological intestinal immaturity. In preterm infants with immature gastrointestinal tracts, development of NEC may be associated with a variety of factors, such as colonization with pathogenic bacteria, secondary ischemia, genetic polymorphisms conferring NEC susceptibility, anemia with red blood cell transfusion, and sensitization to cow milk proteins. To date, a variety of preventive strategies has been accepted or attempted in clinical practice with regard to the pathogenesis of NEC. These strategies include the use of breast feeding, various feeding strategies, probiotics, prebiotics, glutamine and arginine, and lactoferrin. There is substantial evidence for the efficacy of breast feeding and the use of probiotics in infants with birth weights above 1,000 g, and these strategies are commonly used in clinical practice. Other preventive strategies, however, require further research to establish their effect on NEC.

Keywords: Necrotizing enterocolitis, Infant, Premature, Pathogenesis, Prevention

Introduction

Necrotizing enterocolitis (NEC) is one of the most critical morbidities occurring in preterm infants. In spite of improvements in neonatal intensive care, the incidence of NEC has increased to 7% in very-low-birth-weight (VLBW) infants[1]. Mortality from NEC is 15 to 30% and is especially high in infants with lower birth weight, earlier gestation, and surgical interventions[2]. Infants who have recovered from NEC are more susceptible to nosocomial infection, malnutrition, growth failure, bronchopulmonary dysplasia, retinopathy of prematurity, and longer hospitalization[3]. In addition, severe NEC requiring surgical intervention is a significant risk factor for adverse neurodevelopmental outcomes[4]. Although advances in NEC research have been achieved, much remains to be elucidated on disease pathophysiology. NEC arises from multifactorial origins, including intestinal immaturity, infection, and ischemia.

Prevention is important for the management of NEC, because treatment strategies may be ineffective in some cases of clinically significant NEC. In this article, the author reviews the current literature on factors predisposing infants to NEC and strategies for its prevention and management.

Pathogenesis

1. Intestinal immaturity

An underdeveloped gastrointestinal tract in preterm infants may trigger the development of NEC. Decreased intestinal peristalsis may result in extended exposure of the intestinal epithelium to noxious substances. Immature mucus coatings and incompletely formed tight junctions also contribute to disease pathogenesis[5,6]. Additionally, the gastrointestinal tract's immunological functions are too immature in preterm infants to adequately respond to colonization by pathogenic bacteria[7]. For example, Toll-like Receptor-4 expression is down-regulated in the mature intestinal epithelium upon stimulation by gram-negative lipopolysaccharide but is increased in the immature intestinal epithelium, eliciting an exaggerated pro-inflammatory response through up-regulation of the NF-kB pathway[8,9].

2. Infection and colonization by pathogenic bacteria

Prolonged antibiotic exposure is associated with an increased risk of NEC. This association persisted in multivariate analyses that excluded confounding factors, such as gestational age, birth weight, and sepsis[10]. Prolonged antibiotic exposure may not only delay beneficial colonization by normal gastrointestinal flora, but may also promote colonization by pathogenic bacteria[11]. In some instances, the replication rates of pathogens facilitate their outcompetition of normal flora, predisposing preterm infants to NEC, especially in conjunction with intestinal barrier impairment[12].

3. Ischemia

Preterm infants frequently experience ischemic events, such as hypotension, hypothermia, anemia, and patent ductus arteriosus during intensive care. Although experimental and clinical studies have excluded ischemia as a major trigger for NEC[13,14], it may play a secondary role in the pathogenesis. Ischemia can disrupt endothelial cell function and alter the endothelin-1/nitric oxide balance in favor of vasoconstriction, causing expansion of ischemic intestinal lesions[15,16].

4. Additional contributing factors

Small studies have identified contributions from specific genetic polymorphisms, such as mutations in carbamoyl phosphate synthetase[17], vascular endothelial growth factor[18], and interleukin-10 and 12[19] in the development of NEC. There are also concerns that NEC may be associated with anemia with red blood cell (RBC) transfusion[20,21]. Although an exact mechanism remains undefined, it is suggested that severe anemia results in insufficient oxygen to meet the increased requirements of mesenteric vessels after enteral feeding. RBC transfusion may also interrupt the mesenteric vascular tone via an imbalance of nitric oxide and endothelin-1, stimulating the production of pro-inflammatory cytokines as occurs during multiple organ failure[22]. Recently, several *in vitro* studies have reported that sensitization to cow milk proteins may be involved in NEC pathogenesis[23,24]. At present, however, data are insufficient to determine the involvement of these factors in the pathogenesis of NEC.

Preventive strategies

1. Enteral feeding strategies

Human breast milk may protect against NEC by inhibiting gut colonization by pathogenic flora, enhancing maturation of the intestinal barrier, and controlling the pro-inflammatory response. A meta-analysis of a few small randomized controlled trials concluded that human breast milk confers a protective effect against NEC[25,26]. However, these trials varied in their definitions of breast milk and in trial design parameters, such as maternal vs. donor milk, term vs. preterm, fortified vs. unfortified, and feeding exclusively with human breast milk vs. supplementation with formula. A recent randomized controlled trial reported that an exclusively human-milk-based diet (i.e., human breast milk and a human-based fortifier) significantly reduced the incidence of NEC and surgical NEC[27]. In a metaanalysis comparing donor breast milk to infant formula in low-birthweight infants, formula feeding was correlated with a higher incidence of NEC (typical relative risk [RR]. 2.5; 95% confidence interval [CI], 1.2 to 5.1), although it increased short term growth rate[28].

Berseth et al.[29] reported that prolonging small feeding volumes early in life decreased the incidence of NEC in VLBW infants compared with feeding advancement (1.4% vs. 10%, P=0.03). Nevertheless, slow advancement of enteral feeding (15 to 20 mL/kg/day) did not reduce NEC incidence compared with rapid feeding advancement in VLBW infants (30 to 35 mL/kg/day)[30]. Early trophic feeding in VLBW infants did not increase the incidence of NEC[31,32]. Meanwhile, continuous nasogastric tube feeding did not decrease NEC compared with bolus milk feeding[33]. However, these findings are limited by insufficient randomized controlled trials.

2. Probiotics

Immediately after birth, colonization of the intestine in healthy, term infants begins with maternal vaginal flora. *Bifidobacterium* species are usually dominant among the complex intestinal flora that develops during the first few post-natal weeks in breast-fed infants. Preterm infants may have abnormal colonization by intestinal flora due to exposure to pathogenic bacteria in the intensive care unit, antibiotic use, prolonged fasting, and less feeding with breast milk.

Probiotics may protect against the development of NEC through enhancement of the barrier preventing bacterial migration across the intestinal mucosa[34)], competition with pathogenic flora[35)], and modification of the host's response to microbial products[36)].

A recent meta-analysis reported the effect of probiotics on the prevention of NEC[37)]. Enteral probiotic supplementation significantly reduced the incidence of severe NEC (stage II or higher; typical RR, 0.35; 95% CI, 0.24 to 0.52) and mortality (typical RR, 0.40; 95% CI, 0.27 to 0.60). Probiotic supplementation also significantly decreased NEC incidence in subgroup analyses of VLBW infants (typical RR, 0.34; 95% CI, 0.23 to 0.50). There have been no reports of systemic infections with probiotic supplementation in eligible trials. However, there are limitations to the meta-analysis; Birth weight and gestational age of subjects in trials were highly variable, and probiotic supplementation differed widely with regard to timing, dosage, and species of probiotics. Most importantly, no data were reported for efficacy and safety of probiotics in extremely-low-birth-weight infants, the most vulnerable patients.

3. Prebiotics

Prebiotics are indigestible substances that selectively promote the growth and colonization of probiotic lactobacilli or bifidobacteria[38,39)]. Prebiotics can be classified as either natural substances in human breast milk or synthetic substances, such as a mixture of galactooligosaccharides and fructo-oligosaccharides. Riskin et al.[40)] reported that a low dose of lactulose promotes enteral feeding and has a trend toward a lower incidence of NEC. Although randomized controlled trials of prebiotic supplementation in preterm infants have not conclusively proven their preventive effect on NEC[41,42)], they may be efficacious in this population.

4. Glutamine and arginine

In critical patients, Glutamine can be an essential amino acid. It plays an important role as a metabolic fuel[43)] and also maintains the functional integrity of the gut[44)]. A meta-analysis of 5 randomized controlled trials on the effects of glutamine supplementation on NEC showed no statistically effect on its incidence of NEC[45)], but a recent randomized trial reported its statistically significant reduction of NEC incidence[46)].

Arginine is an amino acid important for the formation of nitric oxide[47)]. Compared to control infants, preterm infants with NEC have significantly decreased levels of plasma arginine[48)]. Amin et al.[49)] reported that parenteral arginine supplementation increases plasma arginine levels and decreases NEC incidence. However, interpretation of this study is confounded by its inclusion of many infants with low grade NEC (stage I) in the control group.

5. Additional preventive strategies

Lactoferrin is a major whey protein in mammalian milk and has an important function in the innate immune system. There is high amino acid homology (77%) between human and bovine lactoferrin[50)]. In a randomized controlled trial, enteral bovine lactoferrin supplementation decreased the incidence of NEC when combination with *Lactobacillus rhamnosus* GG[51)]. In addition to the preventive strategies reviewed here, epidermal growth factor (EGF)[52)], heparin-binding EGF[53)], endothelin-1 receptor antagonist[54)], and ω-3 fatty acids[55)] may be candidates for NEC prevention, but confirmatory evidence is required.

Conclusion

Despite improvements in neonatal intensive care, NEC remains a critical disease in preterm infants and confers a high incidence of mortality and many serious complications. In preterm infants with insufficient maturation of the gastrointestinal tract, development of NEC may be associated with a variety of factors, including colonization by pathogenic bacteria, secondary ischemia, genetic polymorphisms conferring susceptibility to NEC, anemia with RBC transfusion, and sensitization to cow milk proteins. To date, a variety of preventive strategies have been developed or used in clinical practice, including the use of breast feeding, various feeding strategies, probiotics, prebiotics, glutamine and arginine, and lactoferrin. Breast feeding and probiotic use in infants with birth weights above 1,000 g have been proven effective in clinical practice. However, other strategies currently lack sufficient evidence for routine use as preventive measures. Therefore, clinical trials enrolling large numbers of infants and employing rigorous controls will be essential to prove the efficacy of other strategies in preventing NEC.

Article information

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