Prevention of Necrotizing Enterocolitis Through Manipulation of the Intestinal Microbiota of the Premature Infant

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ABSTRACT

Purpose: In spite of four decades of research, necrotizing enterocolitis (NEC) remains the most common gastrointestinal complication in premature infants with high mortality and long-term morbidity. The composition of the intestinal microbiota of the premature infant differs dramatically from that of the healthy term infant and appears to be an important risk factor for NEC.

Methods: We review the evidence of an association between intestinal dysbiosis and NEC and summarize published English language clinical trials and cohort studies involving attempts to manipulate the intestinal microbiota in premature infants.

Findings: Promising NEC prevention strategies that alter the intestinal microbiota include probiotics, prebiotics, synbiotics, lacteroferrin, and human milk feeding.

Implications: Shaping the intestinal microbiota of the premature infant through human milk feeding and dietary supplements decreases the risk of NEC. Further studies to identify the ideal microbial composition and the most effective combination of supplements are indicated. (*Clin Ther*. 2016;▮:▮▮▮–▮▮▮)

Key words: s: human milk, lactoferrin, necrotizing enterocolitis, prebiotic, premature infant probiotic, synbiotic.

INTRODUCTION

Necrotizing enterocolitis (NEC) is a common and devastating disease of premature infants. It affects approximately 7% of infants weighing 500 to 1500 g and has mortality rates as high as 30%.[1] The pathophysiology of NEC has been an area of active study for 4 decades. Current thinking suggests that NEC is not a single disease or infection but the final pathway of a variety of insults. Risk factors include prematurity of the innate and adaptive immune responses (eg, poorly regulated inflammatory responses and alterations in intestinal permeability, motility, apoptosis, and autophagy), enteral feeding, an altered intestinal microbiota, and variation in intestinal perfusion.[1–3] The current clinical staging of NEC was initially proposed by Bell et al[4] and modified by Walsh and Kliegman[5] and has endured for 3 decades. The challenges of this classification include disagreements among experts as to the clinical relevance of stage 1 NEC (resulting in variation in inclusion of stage 1 NEC in reports of clinical trials and cohort studies), the lack of distinction between NEC and spontaneous ileal perforation without necrosis, and a lack of evidence regarding applicability to term infants with NEC. Treatment of NEC has changed little throughout the decades: bowel rest, broad-spectrum antibiotics, parenteral nutrition, ventilatory support, blood pressure measurement, and peritoneal drainage or resection of necrotic bowel in severe cases. There is significant short-term morbidity, including abnormal bowel function, prolonged parenteral nutrition requiring central catheter placement, and longer lengths of hospital stay with significantly higher costs.[6] Long-term morbidity includes poor growth, malabsorption, and delays in neurodevelopment.[7]

Two compelling observations shed light on the pathogenesis of NEC. First, the onset of NEC is generally at 2 to 6 weeks of life and tends to occur later in the most premature infants with the highest risk of NEC at 29 to 33 weeks' corrected gestational age.[8] This observation supports the hypothesis that a certain level of maturation of the immune system is required for NEC pathogenesis. It is likely not coincidental that the Paneth cells of the small intestine become functional at about this time.

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These sentinels of the crypts of Lieberkuhn shape the composition of the intestinal microbiota and protect the intestinal stem cells from injury.[9,10] Second, small but carefully performed studies found alterations in the intestinal microbiota before the onset of NEC. The term *dysbiosis* implies an alteration in the composition of the intestinal microbiota and/or microbiome related to disease. Independent investigators have found that an early predominance of Firmicutes (particularly Clostridiaceae) in the first weeks of life predisposes to NEC and that a sudden bloom of Proteobacteria (particularly Enterobacteriaceae) is common in the days just before the onset of NEC.[11–14] The latter observation is particularly compelling in light of the capacity of several Enterobacteriaceae to trigger an inflammatory response and then outcompete other commensal bacteria by selective consumption of the products of inflammation.[15] In this article, we touch briefly on the causes of dysbiosis in the premature infant and review the efficacy of attempts to prevent NEC by dietary interventions designed to correct dysbiosis, including probiotics, prebiotics, synbiotics, lactoferrin, and human milk.

GUT COLONIZATION AND DYSBIOSIS IN PREMATURE INFANTS

For many years, accepted dogma maintained that the in utero environment was sterile and that the intestinal tract of the fetus was not colonized with bacteria until the time of rupture of membranes. Recent studies suggest that the fetal membranes are not impermeable to bacteria and that many fetuses are exposed to microbes in the amniotic fluid before delivery.[16–18] The impact of this early exposure is unclear. Although early colonizers of the infant gut are heavily influenced by mode of delivery,[19] the second wave of colonists in term infants is mostly determined by feeding type, with breastfed infants dominated by bifidobacteria and bacteroides and formula-fed infants dominated by streptococci, staphylococci, and lactobacilli.[20] The second wave of gut colonists in premature infants is less influenced by type of feeding and differs markedly from that of term infants with high numbers of Clostridiaceae and Enterobacteriaceae and relatively low numbers of Bifidobacteriaceae and Bacteroidetes.[21–25] Perhaps the most important influence on the composition of the premature gut microbiota is degree of prematurity.[26] The use of acid suppressive medication delays intestinal transit time, alters the intestinal microbiota,[27] and increases the risk of NEC.[28] In addition, antibiotic administration leads to changes in the composition of the gut microbiota, suppressing growth of both commensal and pathogenic bacteria, and increases the risk of NEC.[25,29,30] Despite (or perhaps in part related to) aggressive cleaning protocols, the neonatal intensive care unit environment is an important source of pathogenic organisms and influences intestinal colonization of infants with prolonged hospitalizations.[31] Other potential influences on the intestinal microbiota of premature infants include duration of feeding tubes, kangaroo skin-to-skin care, periods of gut rest, administration of colostrum to the buccal mucosa,[32] and genetic factors (eg, common mutations in the *FUT2* gene).[33,34] Among the many factors predisposing premature infants to dysbiosis, those with clear associations with NEC include degree of prematurity,[26] formula feeding,[35] antibiotics,[29,36] and acid-blocking agents.[28] The concept of altering the intestinal microbiota or correcting dysbiosis to decrease risk of NEC is promising. We review 5 overlapping strategies: probiotics, prebiotics, synbiotics, lactoferrin, and human milk (Figure 1).

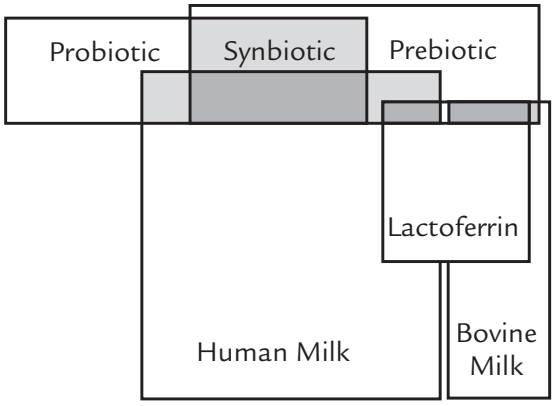

Fig. 1. Dietary and supplemental strategies for altering the intestinal microbiota of the premature infant. Shading represents areas of overlap.

PROBIOTICS

Probiotics are biological formulations or dietary supplements that contain living microorganisms, most commonly one or more of the following genera: *Bifidobacterium, Lactobacillus, Streptococcus,*