First Do No Harm

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The classic definition of Neonatal Necrotizing Enterocolitis (NEC) states that NEC is an inflammatory bowel necrosis that primarily afflicts premature infants after the initiation of enteral

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feeding. However, frequently it seems that is all we know about this disease—how to define it. Despite numerous studies in animal models and clinical trials, we do not know the cause, we cannot predict who will get it, we often do not know how to definitively diagnose it, and we do not have a specific treatment.

National statistics are that NEC affects about 10% of premature infants <1500 grams. It affects patients characteristically between 7 and 14 days of life,¹⁻³ although increasingly NEC has been documented several weeks after birth, particularly in very low birth weight infants.⁴ Susceptibility to NEC appears inversely related to gestational age, thus more immature infants are more likely to get the disease and have a longer window during which they are at risk. The warning signs for NEC are non-specific signs of gastrointestinal distress such as abdominal distension, vomiting, and increased gastric aspirates, but its progression to pneumatosis intestinalis, pneumoperitoneum, shock and death can occur over hours.^{5,6} Currently treatment is merely supportive, including immediate cessation of enteral feeds, institution of nasogastric suction, fluid resuscitation, close monitoring of acid/base and electrolyte balance, broad spectrum parenteral antibiotics, parenteral nutrition, and frequent abdominal radiographs to document progression to pneumoperitoneum. Surgery is indicated for pneumoperitoneum, peritonitis, and intestinal obstruction.^{7,8} However, treatment modalities

are often inadequate because of the rapid progression of NEC from its initial diagnosis. The mortality rate from NEC is 30-50%, and for those that survive, there is risk of stricture, short-gut, intestinal failure, and poor neurodevelopmental outcome.⁹ It has been suggested that one needs to attack the proximal component of the pathophysiologic cascade leading to NEC that, once started, is very difficult to stop. As treatment options and outcomes have been unchanged for decades, probiotic therapy is extremely appealing with both evidence of benefit in multiple clinical trials and biologic plausibility.

Luedtke *et al.* have provided an excellent review of the promise and concerns associated with probiotics and NEC. As noted, probiotics may prevent NEC in a multifactorial manner through intestinal maturation and normalization of gastrointestinal colonization. A summary of recent trials and meta-analyses is also given, noting that baseline NEC rate is a major factor influencing benefit of probiotic supplementation in a population, with the majority of trials showing the greatest benefit being conducted outside of the United States and having much higher baseline NEC rates than commonly found in the US. Concerns include variation in probiotic strains and protocols used in clinical trials which leads to ambiguity regarding optimal formulation and dosage, variation in response by underlying clinical characteristics including NEC rate and gestational age/birthweight of subjects, and unclear regulatory oversight of probiotic products. Many of these cautions apply to use of probiotics in adult diseases as well as preterm infant diseases; however, above all, NEC is a disease of intestinal immaturity. Thus, there are unique considerations for the preterm

infant patient population.

Whenever one is considering disease processes in the preterm infant it is important to remember that immaturity is the key concern—that the preterm infant is essentially a fetus, undergoing development in the extra-uterine environment instead of its expected protected, intrauterine environment. There are changes in physiology, body mass, water/lipid compartments, and receptor expression as well as ongoing neurodevelopment. There are thus concerns beyond sepsis, and as the authors have mentioned, the long term effects of probiotic supplementation in preterm infants remain to be elucidated. Caution is warranted, as more chronic disorders are associated with alterations in the intestinal microbiota.

A current hypothesis is that the intestinal injury in NEC may be the result of synergy in which enteral feeding results in colonization of the uniquely susceptible premature intestine with pathogenic bacteria, leading to an exaggerated inflammatory response.¹⁰ However, the interaction between the intestine and bacterial microflora is a complex relationship with risk and benefit for the host. In a healthy host, beyond merely colonizing the gut awaiting entry into the bloodstream, these microorganisms have a significant impact on intestinal health and gut function. As noted in the review, there is evidence that certain bacteria may stimulate intestinal development rather than just take advantage of intestinal immaturity.

As opposed to the adult intestinal microbiota, which is comprised of more than 10¹³ microorganisms, the newborn gut is sterile at birth. Furthermore, colonization of the blank slate of the preterm intestine is influenced by iatrogenic manipulations in the neonatal intensive care unit (NICU). This includes a hospital environment; frequent use of broad-spectrum antibiotics, opioids, and H₂ blockers; and instrumentation with endotracheal tubes, feeding tubes, and suctioning tubes. The resultant altered microbial flora may have significant implications for development of the immature preterm gut and susceptibility to NEC. Several studies have attempted to understand the development of the microbiota of preterm infants utilizing both culture-based and molecular-based techniques. Recent studies have shown a predominance of *Proteobacteria*, which differs from the adult microbial balance in which *Firmicutes* are dominant.^{11,12} Our lab has specifically shown that the microbiota of

patients with and without NEC differs, with a decrease in diversity and further increase in *Proteobacteria*, specifically *Gammaproteobacteria*, with NEC.¹² While some of the clinical probiotic trials have noted evidence of colonization with the probiotic of interest, none have examined the effect of probiotic therapy on the overall microbial community of the preterm infant. An imbalance in the gut microbial ecosystem, with overgrowth of some organisms and loss of others has been cited as the foundation for several diseases.^{13,14} The concept of a core microbiome suggests that there are key functions required for intestinal homeostasis.^{15,16} The microbiota of a preterm infant without a stable background gut flora may be significantly skewed by the intentional colonization with billions of organisms in a narrow group of probiotics.

Few medications have been specifically studied in the preterm infant population or specifically designed for premature infants, thus the majority of preterm infants receive at least one off-label use medication.¹⁷ Surfactant-replacement therapy for hyaline membrane disease is one of few pharmacologic interventions specifically designed for preterm infants.¹⁸ Widespread acceptance of surfactant therapy came after an understanding of the biology of the immature lung, evidence that exogenous surfactant could specifically replace what was lacking, and multiple specific clinical trials of product and protocol.¹⁹ It was hoped that studies of NEC could follow a similar course; however, while probiotic trials have been conducted specifically in low birth weight infants, a single deficiency to be targeted by therapy remains elusive.

There are many previous examples of harm at the hands of short-term gains in the care of preterm infants. Excessive oxygen therapy originally intended to prevent lung disease is now known to cause Retinopathy of Prematurity and blindness due to the effect of oxygen on the developing vascular network of the preterm eye.²⁰ Corticosteroids were once used liberally to decrease inflammation associated with mechanical ventilation and reduce the incidence of chronic lung disease. However, closer evaluation revealed that while dexamethasone treatment was associated with decreased need for oxygen at 28 days of life, it was also associated with undesirable effects, most concerning decreased weight and head growth at 36 weeks of life.²¹

Multiple studies also suggested an increased risk of cerebral palsy.²²⁻²⁴ A recent review specifically suggests that early steroids increase the risk of cerebral palsy specifically in those at low risk for chronic lung disease.²⁵

For preterm infants with a naïve gut, do we risk giving billions of organisms to all in order to prevent NEC in a few without understanding how these organisms affect the developing gut and intestinal microbial ecosystem? These are questions that are difficult to study and thus answer. There is evidence that probiotics have decreased NEC in many studies. However, concerns regarding their widespread use in preterm infants are valid. There are sins of both omission and commission, and it would be wrong to withhold a valid therapy from vulnerable infants. It is our responsibility to design trials utilizing a commercially available agent that study both short-term and long-term effects. Administration of prebiotics or bacterial derived products are additional options to provide the benefit of probiotics perhaps with less risk. Certainly continued encouragement of breastmilk to decrease the incidence of NEC in preterm infants should be a priority.²⁶

Administration of probiotics is an intriguing therapeutic option with evidence for clinical benefit. Further study into the mechanism of action of specific organisms in models of immature intestine, in order to identify a potential means of optimizing intestinal colonization and influencing outcome of these vulnerable infants is warranted. However, until a single protocol using a specific probiotic preparation at the same dose, administered at the same time to a large number of premature infants across multiple nurseries shows an effect, specific recommendations to practicing neonatologists for the routine use of probiotics to prevent NEC cannot be made. As the authors have stated, trials need to focus on defining optimal target groups and administration protocols.

If indeed microbes provide benefit and influence multiple organ systems besides the gut, then perhaps optimal health and development, rather than just prevention of NEC, should be the goal of potentially manipulating the microbial flora of all preterm infants. Probiotics and NEC require further investigation, but our understanding of the microbiome and preterm infants must reach

further. The premature infant differs from term infants and older patients in multiple ways, including an immature host defense system, an exaggerated intestinal inflammatory response by the immature enterocyte, and altered intestinal flora. It is not merely the presence of bacteria but the balance of “beneficial” and “pathogenic” bacterial communities that makes a difference. Bacteria have been shown to play a key role in intestinal maturation. As such, a healthy microbiota and core microbiome for a preterm infant must still be defined. Studies of probiotics should focus on whole bacterial communities, optimizing colonization patterns for overall health including feeding tolerance, inhibition of pathogenic colonization, anti-inflammation, stimulation of normal growth, and modulation of pro-inflammatory processes. In the neonatal population microbial patterns are not yet established. Probiotic treatment in this patient population may not only temporarily affect bacterial colonization, but influence long-term bacterial pattern imprinting in a naïve host— this is both our challenge and our opportunity.

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ABBREVIATIONS NEC, Neonatal Necrotizing Enterocolitis; NICU, neonatal intensive care unit

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