Probiotics and Necrotizing Enterocolitis

Josef Neu, MD

KEYWORDS

• Probiotics • Necrotizing enterocolitis • Pathophysiology • Dysbiosis

KEY POINTS

- It is clear that routine use of probiotics for prevention of necrotizing enterocolitis (NEC) remains controversial.
- There are currently neonatologists who insist on using probiotics without additional safety and efficacy studies.
- Basic research on the developing microbiome and its interaction with the host will add to understanding of how it might be safely manipulated to prevent diseases such as NEC in the neonate.

INTRODUCTION

One of the most controversial areas in neonatology over the past few years is whether probiotics should be provided routinely to preterm infants for the prevention of necrotizing enterocolitis (NEC). The goals of this review are to (1) provide the reader with a brief overview of NEC and current concepts of its pathophysiology, including the role of intestinal microbes, (2) discuss the microbial ecology of the intestine in preterm infants and factors that may lead to an unhealthy microbial intestinal environment (a "dysbiosis"), (3) summarize studies of probiotics in preterm infants, (4) elaborate on the need for regulation in this area, and (5) discuss alternatives to probiotics and what is the future for the prevention of NEC.

NECROTIZING ENTEROCOLITIS: MORE THAN ONE DISEASE

In this section, several aspects of developmental gastroenterology will be described as they relate to increased susceptibility to intestinal injury such as that seen in NEC. I provide a brief description of NEC, the most fulminant gastrointestinal disease seen in neonatal intensive care. A more comprehensive review of NEC can be found in elsewhere.[1–3] Although NEC can present in several ways, a common characteristic is a

Disclosure: None.
University of Florida, Department of Pediatrics, Division of Neonatology, 1600 Southwest Archer Road, Human Development Building, HD 112, Gainesville, FL 32610, USA
E-mail address: neuj@peds.ufl.edu

Clin Perinatol 41 (2014) 967–978
http://dx.doi.org/10.1016/j.clp.2014.08.014 **perinatology.theclinics.com**
0095-5108/14/$ – see front matter

subtle onset presenting as a slightly distended abdomen, nonspecific instability such as apneas or bradycardias, and changes in appearance and activity of the infant. These highly nonspecific signs and symptoms may subside, but occasionally will fulminate to severe intestinal necrosis with systemic inflammation and shock. Mortality ranges between 20% and 30%, with a greater association in the least mature infants; however, a diagnosis of NEC confers a much greater relative risk of mortality to the larger infants because their baseline mortality is lower.[4] Significant morbidities include severe neurodevelopmental delays, shortened intestine, and inflammatory processes that can affect other organs such as the liver with severe cholestasis.[5] It is thus a very expensive disease, not only in terms of its financial impact,[6] but also in terms of long-term physical disabilities and neurodevelopmental delays.

Progress in the treatment and prevention of NEC over the past several decades has been almost nil.[7] Attempts to decrease incidence have included prolonged periods of nulla per os (NPO), wherein preterm infants would not receive food by the enteral route for weeks after birth or extremely slow institution of enteral feedings,[8] but subsequent studies suggested that this was counterproductive.[9,10] Studies in animals show that lack of enteral nutrition may lead to mucosal atrophy, decreased motility, decreased trophic hormones, and increased inflammation.[11] Numerous studies have now shown that providing at least small amounts of enteral feeding, especially human milk from early on after birth, does not increase the incidence of NEC and may reduce the risk of other complications such as sepsis.[12,13]

Increased survival of very small infants who have a greater propensity to develop this disease than larger infants may be a partial reason for the lack of progress. Use of experimental animal models that do not directly reflect the highly multifactorial pathophysiology of this disease as seen in preterm infants is also a likely reason for lack of progress. For example, a recent study from Sweden showed an increase in NEC together with decreasing mortality between 1987 and 2009.[14] Likewise, what we have been recording in our databases as "NEC" consists of a variety of entities, some of which may not even involve a necrotic intestine or primary inflammatory process. Hence, aiming a "magic bullet" directed at a poorly delineated disease process is likely to miss the target.

For example, babies with congenital left-sided cardiac lesions, such as hypoplastic left ventricle, interrupted aortic arch, coarctation of the aorta, or even a severe left-to-right shunt owing to a persistently patent ductus arteriosus, are at increased risk to develop bowel ischemia, which does not involve a primary inflammatory process seen in typical NEC. Designing a preventative or therapeutic approach based on prevention of inflammation by altering the microbial environment in a disease that involves primarily a lack of intestinal blood flow does not represent a reasonable approach for these forms of ischemic intestinal necrosis. Another entity, spontaneous intestinal perforation (SIP), may present with signs and symptoms similar to NEC, but involves minimal inflammation or necrotic intestine.[15] It occurs early after birth often without the infant being enterally fed. However, the radiologic presentation may be similar to NEC (free intraperitoneal air) and the therapy often includes peritoneal drainage without direct surgical inspection of the bowel and definitive diagnosis of NEC or SIP not being differentiated. Thus, SIP, sometimes mistakenly called "NEC," is unlikely to be amenable to therapies or preventative measures that include manipulations of the inflammatory response, nutritional composition, or the intestinal microbial environment, and should not be clustered in a database with the diagnosis of "NEC," because it can be misleading.

Another often unappreciated fact is that NEC may be very difficult to diagnose. The Bells Staging criteria[16] are often unhelpful in this regard. "Stage 1 NEC" is highly