Review Article

The Developing Microbiome of the Preterm Infant

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ABSTRACT

Purpose: To determine the importance of the neonatal microbiome in intestinal and overall health.

Method: A review of existing literature.

Findings and Implications: The microbiome is increasingly understood to have a significant role in health and disease. However, the microbiome of the preterm infant is unique, with simple microbial communities exposed to a consistent diet in a regulated environment, and development from naive to stable under the influence of the neonatal intensive care unit. This early microbiome encounters a still developing host and thus has the potential to program fundamental pathways with implications for neonatal and later outcomes. (*Clin Ther*. 2016;38:733–739)

Key words: development, microbiome, necrotizing enterocolitis, preterm infant.

INTRODUCTION

The microbiome represents all the bacteria living in or on the host. It has been termed "the forgotten organ," with significant weight, genetic content, cellular content, and metabolic activity.[1] It has been estimated that 100 trillion organisms, upward of 10 times the total number of cells in the human body, comprise the gut microbiome alone.[2] The interaction between the intestine and its microbiome is a complex relation with risk and benefit for the host. In a healthy host, these microorganisms have a dramatic impact on intestinal health and gut function. Important research on the preterm infant microbiome has focused on the intestinal microbiome and neonatal necrotizing enterocolitis (NEC). However, the microbiome has the potential for impact beyond the local intestinal level. This review focuses both on the microbiome in NEC and on the potential for this initial microbiome to have broader health impact.

NEONATAL NEC

NEC is a potentially fatal inflammatory bowel necrosis that primarily affects premature infants after the initiation of enteral feeding. On the basis of large, multicenter, neonatal network databases from the United States and Canada, the mean prevalence of the disorder is ~7% among infants with a birth weight between 500 and 1500 g.[3] For decades, NEC was the focus of various clinical and laboratory studies; however, NEC remains poorly understood, likely because its pathogenesis is multifactorial.

The primary risk factors for NEC are prematurity, bacterial colonization, enteral feeding, and altered intestinal blood flow. One hypothesis that integrates these known risk factors is that 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.[4]

The preterm infant is essentially a fetus, expecting the conditions of the intrauterine environment. For the intestine this includes limited contact with bacteria and food substrate. Microbial colonization of the still immature intestine occurs in the context of an incompletely developed innate immune defense system. This includes altered intestinal mucus, decreased barrier function, decreased levels of protective factors from goblet cells such as trefoil factor, and decreased paneth

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cell-derived defensins.[5] These immaturities increase contact of the preterm gut with the colonizing bacteria. The exaggerated inflammatory response of the immature intestine to both commensal and pathogenic bacteria then leads to excessive inflammation with resultant ischemia and intestinal necrosis, causing the signs and symptoms of disease.[6]

NEC classically occurs between 7 and 14 days of life, but susceptibility is inversely related to gestational age. In very low birth weight (VLBW) infants it can occur up to several weeks of life with a peak incidence around 32 corrected weeks' gestation, emphasizing the role of intestinal development in this process.[7] There is no sex or race predilection. Disease presentation can range from subtle and nonspecific gastrointestinal (GI) signs of feeding intolerance, increased gastric residuals, and increased abdominal girth to fulminant signs/symptoms of systemic shock associated with bowel ischemia and perforation.[3] Pneumatosis intestinalis is the pathognomonic sign for NEC seen on radiographs. It represents air from bacterial fermentation of intraluminal food substrate tracking within the bowel wall. The most severe cases are necrosis of the entire intestine and are termed NEC totalis.[8]

Because pathogenesis of this disease is unknown, treatment is nonspecific. Current treatment strategies are aimed at supportive care of the infant, including bowel rest, antibiotic administration, nasogastric tube placement for decompression, addressing acid/base disturbances, and following closely for clinical and radiographic signs of intestinal perforation. Perforation or clinical deterioration associated with ongoing intestinal necrosis is indication for surgical intervention by either peritoneal drain placement or exploratory laparotomy.[9]

Current treatment methods are often inadequate because of the rapid progression of NEC from its initial diagnosis. There is a high mortality rate of 20% to 30%, up to 50% in infants who require surgery.[3] Morbidity includes risk of stricture, short-gut, and intestinal failure. Furthermore, studies have reported that NEC, particularly surgical NEC, is an independent risk factor for poor neurodevelopmental outcome.[10] The pathophysiologic cascade leading to NEC once started is difficult to stop, suggesting that understanding early aspects of the intestinal injury that precede clinical signs and strategies for prevention are of paramount importance. This has led to a specific interest in understanding the role of the preterm infant microbiome in injury and protection from NEC.

THE MICROBIOME AND NEC

The microbiome is an ecologic system. A healthy ecosystem is characterized by a high diversity of species with accompanying balance, functional redundancy, and resistance to disease. In contrast, a sick ecosystem is termed dysbiosis and is characterized by a low diversity of species, imbalance, and lack of functional redundancy with resultant susceptibility to disease. Diversity in preterm infants decreases throughout their neonatal intensive care unit (NICU) stay, and NEC is associated with dysbiosis.[11]

We have previously used 16s rRNA sequencing techniques to examine the microbiome of patients who develop NEC compared with healthy controls.[12] We found that the microbiome of preterm infants with NEC shifts up to 3 weeks before disease onset with a decrease in Firmicutes and an increase in Proteobacteria.[13] These data suggest a window of opportunity for intervention to prevent pathogenic shift. Additional studies have examined the development of the healthy preterm infant microbiome over time. The microbiome was again examined by 16s rRNA sequencing of prospectively collected fecal samples over the first 8 weeks of life. Preterm infants without NEC were compared with a vaginally delivered, breastfed, full-term infant, cared for at home. The weekly samples for the full-term infant over the first 8 weeks of life clustered closely together at all time points.[13] In contrast, healthy premature infants exhibited clustering at <2 weeks of age, 3 to 5 weeks of age, and >6 weeks of age.[13] This study indicates that timing of microbiome development is important. Together these studies suggest that understanding the early microbiome is key for understanding normal microbiome development in patients who remain healthy without NEC and for understanding what alterations lead to NEC.

THE MICROBIOME AND OUTCOMES

The microbiome of the preterm infant is unique, with simple microbial communities, exposure to a consistent diet in a regulated environment, and development in the context of a simultaneously developing host. A premature infant is vastly different from a full-term infant, with many different needs. It is not just size. Full-term infants have completed in utero development, whereas preterm infants have not. This includes development of all organ systems and of the microbiome itself. The "core" needs of the preterm