The Microbiota of the Extremely Preterm Infant

Mark A. Underwood, MD, MAS*, Kristin Sohn, MD

KEYWORDS

• Microbiota • Dysbiosis • Intestinal tract • Skin • Oral cavity
• Necrotizing enterocolitis • Late-onset sepsis

KEY POINTS

- The intestinal microbiota of the extremely preterm infant differs dramatically from that of term infants, children, and adults with decreased diversity and high numbers of γ-proteobacteria and Firmicutes and low numbers of common commensal microbes.
- Alterations in the intestinal microbiota of the preterm infant precede the onset of necrotizing enterocolitis and sepsis.
- Altering the intestinal microbiota with diet, antibiotics, and prebiotic and probiotic supplements may be less effective in extremely preterm infants, prompting the need for novel approaches to dysbiosis in this population.

INTRODUCTION

Colonization of the fetal skin and intestinal tract begins in utero and is influenced by maternal microbial communities (particularly those that inhabit the distal intestinal tract, the mouth, the vagina, and the skin), timing of rupture of membranes, maternal genetic factors, medications and supplements. Colonization is further influenced by mode of delivery and postpartum environmental exposures and medical procedures, infant genetic factors, medications and supplements, enteral feeding, and maturity of the infant innate and adaptive immune systems. Breakthroughs in recent decades in the analysis of complex communities of bacteria and viruses and studies in germ-free and gnotobiotic animals have vastly expanded our understanding of the importance of interactions between host and microbe. The composition of the microbial community of the intestinal tract and skin impacts inflammatory pathways and is thus important in the pathogenesis of a wide variety of disease processes (**Box 1**).

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Department of Pediatrics, University of California Davis, 2516 Stockton Boulevard, Sacramento, CA 95817, USA
* Corresponding author.
E-mail address: munderwood@ucdavis.edu

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Box 1
Diseases and conditions in which the microbiota plays a role in pathogenesis

Antibiotic-associated diarrhea	Traveler's diarrhea
Necrotizing enterocolitis	Infectious diarrheas
Preterm birth	Sepsis
Infant colic	*Clostridium difficile* colitis
Inflammatory bowel disease	Food and environmental allergies
Irritable bowel syndrome	Celiac disease
Obesity	Diabetes mellitus (types 1 and 2)
Atherosclerosis	Cancer
Atopic eczema	Psoriasis
Seborrhea	Rheumatoid arthritis
Alzheimer and other neurodegenerative diseases	Mood disorders, schizophrenia, and autism

Novel mechanisms by which the microbiota influences host immunity and inflammation have recently been described.[1–3]

The importance of the intestinal microbiota in extremely preterm infants is most clearly evident in considering the risks of developing necrotizing enterocolitis (NEC) and sepsis. The roles of the skin microbiota in sepsis risk and the oral microbiota in pneumonia risk are less clear. Perhaps most compelling is the role of colonizing microbes in shaping and influencing the developing innate and adaptive immune responses in extremely preterm infants and the long-term impact of these host-microbe interactions. An additional layer of complexity is emerging with the realization that nutrients (eg, human milk, infant formulas and fortifiers, vitamins and minerals) are consumed by both host and bacterial cells, often with keen competition and overlapping effects. Host-microbe-nutrient interactions are likely to be particularly important in such processes as growth, brain development, immune development, and disease risk for the most preterm infants. In this article, we use the terms microbiota to refer to the composition of bacteria in a given anatomic niche and dysbiosis to mean an alteration in the microbiota associated with disease. There is evidence of significant colonization of the extremely preterm infant with yeasts, bacteriophages, and other viruses,[4] but discussion of these microbes is beyond the scope of this article.

DEVELOPMENT OF THE INFANT MICROBIOTA

In Utero

The development of tools to characterize the microbiota based on identification of bacterial DNA rather than relying on cultures has expanded understanding of the initial colonization of the neonate tremendously. **Table 1** summarizes the primary bacterial taxa that colonize the preterm infant. It has long been believed that the fetus grows in a sterile environment and that colonization begins at the time of rupture of the fetal membranes. More recent careful studies have shown that the amniotic fluid is not sterile, suggesting that colonization of the fetal skin and gut begins in utero.[5] The role of microbes in triggering preterm labor is perhaps the most clinically relevant observation related to this observation. Chorioamnionitis has long been recognized as a trigger of preterm labor and neonatal infection (particularly in preterm infants). The preponderance of evidence suggests a causal relationship between maternal periodontal disease and preterm labor.[6] For instance, the presence of specific bacteria (eg, *Peptostreptococcus micros* or *Campylobacter rectus*) in maternal gingival plaque was associated with increased risk of preterm delivery.[7] Treatment of periodontal