The Role of the Intestinal Microbiota in Necrotizing Enterocolitis and Neonatal Sepsis

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Definitions: The microbiota is the community of micro-organisms inhabiting an anatomic niche, such as the small intestine, the mouth or the vagina. Dysbiosis means an alteration in the microbiota associated with a disease process. The word microbiome has been used both as a synonym for microbiota and more specifically to refer to the genes expressed by the microbiota. Probiotics are dietary supplements that contain live organisms that confer a health benefit. Prebiotics are dietary supplements that are not digested by the host (e.g., the infant), but stimulate the growth of desirable commensal bacteria. Sepsis occurs when pathogenic microbes invade the tissue or blood causing symptoms of infection. Bacterial translocation occurs when intestinal bacteria leave the lumen of the intestinal tract and penetrate the single layer of enterocytes to arrive in the lamina propria of the small intestine (in close proximity to blood vessels and lymphatics). Necrotizing enterocolitis (NEC) is an intestinal disease that predominantly affects premature infants; the hallmark is a sudden onset of abdominal distention, bloody stools, abnormal abdominal radiographs and sometimes intestinal perforation. NEC is the leading cause of death in very premature infants from 2 to 8 weeks of age. Late onset sepsis (LOS) is a bacterial bloodstream infection that occurs at greater than 48-72 hours. In this abstract we will focus predominantly on bacteria, as the role for viruses, archaea, and fungi are much less clear.

Introduction: The micro-organisms that inhabit skin and mucosal surfaces interact constantly with the host's immune system. In the term infant, these host-microbe interactions have effects over the short term (e.g., neonatal sepsis and infant colic) and over the life span (e.g., altering the risk for autoimmune diseases such as type 1 diabetes, allergic diseases such as food allergies and eczema, and adult diseases such as obesity and metabolic syndrome).[1,2] In the preterm infant, the skin, gastrointestinal tract, and the innate and adaptive immune systems are immature and function only marginally often resulting in prolonged hospital stays and exposure to a variety of medications, medical surfaces, and instruments. As a result, preterm infants develop intestinal dysbiosis increasing the risk of sepsis and NEC. Among the most exciting discoveries in neonatology of the last decade, is evidence that altering the intestinal microbiota of the infant can decrease the risk of these short and long term outcomes (Table 1).[3]

Table 1. The Preterm Infant Gut Microbiome and Risk for NEC Onset[3]

Preterm Infant Microbiome	NEC Risk Factors	LOS
• Breastfed term infants in developing countries are dominated by bifidobacteria and *Bacteroides* • In many developed countries there is a loss of bifidobacteria • Premature infants are dominated by Proteobacteria (especially from 28-33 weeks)	• Intestinal dysbiosis precedes NEC – Increased Proteobacteria – Decreased Firmicutes and Bacteroidetes • Human milk and probiotics decrease NEC risk • Prolonged antibiotics and H2 blockers increase NEC risk	• The bacteria identified in late onset sepsis (>48-72 hours of age) often originate in the gut • Funisitis predisposes to gut dysbiosis which predisposes to LOS with differing organisms • Human milk, probiotics and lactoferrin may be effective at preventing LOS

NEC=necrotizing enterocolitis, LOS=late onset sepsis, H2=histamine 2

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What is the evidence linking the microbiota of the neonate to NEC and sepsis? Perhaps the most compelling example of dysbiosis and neonatal sepsis is infection with Group B streptococcus (GBS). Prior to the 1990s, GBS sepsis was the most common cause of neonatal sepsis and was often fatal. The understanding that GBS is a common colonizer of the maternal genitourinary tract, that it generally does not cause symptoms in the mother, and that acquisition of GBS prior to or during delivery often led to neonatal GBS sepsis prompted universal screening of pregnant women and prophylactic antibiotics during labor resulting in a dramatic decrease in the incidence of GBS sepsis.[4] While GBS sepsis is much less common now, the same pattern of colonization of the neonate with maternal bacteria in the perinatal period occurs with *E. coli* sepsis (the most common cause of neonatal sepsis in the first days of life since the institution of GBS prophylaxis). In premature infants, the most common cause of sepsis after the first few days of life is *Staphylococcus epidermidis*. *S. epidermidis* is a common colonizer of both the skin and the intestinal tract. Detailed studies have demonstrated that *S. epidermidis* reaches the bloodstream through defects in the skin, but even more commonly through translocation of this bacterium across the mucosal surface of the intestine.[5]

The evidence that intestinal dysbiosis increases the risk for NEC in the premature infant includes the following: 1) animal models of NEC demonstrate dysbiosis and the central role of recognition of bacteria by the immature host triggering a poorly modulated inflammatory response,[6-9] 2) medications commonly administered to premature infants such as antibiotics and acid-blockers cause intestinal dysbiosis and increase the risk of NEC,[10-12] 3) human milk partially corrects intestinal dysbiosis and decreases the risk of NEC,[13] 4) probiotics partially correct dysbiosis and decrease the risk of NEC in human trials and animal models,[3] and 5) human milk components, including lactoferrin, epidermal growth factor, and human milk oligosaccharides, decrease the risk of NEC in human studies and/or the incidence of NEC in animal studies.[14-16]

The impact of NEC and LOS is significant. While NEC affects a relatively small number of infants, the mortality rate is high and the costs for survivors are significant including the costs of prolonged hospitalization, surgeries, and the long term complications of NEC including poor growth, home total parenteral nutrition (TPN), and neurodevelopmental delays. The cost of NEC in the U.S. has been estimated at up to $1 billion per year. LOS also has associated mortality and increased length of hospitalization with the increase in costs for a single episode of LOS estimated at $10,000.[17]

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