

# The Influence of Human Milk on the Preterm Infant Gut Microbiome

Steve Frese, PhD and Tracy Shafizadeh, PhD

Over 10% of births are considered preterm, or less than 37 weeks gestation, which accounts for over 500,000 births each year in the United States alone.<sup>1</sup> Infants born preterm are challenged with a number of serious issues, including a significantly higher risk for necrotizing enterocolitis (NEC), which affects 2-5% of NICU admissions.<sup>2</sup> In very low birth weight infants with NEC, between 27-63% of these infants require surgical intervention, and overall there is a 20% mortality rate.<sup>3</sup> Although the exact cause of NEC is unknown, the microbiome, or the collection of microorganisms that reside in the intestinal tract, has been implicated.

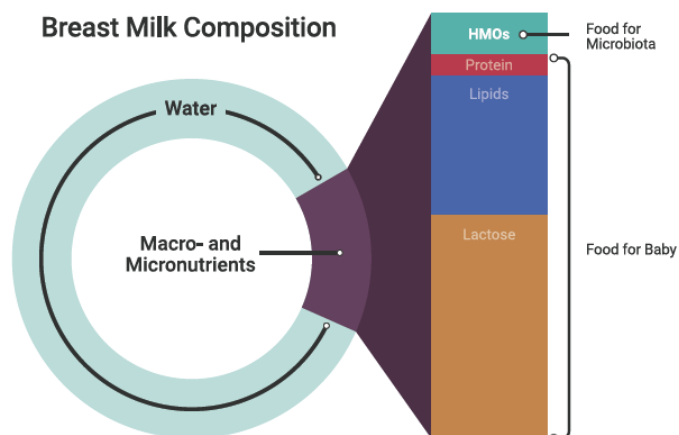
Recent work has indicated that blooms of gut microbial populations associated with gut dysbiosis play a role in driving TLR4-driven inflammation that precedes NEC.<sup>4</sup> Probiotics are hypothesized to alleviate this dysbiosis, but the reported results in the prevention of NEC are not consistent across probiotic organisms and despite mechanistic work in animal models, there is a lack of successful translation of this work to humans. A recent meta-analysis review found that administration of probiotics to infants in the NICU is safe and effective, and can reduce incidence of NEC and mortality.<sup>3</sup> The authors also found that probiotic administration leads to shorter time to full feeds and may reduce incidence of sepsis. However, in the four years since the meta-analysis review was completed further clinical research has concluded that not all probiotics are created equal in their ability to offset the risk of NEC in premature infants.

Despite the increased attention placed on understanding the role of the gut microbiome in human health, we are only beginning to understand how the infant gut microbiome is first established, how diet shapes this community, and the effect this critical period has on infant health.<sup>5,6</sup> The organisms that comprise the gut microbiome are initially acquired at birth, and that community is shaped over time by diet, gut physiology and environmental exposure. It is now increasingly recognized that this early composition of the newborn gut microbiome plays a major role in lifelong disease risk, as well as the acute risk of infection by opportunistic or overt pathogens. Historically, it has been observed that the gut of breast-fed infants was uniformly colonized by *Bifidobacterium*, the keystone gut symbiont of infants.<sup>7</sup> Early *Bifidobacterium* colonization has potentially

profound and beneficial effects for the infant, including a role in important immunological and metabolic programming events in the first few months of life.<sup>6</sup>

*Bifidobacterium longum* subsp. *infantis* (*B. infantis*) is a particular type of bifidobacteria that is well adapted to the infant gut, in part due to its ability to consume complex carbohydrates found in human milk.<sup>8</sup> Interestingly, infants born in the Global South today are still colonized by this organism, but it is essentially absent in the Global North.<sup>9</sup> Changes in human lifestyles resulting from generations of antibiotic use, cesarean section delivery of infants, increasing sanitation, and dietary changes (ie formula feeding) have contributed to a break in transmission of this organism between generations, and result in the high inter-individual variation in the infant gut that is observed today. In the absence of *B. infantis*, microbial populations including *Streptococcaceae*, *Staphylococcaceae*, *Clostridiaceae*, and *Enterobacteriaceae* are often found in the infant gut. High populations of *Enterobacteriaceae* are increasingly recognized as having a negative impact on long term health and represent gut community dysbiosis.<sup>6,10</sup>

To better understand this unique and symbiotic relationship between human milk and *B. infantis*, new techniques have been used to characterize the components of mammalian milk, and the specific role they play in supporting the newborn gut microbiome<sup>11</sup>. Of particular interest is a diverse set of carbohydrates called human milk oligosaccharides (HMO), that naturally make up about 15% of nutrients in human breast milk. Remarkably, these complex carbohydrates are not digestible by the newborn. Instead, HMO are consumed by bacteria in the infant large intestine, or otherwise excreted in the infant stool.



Steve Frese, PhD is a microbial ecologist, and Associate Director of Research and Development for Evolve BioSystems, Inc. Tracy Shafizadeh, PhD is a nutritional scientist and Director of Scientific Communications for Evolve BioSystems, Inc.

The key to this milk-microbe interaction is that not all bacteria can utilize HMO equally. HMO are preferentially consumed by some bacteria, such as *B. infantis*, which can convert these carbohydrates to short chain fatty acids in the infant intestine. In the scientific literature, intestinal short chain fatty acids have been shown to lower intestinal pH, improve gut barrier function and serve as energy signaling molecules during growth and development. This process allows for maximum nutrient utilization from milk and a symbiotic relationship between microbe and host. However, if beneficial bacteria are not present, other potentially harmful bacteria can partially utilize these milk oligosaccharides for growth. An infant gut microbiome colonized by *B. infantis* and fed by human breast milk will flourish and minimize the growth of pathogenic bacteria. Recently, *B. infantis* supplementation has been shown to be efficacious significantly increasing the levels of intestinal *Bifidobacterium* in term, breastfed infants.<sup>12</sup>

While considerable work is yet to be done to validate the efficacy of probiotics in reducing risk of disease, the data indicate that there must be a thoughtful rationale to choosing the appropriate beneficial bacteria, paired with the appropriate food source, for maximum benefit to the host. As microbiome research continues to mature, a specific focus on establishing, or restoring, the newborn gut microbiome may be key to long term health in both premature and term infants alike.

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