Use of *B. infantis* EVC001 in the NICU for Pathogen Defense Through Improved Nutrient Availability

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Infant Gut Dysbiosis

There are many reasons that an infant may need care in a NICU setting, including preterm birth, developmental abnormalities, or traumatic birth events. One common condition across patients in the NICU is gut dysbiosis, which is defined as an overabundance of pathogenic bacteria in the gut microbiome. The organisms that comprise the infant gut are initially acquired at birth and are largely determined by birth mode and diet.[1,2] Gut microbes are passed from mother to infant during vaginal delivery, and human milk selectively promotes the growth of beneficial gut microbes, specifically *Bifidobacterium longum* subsp. *infantis* (*B. infantis*), creating a highly functional and protective gut microbiome in the newborn. However, antibiotic use and C-section delivery can disrupt this mom-to-baby transfer of *B. infantis*, allowing for potentially pathogenic bacteria present on surrounding surfaces of a hospital environment to colonize the infant gut.

Maximizing Nutrient Availability from Human Milk

As mentioned previously, infant diet is a major driver of the early gut microbiome composition. Human milk is not only the optimal nutrition source for the newborn, but also contains unique carbohydrates, called human milk oligosaccharides (HMO), that are indigestible by the infant and instead serve as food for the infant gut microbiome. *B. infantis* is the only bacterium capable of complete digestion and utilization of HMO and is therefore the predominant species typically found in the breastfed infant gut.[3] The products of HMO metabolism by *B. infantis* are lactate and acetate, molecules that are not only fuel for the developing colonocytes, but also signaling molecules that participate in much of the immune and metabolic programming events taking place in the first 100 days of life.[4,5] However, in the absence of *B. infantis*, HMO are not fully utilized, and instead the vast majority are excreted in the infant stool.[6] *B. infantis* is particularly important for infants in the NICU who receive costly donor milk, as the absence of this organism leads to up to 15% loss of the milk nutrients through fecal excretion of HMO, in addition to the loss of the important functional end products, lactate and acetate. Restoring *B. infantis* colonization of the infant gut through probiotic use has been clinically demonstrated in breastfed infants and led to near complete digestion and utilization of HMO in the infant gut.[6] Additionally, restoration of *B. infantis* to the infant gut led to significant improvement in stool quality, thought to be largely attributed to the reduction in HMO excretion.[7]

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Defense Against Pathogen Colonization

Recent studies have linked the pH of infant stool to the composition of the infant gut microbiome, and infants colonized by *B. infantis* exhibited a more acidic pH compared to those who lack this bacterium.[8] This pH differential can be explained by the metabolism of HMO by *B. infantis*, and the subsequent generation of the acidic metabolic end products, lactate and acetate. In recent clinical studies, probiotic use of *B. infantis* EVC001(Evivo®) was shown to reduce the fecal pH of breastfed infants to levels observed in infants naturally colonized by this bacterium[6]. This reduction in fecal pH was accompanied by a dominance of *B. infantis* in the infant microbiome, along with a 93% reduction in the abundance of pathogenic bacteria including *E. coli*, *C. difficile*, *Klebsiella pneumoniae*, and *Streptococcus pneumoniae*, and an 85% reduction in pathogen associated virulence factors.[9] Interestingly, a recent study by Brooks *et al.* demonstrates that the NICU room environment can serve as a reservoir of bacteria for the early colonization of the newborn gut microbiome.[10] Analysis of fecal samples from preterm infants in the NICU, along with sinks and surfaces from the same room, showed that the infants were commonly colonized by nosocomial antibiotic-resistant pathogens also found on surfaces of the hospital. This provides a possible mechanism of how infants in the same NICU are often colonized by the same strains, even if their stay in the NICU is separated by years. It also

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establishes that the HMO in mother's milk, in conjunction with *B. infantis*, provides an important natural defense mechanism against pathogen colonization in the newborn infant at a time when their own immune system has still not yet developed.

It is well documented that infants in the NICU often experience gut dysbiosis. However, utilization of an infant specific probiotic, such as Evivo® (*B. infantis* EVC001) has now been clinically shown to restore the natural colonization of this protective bacterium to the infant gut, and provide both optimal nutrient availability from human milk, along with a mechanism against pathogen colonization in the hospital environment.

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