Immune Development in the Neonate: The Role of the Gut Microbiome

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A direct role of the gut microbiome in the education and function of the immune system in humans has now been established, but the exact mechanisms by which our gut microbes orchestrate immune function continues to be explored. The short period of time from birth through weaning is a critical window of immune development, including establishment of adaptive immunity as well as immune tolerance. Recent studies now highlight the important interaction between the newborn gut microbiome and the development of the immune system, specifically during the first 100 days of life, which impacts both acute pathogen defense and potentially longer-term risk of auto-immune disorders later in life.[1,2,3] During this same period of time, the infant gut microbiome also undergoes pronounced development from a nearly sterile environment in utero, to the rapid acquisition of gut microbes beginning at birth. The composition of the infant gut microbiome is largely dependent on birth mode, infant diet and exposure to antibiotics, and the resulting community of microbes highly influence gut function, immune system programming and nutrient utilization by the infant.[4,5]

> Specifically, the role of *Bifidobacterium* in immune development is now thought to be particularly important.

As the infant gut microbiome takes shape during these early days of life, the presence or absence of specific bacteria have the potential to directly influence the conditions under which the newborn immune system develops. Recent reports suggest that microbial-driven intestinal inflammation during infancy can have significant long-term health consequences, possibly through disruption of immune system maturation.[2] A longitudinal study of newborn infants found that gut dysbiosis in the first months of life is associated with altered development of the immune system, characterized by increased circulating endothelial cells, activated effector T cells, and inflammatory cytokine production. Specifically, the role of *Bifidobacterium* in immune development is now thought to be particularly important,[6] where low levels of this bacterium early in life are associated with higher risk of autoimmune disorders at later time points.[7] Further studies reveal increased colonic mucin layer degradation and significantly increased fecal endotoxin levels in infants who lack *Bifidobacterium*.[8,9]

> Restoration of *Bifidobacterium* resulted in an 80% reduction in the abundance of pathogenic bacteria associated with intestinal inflammation and antibiotic resistance gene carriage.

Numerous publications have documented *Bifidobacterium longum* subsp. *infantis* (*B. infantis*) as the predominant strain to colonize the breastfed infant microbiome due to its unique ability to consume human milk oligosaccharides (HMOs).[10] These complex carbohydrates found in breastmilk are a collection of over 200 chemical structures which are completely indigestible by the human body. Instead, HMOs are broken down and utilized by gut microbes, and preferentially support the growth of *B. infantis* in the infant gut. However, more recent studies reveal that *B. infantis* is now far less abundant in the gut microbiome of infants born today in industrialized nations compared to reports from low income countries.[8,11] This is hypothesized to be due to common medical and dietary practices used in industrialized countries, such as C-section delivery, formula feeding and widespread antibiotic use, which are known to disrupt the transfer and growth of beneficial gut bacteria passed from mom to baby during vaginal delivery. Recently, probiotic supplementation with *B. infantis* EVC001 in exclusively breastfed infants has been shown to effectively restore *Bifidobacterium* to levels observed in infants naturally colonized by these bacteria.[8] Importantly, this restoration of *Bifidobacterium* resulted in an 80% reduction in the abundance of pathogenic bacteria associated with intestinal inflammation and antibiotic resistance gene carriage, as well as higher risk for the development of asthma, eczema, allergy and T1D later in life. This, together with new evidence highlighting the importance of the first 100 days of life in immune development, have spurred ongoing studies investigating the beneficial effects of feeding *B. infantis* EVC001 to breastfed infants in reducing enteric inflammation.

This dynamic period of development for both immune function and gut microbiome composition, along with the ability to restore protective bacteria to the infant through

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supplementation, presents a new opportunity for clinicians to positively influence the health trajectory of newborns under their care.

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