The Benefits of Human Milk Oligosaccharides (HMOs) in Infant Nutrition

In this feature, Neonatal Intensive Care interviews clinicians and researchers about important topics in neonatal care and products that support best practices for vulnerable preterm infants. This interview is with Victoria Niklas, MD, Vice President, Innovation and Medical Communication, Prolacta Bioscience, and Professor of Pediatrics, UCLA David Geffen School of Medicine, Los Angeles; and Chloe Autran, PhD, HMO Business Development Manager, Prolacta Bioscience

Neonatal Intensive Care: HMOs and infant nutrition—these are subjects of increasing interest to researchers and to neonatologists and other healthcare professionals who care for premature infants. What, exactly, are HMOs?
Chloe Autran: Human milk oligosaccharides (HMOs)—are a family of approximately 200 structurally complex and diverse sugars that are unique to human milk.[1] HMOs are the third-most-abundant component in human milk, after lactose and lipids, and are more abundant than protein.[2] Although hundreds of structures of HMOs are found in human milk, an individual mother may have far fewer.[1,3] Indeed, the concentration and spectrum of HMOs in an individual woman's milk may vary across the stages of lactation and between women due to genetic factors. Nutritional and environmental factors may also play a role, although the precise nature of these influences is not well defined.[3]

HMOs provide many benefits to the developing infant, but unlike the nutritional components in human milk (lactose, fats, and proteins), HMOs are not metabolized by the infant as an energy source. The majority of HMOs pass through the stomach and the small intestine, arriving in the large intestine, where beneficial bacteria metabolize them and support the establishment of a healthy gut microbiome.[1] In addition to this prebiotic function (influence on the infant's gut microbiome), HMOs function as decoy receptors, blocking the action of toxins and infection by bacteria and viruses in the gut. Since a low concentration of HMOs is found in the bloodstream and the urine of breastfed infants, HMOs may also be absorbed across the gut lining, although this represents only a fraction of the HMOs consumed by the infant. The precise role of HMOs in the circulation is not fully understood and may relate to the role of HMOs in immune cell maturation, trafficking, or overall function in the gut or the systemic immune system. In this way, HMOs may play a role in the maturation of the immune system, thereby reducing the infant's susceptibility to infections.[2] Moreover, a subset of HMOs are purported to affect brain development.[4]

NIC: There are many different HMOs in breast milk. What are HMOs composed of, and what are the implications of the different types?
CA: The structures of individual HMOs are complex, but they all follow a basic blueprint. HMOs are made up of a combination of five monosaccharide "building blocks." Glucose and galactose form the lactose backbone, which is common to all HMOs. Lactose can be elongated with the addition of lacto-N-biose or N-acetyllactosamine, which are both disaccharides consisting of galactose and N-acetylglucosamine. Repeating units of these disaccharides can extend HMOs in a linear or branching fashion. The addition of the individual monosaccharides fucose or sialic acid can occur as terminal residues directly on the lactose backbone or on the extended chain of more complex structures. The addition of sialic acid introduces a negative charge, and thus all sialylated HMOs are acidic HMOs. By contrast, all other HMOs (which can be subdivided into fucosylated and non-fucosylated HMOs) have a neutral charge and are collectively referred to as neutral HMOs.[3] Although more complete data are emerging, different HMOs likely have different functions; therefore, a complete spectrum of HMOs are necessary to provide the infant with the full benefits of HMOs.[2]

NIC: What is the most well-studied function of HMOs in an infant's body?
CA: The prebiotic function of HMOs is the oldest known and most well-studied function.[3] Prebiotics are substances that induce the growth and stimulate the function of beneficial bacteria, such as the *Bifidobacterium* and *Lactobacillus* species, in the gut.[5,6] Prebiotics support the growth of beneficial bacteria and reduce the growth of harmful bacteria and pathogens, thus improving the health of the infant's gut microbiome. A healthy microbiome reduces the risk of dysbiosis-related diseases, such as necrotizing enterocolitis (NEC) and sepsis. Reduction of dysbiosis risk in preterm infants is important, as the use of broad-spectrum antibiotics, invasive procedures, and prolonged hospitalization increase this risk.[6]

NIC: What other functions do HMOs serve?
CA: HMOs function in several ways to prevent infections throughout the gut. HMOs resemble glycan receptors used by pathogens to infect epithelial cells lining the gut. Moreover, HMOs may block the binding of toxins to intestinal cells in the gut. Therefore, HMOs act as "decoy receptors," blocking infections by bacteria and viruses or the action of epithelial toxins. The binding of HMOs to other glycans on epithelial cells also influences gene expression by epithelial cells that are important for epithelial cell growth, repair, and maturation in the maintenance of barrier function in the gut. HMOs also play an essential role in the maturation of the newborn's immune system by interacting with various immune cells in the gut and in systemic circulation, thereby regulating immune cell activity and

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inflammation.[3,7] In addition, some studies indicate that sialylated HMOs may influence neurodevelopment by functioning as a supplementary source of sialic acid, which is critical for brain development. Collectively, other functions of HMOs are not as well described in infants but are supported by extensive *in vitro* and *in vivo* animal models, and the extended benefits of HMOs in newborn infants have yet to be fully defined.[4]

NIC: How do HMOs reduce disease and benefit a premature infant's health and development?
Victoria Niklas: HMOs may be the "secret ingredient" giving human milk its myriad of health advantages beyond nutrition to foster appropriate growth. Many of the health outcomes attributed to an exclusive human milk diet can be tied back to the immunity, prebiotic, and gut maturation benefits that HMOs promote.[1] These health outcomes have included significant decreases in mortality, NEC, late-onset sepsis, retinopathy of prematurity, and bronchopulmonary dysplasia in infants weighing between 500 and 1250 grams who were fed an exclusive human milk diet including a human milk-based human milk fortifier.[8,9]

There is ample evidence showing that a cow milk-based diet incites NEC by promoting the expansion of pathogenic bacteria in dysbiosis, as well as damaging the intestinal lining, thereby increasing gut permeability and permitting bacterial invasion into the gut lining. Bacterial invasion results in a proinflammatory cascade that is characteristic of NEC, resulting in further damage to the intestinal epithelium and, in severe cases, leading to the destruction of the intestine with perforation, which may lead to death. As a bloom of pathogenic bacteria may precede the onset of NEC, dysbiosis may be a primary risk factor for infants that go on to develop NEC. Because HMOs have the potential to prevent dysbiosis, their actions in the gut may be vital in reducing early steps in the pathogenesis of NEC.[10]

NIC: Some formula companies are adding one or two "HMOs" to their nutritional products for term babies. Are these HMOs "magic bullets" of some kind? Would a formula containing only a few HMOs make sense for premature infants?
VN: No cow milk-based formula contains the concentration and spectrum of oligosaccharides that are naturally found in human milk. The diversity of HMOs in human milk suggests that individual HMOs, or a group of a small number of HMOs, would not be sufficient to provide the mutual benefits of HMOs that reduce infections, support the immune system, and enhance an infant's growth and development.

To imitate the beneficial effects of mother-made HMOs, some cow milk-based infant formulas have been manufactured to contain one or two synthetically engineered oligosaccharides. These additions at best represent a mere fraction of the possible oligosaccharide content in human milk.[1] In fact, feeding infants just one or two of the up to 200 known HMOs may alter the development of the microbial community in the gut, leading to unintended short and long-term adverse health outcomes related to an altered microbiome in the preterm infant, such as NEC, sepsis, immune cell activation, and uncontrolled inflammation.[1,7,11]

NIC: Some healthcare providers are adding probiotics to the care plan of preterm and term infants. Do probiotics take the place of HMOs, or are they both critical in a premature baby's diet?
VN: Probiotics are beneficial bacteria intended to promote a healthy, balanced gut environment in an infant, in which pathogenic organisms do not outnumber "good" bacteria, such as *Bifidobacteria* and *Lactobacilli*. Prebiotics stimulate the growth and function of beneficial bacteria, while probiotics are the general term used to describe beneficial bacteria. When these bacteria are purified and isolated for consumption, they are called probiotics. HMOs are prebiotics that are naturally occurring in human milk, so infants fed human milk are receiving the prebiotic benefit of HMOs. In addition, infants fed fresh mother's milk also receive commensal bacteria comprising the milk's microbiome.[6] The microbiome of milk is significantly reduced or eliminated with pasteurization.[12] While some evidence suggests that probiotics may prevent NEC and sepsis in deficient birth weight infants, more research is needed to determine whether the addition of probiotics is of benefit to preterm infants.[13]

NIC: Prolacta's human milk fortifiers and ready-to-feed premature infant formulas—indeed, all of Prolacta's products—are 100% human milk based. Is there an HMO advantage here?
VN: There is a benefit to an exclusive human milk diet, whether based on mother's milk or donor milk, fortified with an exclusively human milk-derived human milk fortifier. The manufacture of Prolacta's donor milk, ready-to-feed products, and fortifiers uses batches of donor milk collected from 100 or more donors. Hence, all products contain a full spectrum of HMOs, thereby maximizing the various health benefits of HMOs.[14,15] The HMO advantage in an exclusive human milk diet is the full spectrum of HMOs.

NIC: Prolacta products are manufactured starting with 100% human donor milk, but that milk goes through a robust production process that includes pasteurization, ultrafiltration, and formulation. What does that mean for the final products?
VN: Prolacta's industry-leading manufacturing practices preserve the concentration and diversity of naturally occurring HMOs in its products. As demonstrated in laboratory studies, HMOs are unaffected by the proprietary pasteurization and ultrafiltration methods Prolacta uses in the manufacture of its human milk fortifiers. Additional studies demonstrate that the prebiotic activity of the HMOs is preserved as well.[15]

NIC: If a premature baby is already consuming breast milk or donor milk containing HMOs, what's the added benefit of a fortifier made from human milk?
VN: The key proven benefit of using a human milk-based fortifier is this: Fortifying human milk with a product made from human milk keeps a preterm baby on an exclusive human milk diet devoid of the deleterious effects of cow's milk. Moreover, clinical evidence has demonstrated that when used as part of an exclusive human milk diet, Prolacta's 100% human milk-based neonatal fortifiers—containing the full spectrum of mother-made HMOs—are associated with lower mortality and morbidity in extremely premature infants weighing between 500 and 1250 grams without compromising growth.[16]

NIC: With all the research currently being done on HMOs, can you comment on other areas where they may have an impact on human health?
VN: HMOs are indeed the subject of much current research, but a great deal remains to be discovered about the precise functions and potential clinical applications of HMOs. The benefits of HMOs may go beyond infancy. HMOs may even serve a purpose

as therapeutics for adults to treat diseases where dysbiosis plays an essential role, such as inflammatory bowel diseases and obesity.[17]

Currently, however, preterm infants born weighing less than 1250 grams should most certainly always receive an HMO-rich exclusive human milk diet.[8,9,16]

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