

## Potential Beneficial Effects of Human Milk Oligosaccharides

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### Expanded Commentary from the Faculty

Oligosaccharides are a major component of human breast milk, with levels peaking in the colostrum and ranging from between 5-15 g/L over the course of lactation.<sup>1</sup> Compared to other species, human milk oligosaccharides (HMO) are more diverse and >100-fold more plentiful, suggesting an important role for HMO in infant development.<sup>2</sup> Formula-fed infants receive bovine- or plant-based oligosaccharide in lieu of HMO, but preclinical research and the observed differences in outcomes between formula-fed and breast-fed infants suggest that HMO confer benefits that cannot be replicated by nonhuman oligosaccharide sources. In addition, HMO are not digested by the infant and are resistant to pancreatic enzymes, suggesting that the primary role of HMO is not nutritional. The commercial availability of oligosaccharides for the supplementation of formula has made the role of HMO testable.

All oligosaccharide in human milk is lactose-based, and the diversity in HMO comes from elongation of the lactose core with glucose, galactose, N-acetylglucosamine, fucose, and sialic acid monosaccharides. This results in great diversity in the oligosaccharides from human milk, with hundreds of structural variants identified.<sup>3</sup> Supplemental oligosaccharides added to formula are galactose-, dextrose-, or fructose-based; these are believed to restore some of the diversity currently lacking in formula.

The potential benefits of HMO have been largely inferred through comparison of formula- and breast-fed infants, and through preclinical research. HMO was discovered by its effect on the growth of *Bifidobacterium* species, and HMO appear to be important for the development of the infant's intestinal microbiota. Metabolism of HMO by *Bifidobacterium* species promotes the growth of other commensal bacteria over the growth of pathogens such as *Clostridium* species.<sup>4</sup> However, HMO appear to have a more direct role in preventing infection of the gut. HMO resemble the glycans that decorate epithelial cells, and are thought to interfere with bacterial, viral, and fungal adhesion to the cell surface—thereby interfering with a crucial step in pathogen colonization.<sup>5</sup> The microbiota of infants fed formula supplemented with HMO more closely resembles that of breast-fed infants, and the stool of infants fed HMO is similar to that of breast-fed infants.<sup>6,7</sup> In rat models, HMO have been found to have a protective effect against necrotizing enterocolitis.<sup>8</sup> Aside from these effects on the development of the microbiome, HMO have an effect on the maturation of the immune system, and HMO has been proposed to protect against the development of allergy.<sup>9</sup> Furthermore, a small fraction of HMO enters the systemic circulation, as do the products of bacterial HMO metabolism; sialic-acid containing gangliosides are an essential nutrient for brain development derived from bacterial metabolism of HMO.

From a clinical standpoint, the research on potential benefits of HMO supplementation is still in progress. Trials in infants fed HMO supplemented formula suggest they are safe (eg, growth is comparable to infants fed standard formula).<sup>10,11</sup> Initial clinical data also support some of the predictions based on preclinical work; for example, inflammatory cytokines are reduced in infants fed oligosaccharide-supplemented formula, and infants fed HMO-supplemented formula may have fewer signs of infection.<sup>12,13</sup> However, additional clinical trials are needed to fully define the benefit of HMO supplementation.

## Discussion Guide

- Do we currently have policies and procedures in place for HMO supplementation?
- Is the evidence supporting supplementation of formula with human milk oligosaccharides strong enough to warrant a change in our clinical practice?
- Are there specific cohorts of infants who would especially benefit from HMO supplementation? For example, preterm vs full-term infants.
- What are the barriers to adopting HMO supplementation in our institution?
- Are there other concerns or issues we haven't talked about?

## Suggested Readings and Resources

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13. Puccio G, Alliet P, Cajozzo C, et al. Effects of infant formula with human milk oligosaccharides on growth and morbidity: A randomized multicenter trial. *J Pediatr Gastroenterol Nutr*. 2017.