SHAPING THE GUT MICROBIOME IN COW'S MILK PROTEIN ALLERGY: THE PIVOTAL ROLE OF

Human milk oligosaccharides

Importance of early-life microbiome in driving immune maturation and determining allergy outcomes

The gut microbiome, defined as all of the microbial inhabitants (microbial community) and their collective genomes, plays a key role in immune system maturation and immunoregulation and therefore has significance in prevention or development and manifestations of allergic disease.[1-3]

The developing gut microbiome undergoes three distinct phases of microbiome progression in the first 1000 days of life:

- a developmental phase *(months 3-14)*
- a transitional phase *(months 15-30)*
- a stable phase *(months 31-46)* [4]

During infancy, the predominant beneficial bacteria in the gut are Bifidobacterium and Lactobacillus which support development of the infant immune system.[5] The gut microbial community acquired in early infancy has been proven to be critical in the determination of mucosal immune response and tolerance, linked to microbial structure and function.[6] In infants with a higher overall bacterial diversity, the infant microbiome is shifted towards that of an adult at a faster rate[7] which suggests that maintaining the infant microbiota community (i.e. lower diversity) for as long as possible could present an opportunity for the prevention of allergic manifestations.[8] For example, where allergic sensitization, eczema, wheezing or asthma exist in infants, lower abundance of Lactobacillaceae and Bifidobacteriaceae and higher abundance of Bacteroidaceae, Clostridiaceae, Enterobacteriaceae in their microbial community has been observed.[9]

Increasing evidence suggests that dysbiosis, could influence the occurrence of food allergy and food allergy-related conditions later in life.[10,11]

Microbiome alterations (dysbiosis) have a pivotal role in the development of food allergy.[10] Increasing evidence suggests that dysbiosis, could influence the occurrence of food allergy and food allergy-related conditions later in life.[10,11] Some of the risk factors for dysbiosis and food allergy development include genetics, cesarian delivery, feeding and medication (including antibiotics), all of which are intrinsically linked to the gut microbiome.[3]

HMO play a pivotal role in delivering immune support.[12]

The role of HMO in breast milk

A significant component of breast milk is human milk oligosaccharides (HMO) which play a key role in immune support [12] and facilitating microbiome progression in early life. HMO act as substrates for Bifidobacterium, driving up levels of short chain fatty acids (SCFA),[3] which are by-products of microbiome fermentation that regulate immune responses.[2] In the absence of breast feeding, exclusive and partial formula-feeding have been shown to shift the gut microbiome toward adult patterns (higher diversity), increase proinflammatory bacteria, increase gut permeability, and result in lower concentrations of fecal SCFA.[6] In addition, infants who are breastfed for shorter periods (or not breastfed) suffer more infectious diseases, such as gastroenteritis, acute otitis media, and more immune-mediated diseases.[13]

THE BENEFITS OF HMO IN PRIMING THE IMMUNE SYSTEM AND PROMOTING INFANT HEALTH: THE RATIONALE FOR HMO SUPPLEMENTATION

More than prebiotics

HMO are non-digestible carbohydrates, identified as the most important bifidogenic factor in human milk[14,15] Beyond their role as prebiotics, HMO have significant impact on the microbiota. HMO provide protection against certain harmful pathogens due to their antimicrobial properties and adhesive properties that prevent growth and proliferation of harmful bacteria by modifying the host-microbe interaction.[16,17]

HMO serve as both a food source for beneficial bacteria but also stop growth and proliferation of harmful bacteria by preventing bacterial adhesion to the intestinal epithelium.[16]

HMO selectively serve as food for beneficial bacteria and suppress the growth and proliferation of pathogenic bacteria.

4 WAYS HMO SUPPORT THE INFANTS MICROBIOTA AND IMMUNE SYSTEM

Promoting beneficial gut bacteria

Eliminating pathogens through a decoy effect

Strengthening the gut barrier

Promoting a more balanced Th1/Th2 response

HMO SUPPORT THE IMMUNE SYSTEM AND PROMOTE THE DEVELOPMENT OF MICROBIOTA

HMO influence the development of the gut microbiome in early childhood

HMO in breast milk have been identified as having the greatest influence on shaping the gut microbiome, and in particular, 2'fucosyl-lactose (2'-FL) and lacto-N-neotetraose (LNnT) have been shown to be important modifiers of bacterial composition in early infancy.[13]

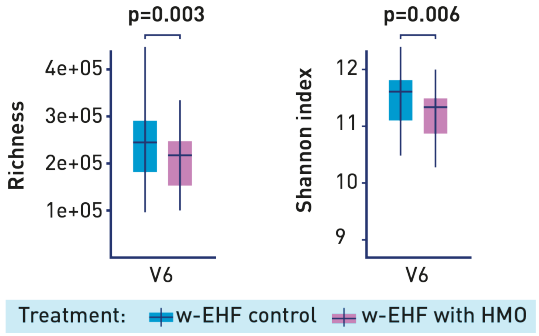
Clinical evidence demonstrates that the addition of 2'-FL and LNnT to a standard infant formula fed to healthy infants leads to a significantly different faecal microbial composition at 3 months of age, compared to those who received formula without HMO supplementation i.e. the microbiota represented that of breastfed infants with a higher abundance of *Bifidobacteriaceae*.[18] Clinical significance was also demonstrated by the fact that less antibiotics were required in the healthy infant group supplemented with HMO.[18]

HMO supplemented formula positively shapes the gut microbiome in infants with CMPA

In the CINNAMON study, whey based extensively hydrolyzed formula (w-eHF) supplemented with 2'-FL and LNnT further demonstrated the microbiome-modulating benefits of HMO in infants with CMPA, previously observed in healthy infants.[19]

The w-eHF with 2'-FL and LNnT, in comparison with a w-eHF without HMO, was associated with lower microbial diversity in infants at 12 months of age.[19] HMO supplementation appears to slow the premature shift towards an adult-type gut microbiome in contrast to infants receiving no or only some breast milk.[19]

Further sub-analysis of the CINNAMON microbiome data was conducted in infants aged less than 3 months to assess whether the change in Bifidobacterium abundance between 90 and 120 days of the study was affected by mode of delivery. Bifidobacterium abundance in those infants receiving w-eHF with 2'-FL and LNnT was much more prominent in those born through Caesarean section compared to vaginal delivery. Thus, highlighting that the beneficial effect of supplemental HMO on Bifidobacterium was greatest in infants born via Caesarean section.[3]



(Adapted from Pedersen et al. 2020 [19] Chart not drawn to scale.)

At 12 months, infants who received w-eHF supplemented with 2'-FL and LNnT had a lower diversity, measured by Richness and Shannon Index. [19]

High levels of HMO 2'-FL and LNnT in breast milk may promote an early high bifidobacteria-dominated gut microbiota in infants[13]

Infants with CMPA fed HMO supplemented formula have significantly fewer upper respiratory tract infections

Infants with CMPA fed whey based eHF with 2'-FL and LNnT in the CINNAMON study showed a statistically significant reduction in the frequency of upper respiratory tract infections each month and a promising trend towards a reduction in the frequency of lower respiratory tract infection. Additionally, in the per protocol group, there was a significant reduction in the risk of ear infections.[20]

Nestlé Health Science have developed a blend of breast milk-identical HMO containing two of the most significant HMO found in breast milk

Nestlé Health Science is committed to HMO research in infants with CMPA. Our allergy management portfolio includes extensively hydrolyzed (Althéra® HMO and Alfaré® HMO) and amino acid-based (Alfamino® HMO) formulas supplemented with 2'-FL and LNnT for the management of infants with CMPA. Our range of hypoallergenic speciality formulas is supported by clinical evidence that confirms the tolerance, safety, and growth efficacy of Althéra ® HMO, Alfaré® HMO and Alfamino® HMO for infants with CMPA.

The addition of the HMO 2'-FL and LNnT to hypoallergenic extensively hydrolysed formula, positively shapes the gut microbiome of infants with CMPA[12]

Conclusion

HMO possess an array of functions and targeted effects, including priming the infants immune system, supporting age adequate development of the infants microbiome, and correcting dysbiosis. Breast milk identical HMO, therefore, could contribute to the critical window for healthy infants and infants with CMPA to shape the microbiome and drive immune maturation.

What's next, for understanding the impact of 2 HMO in infants with CMPA?

Nestlé Health Science is making great strides in further understanding the impact of HMO in the management CMPA. In 2022 we expect further clinical evidence from the CINNAMON study to support the impact of HMO on the microbiome and metabolome in infants with CMPA.

1.McDermott A, Huffnagle G. Immunology 2014;142: 24–31. **2.**Nance CL *et al. Children*. 2020;7:50. **3.**Vandenplas *Y et al. EMJ Allergy Immunol.* 2021;6[1]:25-32. **4.**Stewart CJ *et al. Nature.* 2018;562:583-8. **5.**Wall R *et al. Clin Med Pediatr.* 2009;3:45–54. **6.**O'Sullivan A *et al. Nutrition and Metabolic Insights.* 2015:8(S1) 1–9. **7.**Moore RE, Townsend SD. *Open Biol*. 2019;9: 190128. **8.**van den Elsen LWJ *et al. Front. Pediatr.* 2019;7:47. **9.**Zimmermann *et al. J Allergy Clin Immunol.* 2019;143(2):467-485. **10.**Canani R *et al. Front Immunol.* 2019; 10: 191. **11.**Tanaka M and Nakayama J. Allergology *International.* 2017;66:4:515-522. **12.**Gregory KE. *Curr Pediatr Rep.* 2013;1:(4). **13.**Vandenplas Y, *et al. Nutrients.* 2018;10:1161.**14.**Lewis, Z.T *et al. Microbiome*. 2015;3:13. **15.**Sprenger, N. *et al. PLoS ONE* 2017;12:e0171814. **16.**Santos A *et al. EMJ Allergy Immunol.* 2020;5[Suppl 2]:2-10. **17.**Moossavi S *et al. Front. Pediatr.* 2018;6:197. **18.**Berger B *et al. mBio* 2020 ;11:e03196-19. **19.**Pedersen *et al. Abstract. Presented at FAAM-EUROBAT Digital* 2020 16-17 October, 2020. **20.**Vandenplas Y, *et al. Nutrients*. 2022;14:530.

Nestlé HealthScience®