# Immune Benefits of HMO Supplementation in Infants with CMPA

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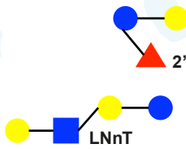
## HMO are the preferred substrate for infant-type bifidobacteria

### Human milk oligosaccharides (HMO):

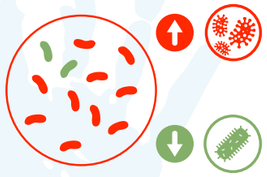
A highly abundant and diverse group of complex carbohydrates that make up the 3rd largest component of human milk solids.

Act as the specific substrate for infant-type bifidobacteria and promote the establishment of other beneficial microbiota in early infancy.

Uniquely support gut and immune health via direct interactions with the gut epithelium and production of specific immune-modulating metabolites.




### Cow's milk protein allergy (CMPA) is globally one of the most prevalent food allergies in infants and young children.

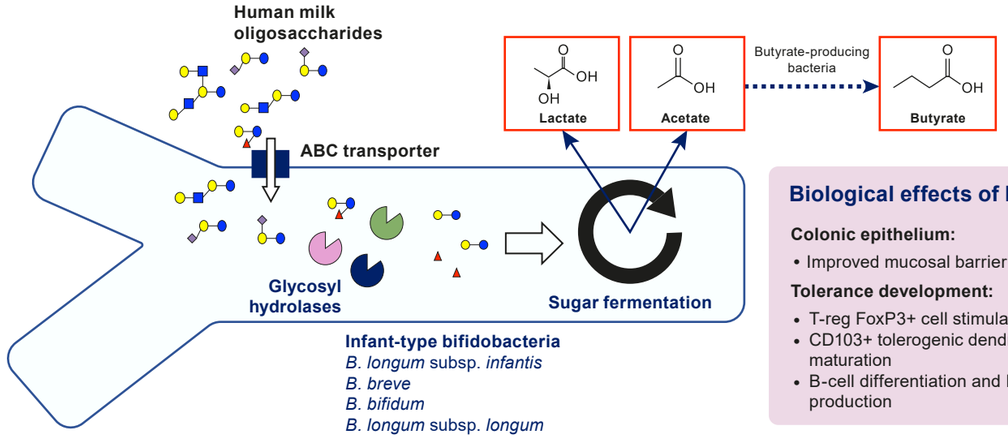



**CMPA in non-breastfed infants is associated with intestinal microbial dysbiosis, characterised by the suppression of infant-type bifidobacteria and the enrichment of potentially pathogenic proteobacteria (e.g., *E. coli* or *Klebsiella*).**

### Breast milk-identical HMO have been added to hypoallergenic formula for infants with CMPA unable to breastfeed


In a randomised controlled study, a whey-based, extensively hydrolysed formula (w-EHF, Althéra HMO) with 2'-FL and LNnT was proven to be hypoallergenic, safe and tolerated by 98.4% of infants with CMPA

### HMO utilisation by infant-type bifidobacteria and related bacterial metabolites




**Infant-type bifidobacteria**
*B. longum* subsp. *infantis*
*B. breve*
*B. bifidum*
*B. longum* subsp. *longum*

### Biological effects of butyrate

**Colonic epithelium:**
- Improved mucosal barrier function

**Tolerance development:**
- T-reg FoxP3+ cell stimulation
- CD103+ tolerogenic dendritic cell maturation
- B-cell differentiation and IgG/IgA production

## The CINNAMON study

The CINNAMON study was a randomised, double-blind, controlled clinical trial in non-breastfed infants with CMPA. It assessed the effects of a w-EHF (Althéra HMO), containing lactose and supplemented with 2'-FL and LNnT, in regard to adequate growth, safety and tolerance. The effects of 2'-FL and LNnT on the infant's microbiome, metabolome and infective morbidity were also assessed.

### Nutritional and clinical outcomes

The w-EHF with 2'-FL and LNnT supported normal growth in infants with CMPA, and was effective in resolving symptoms of CMPA within one month

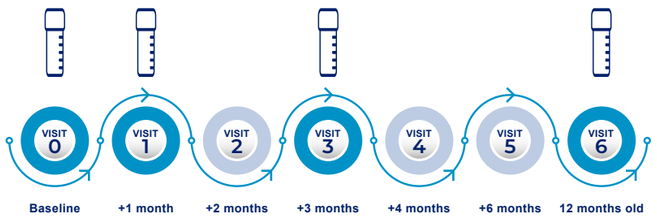
The HMO-supplemented w-EHF displayed immune-enhancing properties, with a protective effect against respiratory and ear infections in infants with CMPA

### Microbiome analysis

The exploratory objective of the study was to assess the effects of 2'-FL and LNnT on the faecal microbial ecosystem in this population

Stool samples were collected at various timepoints during this study and shotgun metagenomics, as well as targeted metabolomic analyses were performed

### Study visit schedule and stool collection

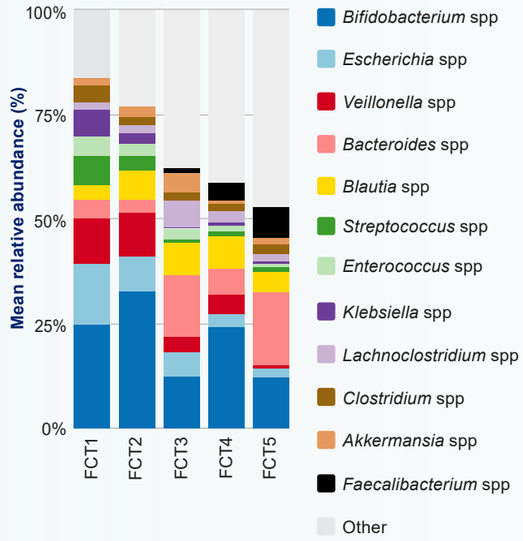



## Results

### HMO partially correct dysbiosis in infants with CMPA

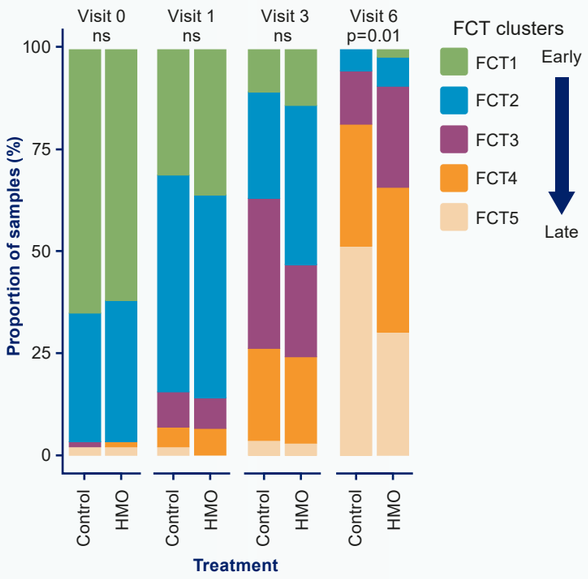

Feeding with an HMO-supplemented hypoallergenic formula containing 2'-FL and LNnT in infants with CMPA partially corrected the intestinal microbial dysbiosis by enriching infant-type bifidobacteria, and reducing the abundances of other bacteria such as proteobacteria.

### Early bacterial colonisation of the infantile gut



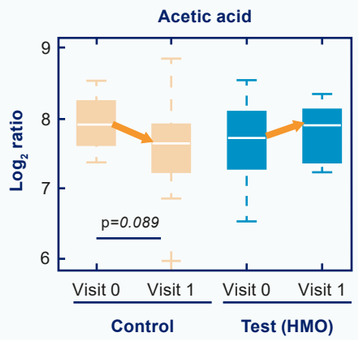

This graph shows stages of early colonisation with the 12 most common gut bacteria, illustrating 5 stages of colonisation in the first year of life; Faecal Community Types (FCT) 1 to 5

### The progression to an adult-type microbiome was different between formula groups




Supplementation with 2'-FL and LNnT delayed the transition of the microbiome composition towards an adult-like pattern (FCT5), which may prolong the window period for early immune modulation.

### HMO regulate production of short-chain fatty acids and other metabolites




There was an early increase in acetate production in the HMO group, whereas in the control group, acetate decreased.

Other metabolomic effects of 2'-FL and LNnT included a decrease in conjugated bile acids, and reduced bacterial breakdown of amino acids via the Ehrlich pathway. The clinical implications of these findings are yet to be determined.

## Effect of complementary diet

### The overall effect of HMO on the microbiome and metabolome was stronger in infants in the first 6 months of life.

There was a major shift in microbiome composition and metabolome profile at around 6 months of age, due to the effects of complementary diet and increased bacterial fermentation of dietary fibre. HMO shape the microbiome composition for this transition and promote healthy early immune development.

## Clinical Implications

Feeding with an HMO-supplemented hypoallergenic formula containing 2'-FL and LNnT in infants with CMPA partially corrected the intestinal microbial dysbiosis by enriching infant-type bifidobacteria and reducing the abundances of proteobacteria.

Supplementation with 2'-FL and LNnT contributed to a healthier, age-appropriate gut microbiome and promoted immune-modulatory effects, including a lower rate of respiratory tract infections and otitis media.

**Abbreviations:** ABC: ATP-binding cassette transporters; *B.: Bifidobacterium*; CMPA: cow's milk protein allergy; EE: early enrollment; FCT: faecal community type; FOXP3+: Forkhead box P3+; HMO: human milk oligosaccharides; LNnT: lacto-*N*-neotetraose; NS: not significant; SCFA: short-chain fatty acid; T-reg: T regulatory cell; w-EHF: whey-based extensively hydrolysed formula; 2'-FL: 2'-Fucosyllactose.

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