ADVANCING THE MANAGEMENT OF COW'S MILK PROTEIN ALLERGY:

Human Milk Oligosaccharides Part 2

Cow's milk protein allergy (CMPA) is an immune-mediated disease characterised by allergic reactions to cow's milk protein. CMPA is also associated with increased gut permeability and an altered gut microbiota which affects the maturation of the immune system, leaving infants at a higher risk of developing infections and future allergies. Human milk oligosaccharides (HMO) are proven to nurture infants' immune systems and reduce the risk of infections.

Infants with CMPA are at a higher risk of infections and future allergies

The first 1,000 days of life are a window of opportunity to set solid foundations for infants' future health. This period is a time of rapid physiological change and plasticity with significant potential for lasting effects.[1] It is also a period of heightened vulnerability.[2] Infants are born with a functionally immature intestine[3] and a developing gut microbiota[4] and immune system.[5] The maturation of these three systems is complex and closely linked.[6]

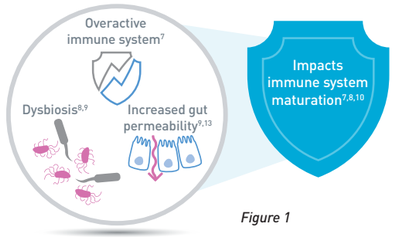

Figure 1

CMPA is a **reproducible immune-mediated allergic response** to otherwise harmless cow's milk protein[11] and is one of the most common food allergies in infants, affecting up to 3%.[11] Clinical manifestations are variable in type and severity, and may involve the skin, the gastrointestinal (GI) and respiratory tracts.[12] Infants with CMPA also have an increased gut permeability[13] and altered gut microbiota composition (dysbiosis),[8,9] which can affect immune system maturation **(Fig.1)** and can result in long-term health consequences.[10] Food allergy is associated with an increased risk of infections:[14-16]

- **Recurrent ear infections during childhood[14,15]: 2x**
- **Respiratory tract infections in the first two years of life[16]: 3.9x**

Children diagnosed with CMPA in infancy are at a higher risk of respiratory atopy and atopic dermatitis by 10 years of age:[15]

- **Asthma: 6.7x**
- **Atopic eczema: 3.6x**
- **Allergic rhinitis: 3x**

Breastfeeding is best

Breastfeeding is the gold standard for infant nutrition and should always be supported.[12] In the case of CMPA, it may require excluding cow's milk protein from the mothers' diet.[12] If breastfeeding is not possible for any reason, then hypoallergenic specialty formulas with proven clinical efficacy are recommended. Extensively hydrolysed formulas are supported as first-line management for the majority of infants with CMPA (~90%), while amino acid-based formulas are reserved for those with severe symptoms (~10%).[12] However, while an elimination diet with hypoallergenic specialty formulas relieves symptoms, dietary avoidance alone does not support the immune system.

HMO support the immune system

Breast milk contains large quantities of HMO, non-nutritive components known to support infants' developing immune systems.[17] They represent the third most abundant solid component after lactose and lipids. Out of approximately 200 HMO, 2'-fucosyllactose (2'FL) and lacto-*N*-neotetraose (LNnT) are two of the most significant, typically accounting for more than 30%.[18,19] The unique structures of HMO are essential for their four immune related benefits:[20]

1. HMO shape early-life intestinal microbiota, selectively supporting the growth of beneficial bacteria, such as *Bifidobacterium*.[21]

2. HMO prevent pathogen growth and adhesion by acting as decoy receptors. For example, 2'FL has been shown to bind to *Campylobacter jejuni* (a common cause of diarrhoea in infants) leading to its intestinal clearance.[22]

3. HMO help to strengthen the gut barrier by inducing differentiation and influencing intestinal cell gene expression and surface glycosylation.[23]

4. HMO directly and indirectly modulate mucosal and systemic immune function, ultimately guiding the immune system maturation.[17]

Clinical benefits of 2'FL and LNnT

For more than 50 years, HMO, and more specifically 2'FL and LNnT, have been an exciting area of research at Nestlé. This has led to 5 clinical trials with formula supplemented with structurally identical 2'FL and LNnT (not sourced from human milk), in both healthy infants[24,25] and infants with CMPA.[26-28]

Assessment of hypoallergenicity and safety

The IVORY trial demonstrated that Althéra® HMO, a whey-based extensively hydrolysed formula supplemented with 2'FL and LNnT, is both safe and well tolerated in infants with CMPA. It met the widely adopted American Academy of Pediatrics hypoallergenicity criteria, ensuring with 95% confidence that 90% of infants with documented CMPA will not react to the formula under double-blind, placebo-controlled conditions.[26]

Effective symptom relief & normal growth

The CINNAMON trial confirmed that Althéra® HMO effectively relieves symptoms of CMPA.[29] Althéra® HMO furthermore promoted normal growth in line with WHO growth standards.[29]

Reducing the risk of infections

In the CINNAMON trial, infants fed Althéra® HMO had 42% significantly fewer upper respiratory tract infection episodes **(Fig. 2A)**. A trend towards a reduced risk of lower respiratory tract infections (LRTI) by 34% and GI infections by 40% was also observed, as well as a 71% reduced risk of otitis media.[28] In the per protocol analysis, the risk of otitis media was significantly reduced by 100% ($p<0.05$). Whilst the risk reduction for all infections was not statistically significant, these results are in line with the 55% and 70% significant risk reduction for LRTI and bronchitis, respectively, that was observed in healthy infants fed a standard infant formula supplemented with the same quantity of 2'FL and LNnT, who were followed from birth and over a longer time period **(Fig. 2A & 2B)**.[24,28,29] The clinical trial in healthy infants also demonstrated a significant reduction in associated medication use **(Fig. 2B)**.[24]

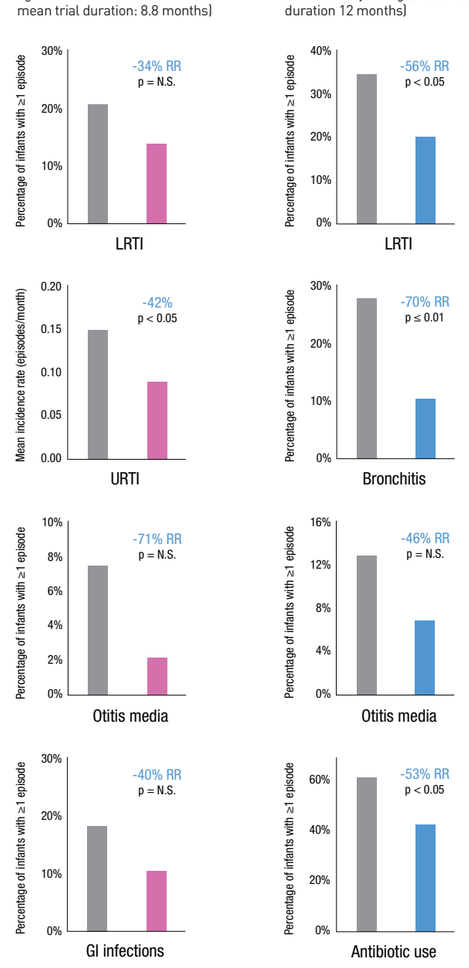

Figure 2: *Reduction in parent-reported adverse events and medication use in randomized, double-blind, controlled trials.*
A. *Results in infants with CMPA (CINNAMON), comparing Althéra® HMO with 2'FL and LNnT (pink) to a control formula (Althéra®) without 2'FL and LNnT (grey).*
B. *Results in healthy infants, comparing a standard infant formula with 2'FL and LNnT (blue) to a control standard infant formula without 2'FL and LNnT (grey).*
LRTI: lower respiratory tract infection; **URTI:** upper respiratory tract infection; **N.S.**: not significant; **RR:** risk reduction.

Positive effect on the gut microbiota

The addition of 2'FL and LNnT to a standard infant formula was also shown to positively shift the gut microbiota composition of healthy infants towards that of healthy breastfed infants, notably with higher counts of *Bifidobacteria*. This improved microbiota was associated with a reduction in antibiotics during the first year of life.[30]

Advancing CMPA management

Decades of research have helped to better understand the unique immune-nurturing properties of HMO. Althéra® HMO, Alfaré® HMO and Alfamino® HMO are for effective relief from the symptoms of CMPA.[12,26,29,31-34] The addition of 2'FL and LNnT has been additionally shown to reduce the risk of infections.[24,28,29] Clinical trial data from healthy infants also suggest supplementing hypoallergenic speciality formulas with 2'FL and LNnT could help to address gut microbiota dysbiosis seen in infants with CMPA. Further data are expected in 2021 from the PLATYPUS trial, evaluating the growth of infants with CMPA who require an amino acid-based formula and were fed Alfamino® HMO.[27]

IMPORTANT NOTICE: Mothers should be encouraged to continue breastfeeding even when their infants have cow's milk protein allergy. This usually requires qualified dietary counseling to completely exclude all sources of cow's milk protein from the mothers' diet. If a decision to use a special formula intended for infants is taken, it is important to give instructions on correct preparation methods, emphasizing that unboiled water, unsterilized bottles or incorrect dilution can all lead to illness. Formula for special medical purposes intended for infants must be used under medical supervision.

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