Gut and immune health:
The safety and value of synbiotics in the management of infants with cow's milk allergy (CMA)

What is Infant Cow's Milk Allergy (CMA)?

Infant Cow's Milk Allergy (CMA) is a multi-system organ disease. It describes an abnormal immune response to proteins found in cow's milk or products containing cow's milk proteins. It results in allergic symptoms (e.g., urticaria and asthma) which affect the skin, gastrointestinal (GI) tract and respiratory systems[1].

A Paradigm Shift in Management of CMA

In recent years, there has been a paradigm shift in the management of CMA, from total allergen avoidance to active management, by specific stimulation of the gut microbiota2.

The gut microbiome plays an important role in immunity. Manipulation of the gut microbiome in infants can help to promote a resilient immune system and offers an exciting treatment option for CMA[2,3,4]. Biotics are gaining popularity across the globe, and the COVID-19 pandemic has further increased consumer interest. This factsheet explores the safety and value of using synbiotics in management of infants with CMA.

Synbiotics in the management of CMA

Gut and Immune Health: What is the Link?

The first 1000 days of life are a crucial period for the development of the gut microbiota and subsequently, the immune system. 70% of immune cells are organized in the gut-associated lymphoid tissue, and immune maturation depends on gut microbiota signals[3].

Human breast milk specifically supports the gut microbiome development in infants by providing an abundance of pre- and probiotics. More recently, infant formulas with added synbiotic blends of pre- and probiotics have become available, to mimic the components of human milk to benefit the gut microbiota.

What are Pre-, Pro- and Synbiotics?

Prebiotics: Substrates that are 'selectively utilized by host microorganisms conferring a health benefit'[5].

Probiotics: 'Live microorganisms which when administrated in adequate amounts confer a health benefit on the host'[6]. Synbiotics: The combination of Pre- and Probiotics[7,8].

Gut Health and Allergy: What is dysbiosis and why does Dysbiosis Matter?

Dysbiosis encompasses a loss of organisms that are beneficial to the host and expansion of the bacterial species that have the potential to cause harm[9]. Gut microbiota dysbiosis in infant gut microbiota has been found to precede food sensitization[10]. Additionally, lower gut microbial richness at three-months-old is associated with an increased likelihood of food sensitization by one-years-old[10].

Interestingly, the gut microbiota is not only important for the development of food allergies - it can also part of the solution. Long- term resolution of CMA is associated with higher gut microbiota diversity[4].

As mentioned previously, there is a new paradigm shift towards active management of CMA through modulation of the gut microbiota[2]. This includes specific targeting of the gut microbiota with a synbiotic blend of pre- and probiotics.

What are Some of the Possible Benefits of Using Synbiotics in the Management of CMA?

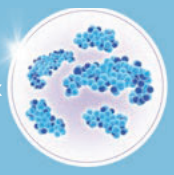
Studies in infants with or at risk of CMA have shown formula containing synbiotics can lead to:

- Less constipation and dry stools[11]
- Improved stool consistency and stool colour[12]
- Reduced need for medication for functional GI disorders[13]
- Improvement of skin symptoms (in those with IgE-mediated CMA)[11]
- Lower use of dermatological medication[14]
- Reductionofasthma-likesymptoms/ medication at one-year follow up[15]
- Fewer reports of infections and of antibiotic use[14,16]
- Fewer reports of hospitalization[17]

What is the Supporting Evidence for its Efficacy?

The addition of synbiotics to hypoallergic infant formula offers an novel new treatment option for CMA. This section reviews the supporting evidence for its efficacy.

Prebiotics:

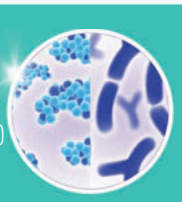


A study reviewing six clinical trials found that the addition of short-chain galacto-oligosaccharides (scGOS) and long-chain fructo-oligosaccharides (lcFOS) (in a ratio of 9:1) to infant formulas resulted in sustained positive effects on stool consistency and frequency[18].

Probiotics:

Bifidobacterium breve is a natural speciesin the infant gut. Itis considered the most dominant bifidobacterial species in breastfed infants[19]. Clinical trials have demonstrated that in pre-term infants, B. breve M-16V helps to establish the intestinal microbiota and prevents infections[20].

Synbiotics:



Three Randomised Control Trials (RCTs) have demonstrated that synbiotics (short-chain fructo-oligosaccharides (scFOS)/ lcFOS/B. breve M-16V) can beneficially modulate the gut microbiota in formula-fed infants with CMA to closely resemble that of a healthy breastfed infant[13,14,16].

Biotics: Science to application

How Do We Review the Safety of a Biotic?

When reviewing the safety of biotics, it is important to consider safety data evaluating factors such as origin, traceability, impact on growth and development, and history of use (e.g., adverse reaction, fatal events, gene transfers etc.). Along with strain-specific clinical data, it is also important to consider long-term follow-up data, documentation of clinical practice and strain properties (e.g., antibiotic resistance).

Safety assessment systems such as the Qualified Presumption of Safety (QPS) system by the European Food Safety Authority (EFSA) and the Generally Recognized as Safe (GRAS) list by the Food and Drug Administration (FDA) have been developed to provide a generic safety evaluation framework for biological agents added to foods.

What Safety Data is Available for Use of Probiotics in Infants?

The safety of B. breve M-16V has been extensively studied since 1994, including in pre-term infants21. There are 12 clinical trials with documented safe use of probiotics (B. breve M-16V) in infants.

Evidence for Safe Use of Probiotics

Patient Group	Study Author and Year
Extremely premature infants	Akiyama et al. 1994[21]
Premature infants	Sato et al. 2003[23], Fujii et al. 2006[24]
Low birth weight infants	Li et al. 2004[25], Wang et al. 2007[26]
Neonates at an intensive care unit	Satoh et al. 2007[27], Patole et al. 2014[28]
Healthy, term infants	Hattori et al. 2003[29], Taniuchi et al. 2005[30] Morinaga internal data (unpublished).

RCTs Assessing Safe Use of Hypoallergenic Formula with Synbiotics

Study Author and Year	Patient Group	Product Used*	Duration
Abrahamse et al. 2016[22]	Healthy infants	EHF and synbiotics	13 weeks
Harvey et al. 2014[12]	Healthy infants	AAF and synbiotics	16 weeks
Burks et al. 2015[13]	Infants with CMA	AAF and synbiotics	16 weeks
van der Aa et al. 2010[11], van der Aa et al. 2011[15]	Infants with atopic dermatitis	EHF and synbiotics	12 weeks

***EHF =** Extensively hydrolysed formula. ***AAF =** Amino acid-based formula.

What Safety Data is Available for Use of Synbiotics in Infants?

Five clinical studies have assessed the safety and efficacy of synbiotics in allergy management in infants[11,12,13,14,15,16,22]. These RCTs demonstrate that hypoallergenic formulae with synbiotics are safe, well tolerated and support normal growth.

What Does the Future Like Look in 10 Years' Time Regarding Biotics in Infant Formula?

In recent years infant formula has developed to include ingredients (such as prebiotics, probiotics and synbiotics) similar to those found in human breast milk. Going forward, it is likely that formula will continue to evolve. As this happens, we also need to further understand the role of the gut microbiota in infant health as well as making use of the most up-to-date safety and efficacy information available on biotics.

Which Factors Should a Clinician Consider When Selecting an Infant Formula?

Breastfeeding (BF) should be promoted where possible. When selecting an infant formula, it is important to consider both benefit and safety. In clinical practice, the most important questions to ask are "Will the product be effective in managing the infants' allergic symptoms?", "Will it do any harm to the child?" and "Are there are any contraindications?"

Why Should Synbiotics Be Considered in the Dietary Management of CMA?

The gut microbiota is not only important in the aetiology of CMA but can also be part of the solution, through modulation of the gut microbiota, thereby rebalancing the dysbiosis commonly seen in CMA.

Synbiotics are a safe and efficacious way of modulating the gut microbiota. They have been extensively researched, with high-quality clinical trials demonstrating that they are suitable for use in infants. In summary, the use of synbiotics in dietary management of CMA offers an exciting new treatment option.

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