Danone Nutricia Campus

Latest insights on the role of pre- and synbiotics in the dietary management of cow's milk allergy and infection outcomes

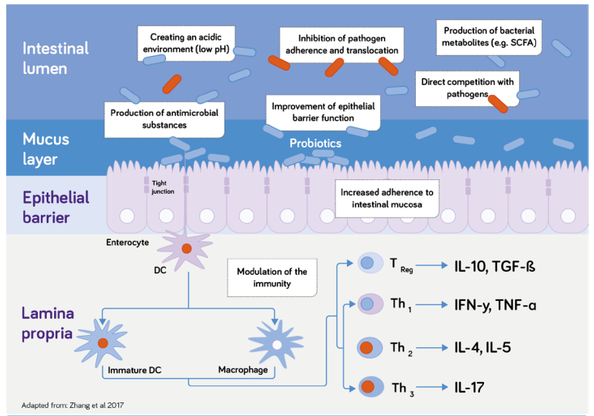
This article is part of a series of discussions on the role of gut microbiota in the dietary management of cow's milk allergy (CMA) and focuses on the potential role of gut microbiota, and pre- and synbiotics in the dietary management of CMA and potential role in infection outcomes.

The role of gut microbiota in the development of the immune system and the defence against infections

Infants are particularly susceptible to infections in early life as their immune system is not yet fully functional.[1,2] The establishment of a balanced gut microbiota in early life is important as it has been suggested to be one of the main factors driving the development and appropriate functioning of the immune system and may help to protect infants against infections (Figure 1).[1,3]

Human milk contains natural prebiotic oligosaccharides and probiotic bacteria that influence the microbiota

Human milk provides the infant with the best possible nutrition and is known to protect the infant against infections.[5] It contains a wide range of health protective components,[6,7] for example, human milk prebiotic oligosaccharides and beneficial bacteria (probiotics), stimulating the growth of specific bacteria including bifidobacteria, and influencing gut microbiota development.[1,3,7] The gut microbiota of healthy breastfed infants is typically dominated by bifidobacteria, compared to formula-fed infants.[8] The increased abundance of bifidobacteria has been linked to appropriate development and functioning of the immune system, as well as providing resistance to infections by preventing colonisation by pathogens or pathogen overgrowth (Figure 1).[9]



Adapted from: Zhang et al 2017

Figure 1 The gut microbiota acts as a barrier against pathogens[4]

The gut microbiota may help to protect against infections via stimulation of the innate and adaptive immune system.23 The gut microbiota can also act as a barrier against the infiltration and colonisation of pathogens, and therefore protect the infant against infections, e.g. in the following ways: [23]

- Competition for adhesion sites and nutrients
- Production of bacterial metabolites such as SCFA
- Creating an acidic environment (low pH)
- Production of anti-microbial substances such as anti-microbial peptides
- Supporting the epithelial and mucosal barrier

Research shows that infants with CMA have an aberrant gut microbiota composition (dysbiosis)

Infants with CMA show an aberrant gut microbiota composition (dysbiosis), with typically lower levels of beneficial bacteria, i.e., bifidobacteria, and increased levels of adult-like clostridia group Eubacterium rectale/Clostridium coccoides (ER/CC).[10,13]

Given the important role of naturally occurring prebiotics and bacteria in human milk in the establishment of a healthy microbiota and the developing immune system, and recognizing that breastfeeding is not always feasible in allergic infants, there is a compelling rationale to combine pre- and probiotic ingredients in hypoallergenic formula for the dietary management of cow's milk allergy to restore the gut microbiota and modulate the immune system.

The combination of pre- and probiotics is known as synbiotics.[14] In addition to these ingredients reflecting the natural functionality of human milk, the objective of combining pre- and probiotics is to achieve stronger positive effects than with either component alone (synergy), in which the prebiotic stimulates the growth and activity of the probiotic and other health-promoting bacteria already present in the gut.[15]

Clinical findings show that pre-, pro- and synbiotics can rebalance gut microbiota composition

Clinical studies in healthy and preterm infants have shown that specific prebiotic oligosaccharides (scGOS/lcFOS) are able to positively impact gut microbiota composition by stimulating the growth of bifidobacteria[16] and reducing the presence of clinically relevant pathogens in the infants' gut (**Figure 2**).[17]

More recent studies in infants with CMA have shown that an amino acid-based formula (AAF) including a specific synbiotic mixture (scFOS/lcFOS/pAOS/B. breve M-16V) effectively resolved allergic symptoms[18,19] and beneficially modulated the gut microbiota composition.[19]

CMA infants that received the AAF with specific synbiotics (scFOS/lcFOS/B. breve M-16V) showed a gut microbiota composition closer to the profile seen in healthy breastfed infants compared to infants receiving an AAF without synbiotics at 8 weeks, with increased percentages of bifidobacteria and reduced percentages of adult-like clostridia group ER/CC[13] at 8 weeks and 26 weeks (**Figure 3**).[20]

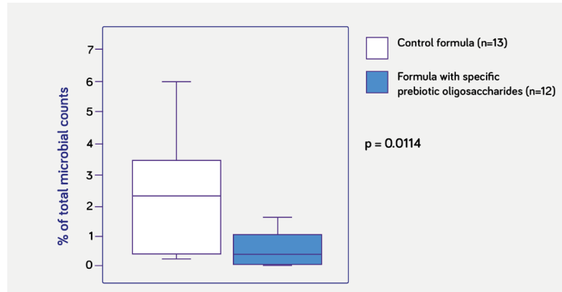


Figure 2 Proportion of clinically relevant pathogens

Stimulation of bifidobacteria by prebiotic oligosaccharides (scGOS/lcFOS) induced a reduction of clinically relevant pathogens in the faecal microbiota (p=0.011), expressed as a percentage of total bacteria in the gut.[17]

The potential role of pre- and synbiotics on infection outcomes

In addition to the effects of synbiotics on rebalancing gut microbiota, some clinical studies have also shown a potential role of pre- and synbiotics for the improvement of infection outcomes. A clinical trial with infants at risk of atopy demonstrated that 6 months' intervention with a hydrolysed infant formula containing specific prebiotic oligosaccharides (scGOS/lcFOS) resulted in a reduction of the total number of infections, cumulative incidence of infections, and recurring infections.[21] The 2-year follow-up data of this study showed a significant reduction of the total number of infections, upper respiratory tract infections, fever episodes, and antibiotic prescriptions (**Figure 4**).[22] The effects seen after 2 years may suggest an imprinting effect of the specific microbiota modulation early in life.[21,22]

In a study of infants with CMA (total n=71), differences have been reported between the 2 study groups (AAF with and without specific synbiotics (scFOS/lcFOS/B. breve M-16V)) with respect to the adverse events and concomitant medication. Although not primary endpoints of the study, a significant reduction was observed in the subjects receiving the synbiotic-containing AAF regarding the medication subcategory systemic anti-infectives during the 8-week intervention (test 8.6% vs. control 34.4%, P = 0.018)[13] and incidence of ear infection during the 26-week study period (test 0% vs. control 20%, P = 0.011), which may suggest a beneficial effect on the immune system.[20]

Interestingly, comparable results were reported in an earlier study with an AAF with a specific synbiotic mixture (total n=54) showing that significantly fewer subjects in the test group (AAF with scFOS/lcFOS/pAOS/B. breve M-16V) were reported to have infection as adverse events (test group 2%, control 10%, P = 0.008), and lower use of medications categorised as antibacterials for systemic use (test 17%, control 34%; P = 0.049).[19]

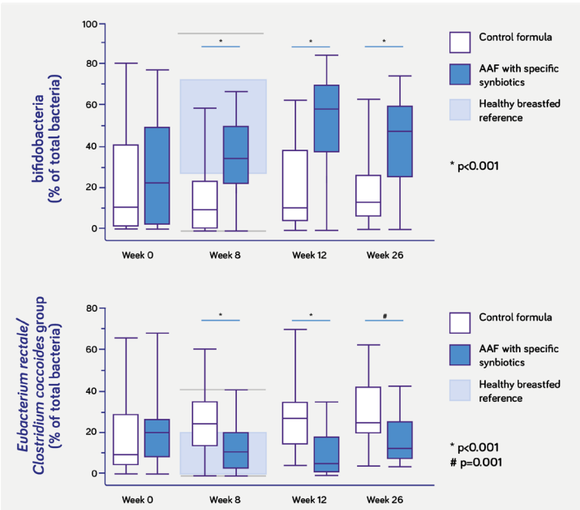


Figure 3 Gut microbiota composition in infants with CMA

Early dietary intervention with an AAF with specific synbiotics (scFOS/lcFOS/B. breve M-16V) resulted in significantly increased bifidobacteria and decreased ER/CC at weeks 8, 12, and 26, with percentages close to levels seen in age-matched healthy breastfed infants at 8 weeks of intervention.[13,20]

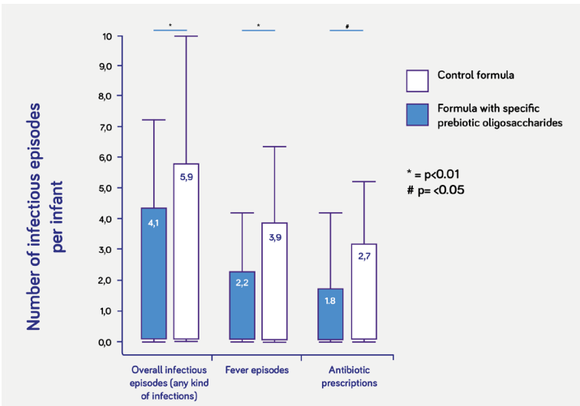


Figure 4 Episodes of infections, fever and infections requiring antibiotic prescriptions

Early dietary intervention with an AAF with specific synbiotics (scFOS/lcFOS/B. breve M-16V) resulted in significantly increased bifidobacteria and decreased ER/CC at weeks 8, 12, and 26, with percentages close to levels seen in age-matched healthy breastfed infants at 8 weeks of intervention.[13,20]

Key messages

- Infants with CMA show an aberrant gut microbiota composition (dysbiosis) characterized by typically lower levels of beneficial bacteria, i.e., bifidobacteria, and increased levels of adult-like clostridia group ER/CC. Recent studies in CMA infants have shown that hypoallergenic formulas with specific synbiotics can bring the gut microbiota composition close to that of healthy breastfed infants, reflected by an increase in bifidobacteria and a reduction in adult-like clostridia group ER/CC.
- A potential role of prebiotics in the improvement of infection outcomes has been shown previously. Interestingly, studies with hypoallergenic formula including synbiotics have also shown lower infectious events reported as adverse events in the synbiotic group versus the control group. These findings deserve further study in infants with CMA.

Abbreviations

- AAF: Amino acid-based formula
- scGOS/lcFOS: Short-chain galactooligosaccharides and long-chain fructo-oligosaccharides in a 9:1 ratio
- scFOS/lcFOS: Short-chain fructo-oligosaccharides and long-chain fructo-oligosaccharides in a 9:1 ratio
- pAOS: Pectin-derived acidic oligosaccharide
- *B. breve* M-16V: *Bifidobacterium breve* M-16V
- ER/CC: *Eubacterium rectale/Clostridium coccoides*

References

1. Martin R, et al. Benef Microbes. 2010;1(4):367-382.
2. Simon AK, et al. Proc R Soc B Biol Sci. 2015;282(1821)
3. Weng M, et al. J Dev Orig Health Dis. 2013;4(3):203-214.
4. Zhang M, et al. Front Immunol. 2017;8:942.
5. Duijts L, et al. Matern Child Nutr. 2009;5(3):199-210.
6. Hamosh M, et al. Pediatr Clin North Am. 2001;48(1):69-86.
7. Newburg DS, et al. J Pediatr Gastroenterol Nutr. 2000;30 Suppl 2:S8-17.
8. Harmsen HJ, et al. J Pediatr Gastroenterol Nutr. 2000;30(1):61-67.
9. Scholtens PAMJ, et al. Annu Rev Food Sci Technol. 2012;3(1):425-447.
10. Canani RB, et al. ISME J. 2016;10(3):742-750.
11. Ling Z, et al. Appl Environ Microbiol. 2014;80(8):2546-2554.
12. Thompson-Chagoyan OC, et al. Pediatr Allergy Immunol. 2010;21(2p2):e394-e400.
13. Candy DCA, et al. Pediatr Res. 2018;83(3):677-686.
14. Gibson GR, et al. J Nutr. 1995;125(6):1401-1412.
15. Shamir R, et al. John Wiley and Sons. 2015.
16. Knol J, et al. J Pediatr Gastroenterol Nutr. 2005;40(1):36-42.
17. Knol J, et al. Acta Paediatr. 2005;94(0):31-33.
18. Harvey BM, et al. Pediatr Res. 2014;75(2):343-351.
19. Burks AW, et al. Pediatr Allergy Immunol. 2015;26(4):316-322.
20. Fox AT, et al. Clin Transl Allergy. 2019;9(1):5.
21. Arslanoglu S, et al. J Nutr. 2007;137(11):2420-2424.
22. Arslanoglu S, et al. J Nutr. 2008; 138(6):1091-1095.
23. Sassone-Corsi M, et al. J Immunol. 2015;194(9):4081-4087.