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The role of the gut microbiota on allergy development in early life

Nutricia presents the first in a three-part series of discussions around allergies in early life. These articles will focus on the important role of gut microbiota in early life and the role of pre- and probiotics in the prevention and dietary management of cow's milk allergy (CMA).

In the grip of a pandemic

The prevalence of allergic diseases, such as food allergy, atopic eczema, allergic rhinitis and asthma, are rising dramatically worldwide in both developed and developing countries, affecting 30–40% of the population.[1] The global rise of food allergy is particularly problematic in infants, who are bearing the greatest burden of this rising trend.[2]

CMA is one of the most common childhood food allergies affecting up to 5% of the population.[3] Although most infants with CMA outgrow their allergies by school age, an increasing number may have persistent symptoms or develop other allergic conditions over time, also referred to as the allergic march.[2-4]

The key for allergy management today is targeted exposure in a controlled microbial environment.

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Gut microbiota and the immune system

Microbial interactions are important drivers in the maturation of the immune system, with 70–80% of immune cells residing in the gut.[5] The gut microbiota provides many useful functions including protection from harmful pathogens, strengthening the body's immune defences and performing vital metabolic tasks.[6] The immune system develops quickly during the first 1000 days of life; developing and maintaining a balance between the gut microbiota and the immune system is essential to maintain health, especially in infants and children.[7] The development of allergic diseases is influenced by genetic, environmental factors and transmission from the mother to the fetus. These play a critical role in the development of the immune system and the gut microbiota.

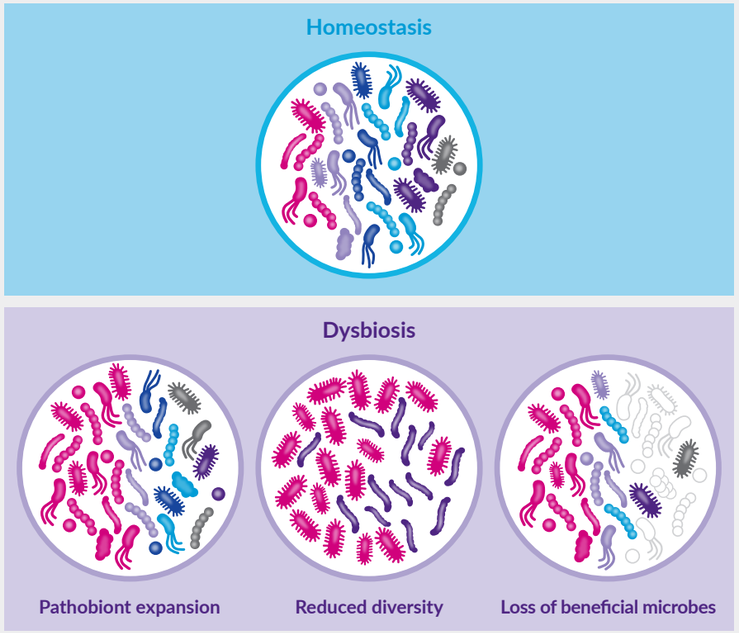
Factors which influence gut microbiota in early life[8–10]

- Gestational age
- The maternal environment
- Delivery mode (vaginal or caesarean)
- Nutrition (breast *vs.* formula feeding)
- Use of antibiotics
- Diet
- Air pollution

The impact of gut microbiota dysbiosis on health and the development of allergy

The gut of a healthy breast-fed infant is typically dominated by bacteria of the *Bifidobacterium* species. These species are first transmitted from the mother during birth and via the breast milk.[11,12] In addition to bacteria, breast milk also contains non-digestible oligosaccharides that are readily consumed by these same species of Bifidobacteria. By contrast, C-section delivery, use of antibiotics and formula-feeding can lead to a loss of these beneficial microbial organisms, and the expansion of pro-inflammatory pathobionts, many of which are species of Proteobacteria or *Clostridium*, e.g. *C. perfringens* and *C. difficile*.[11,12] These changes result in a shift in metabolic capacity, and activity of the gut microbiota and can lead to health consequences in later life.[13]

Disruption of the gut microbiota in early life has been linked with numerous clinical disorders e.g. asthma, metabolic syndrome, cardiovascular disease and obesity.[14] Many studies have shown that abnormal gut microbiota trajectories in infants may delay the development of oral tolerance and these play an important role in the development of food allergies, such as CMA.[15] Infants with food allergies such as CMA have been shown to have low levels of bifidobacteria and lactobacilli in their gut microbiota compared with healthy, breast-fed infants.[16]



Reference: Peterson & Round *Cellular Microbiology* 2014 Jul; 16(7): 1024–1033

Fig 1: *A loss of beneficial microbes, expansion of pathobionts, and loss of diversity are events that encompass dysbiosis. During healthy, homeostatic conditions the microbiota is composed of a diversity of organisms that are known to benefit host development and health. However, environmental insults, such as antibiotic use or diet can lead to disruptions in the structure of the microbial community. These disruptions can lead to a loss of organisms that are beneficial to the host and a subsequent overgrowth of commensals that have the potential to cause harm.*

Nutritional support for infants with CMA

Nutritional support is an essential part of the clinical management of infants with CMA.

CMA can present with a variety of symptoms, generally affecting the respiratory tract, the skin and the GI tract. It is classified according to the different immune responses, which include IgE-mediated (immediate) or cell mediated/non IgE-mediated (delayed) reactions and is associated with the development of other allergies.[3]

Recognising that breast feeding is not always possible, ways to support the development of the microbiota of formula-fed infants have been sought, resulting in the addition of prebiotic oligosaccharides and specific probiotic strains, alone or in combination, in several commercially available infant formulas.[17,18]

A growing amount of clinical evidence shows that pre- and probiotics can have beneficial effects in infants at risk of, or living with allergies. Pre- and probiotics aim to influence the status of the tissue directly, or indirectly, via the gut microbiota thereby aiming to prevent the onset of an allergic disease.[19,20]

Future of allergy management for CMA patients

The mainstay of dietary management of CMA infants is the avoidance of all cow's milk and cow's milk protein-based infant formulas. Breast feeding is the gold standard for infant nutrition however it may not always be possible for all CMA infants. Therefore healthcare professionals may prescribe specialised infant formulas based on hydrolysed protein or amino acids for dietary management.

Due to the recognition that there is gut microbiota dysbiosis in allergy, there is a compelling rationale for the addition of both pre- and probiotic ingredients to formula for infants with CMA. A blend of pre- and probiotics is termed synbiotics.

Synbiotics allude to a synergy in which the prebiotic compound selectively stimulates the colonization of the probiotic bacteria and other bifidogenic bacteria.[21]

Nutricia believes that there is a strong rationale to include pre-, pro- and synbiotics in the diet of these infants and has an extensive clinical trial programme underway investigating the role of these ingredients in the primary prevention and dietary management of CMA.

Nutricia continues to collaborate with global experts to further its understanding of the impact of nutrition on food allergy.

For more information visit **www.nutriciaresearch.com/allergy/**

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