

Invited Commentary

Prebiotics in infancy and childhood; clinical research warranted

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The increase in immune-mediated disorders has been strongly linked to reduced early microbial exposure. Vital for the development of immune function, the gut microbiota represent by far the greatest microbial exposure. There is an enormous shift from the 'sterile' milieu present *in utero* to reach full intestinal colonisation with microbes which ultimately outnumber host human cells by more than 10:1. These micro-organisms form an integral part of the intestinal mucosal defence system⁽¹⁾. Emerging evidence suggests that deviant development of the intestinal microbiota and mucosal defence system are key players not only in intestinal but also in non-intestinal immune disorders such as allergic and autoimmune disease⁽¹⁾. Due to immature intestinal immune function, the newborn infant is susceptible to intestinal and systemic infections. Several studies have shown that exclusively breastfed infants, particularly in developing countries as also in developed countries, are less prone to develop infections as compared to formula-fed infants⁽²⁾. Human milk is abundant in protective factors, including a large variety of complex non-digestible oligosaccharides⁽³⁾. Some of these serve as decoy receptors preventing attachment of potential pathogens to the intestinal lining; and being non-digestible, they pass through the small intestine to enter the colon where they promote colonisation by a 'healthy' gut microbiota, particularly bifidobacteria. A second more direct immune effect appears to be mediated by the production of fermentation products. Oligosaccharides are fermented by colonising bacteria to produce SCFA, which have direct nutritive and anti-inflammatory effects⁽⁴⁾. SCFA can also promote intestinal integrity through effects on epithelial cell proliferation and differentiation. Collectively, and bearing in mind that the amount of oligosaccharides in bovine milk and in infant formulas is much lower and the structures considerably less diversified, these findings provided a strong foundation to explore the effects of oligosaccharide supplementation in infancy in the treatment and prevention of infectious and immune-mediated diseases. Commercially available prebiotics added to some infant formulas are usually in the form of oligosaccharides (although of much less complexity than in human milk). The European Society of Gastroenterology, Hepatology and Nutrition Committee on Nutrition recently published a systematic review and comment on the supplementation of infant formula with probiotics and prebiotics⁽⁵⁾. They concluded that with available data, prebiotic-supplemented

formulae do not raise safety concerns with regard to growth restriction or other adverse effects in healthy infants. However, the committee stated that there is not enough evidence to recommend the routine use of prebiotic-supplemented formulae, and identified the need for well-designed, randomised, controlled trials in this area.

There are now several published clinical trials in infancy that have demonstrated the effects of prebiotics on gut microbial composition⁽⁵⁾. Even though some positive effects of prebiotics on gut microbial composition⁽⁵⁾ and immune function (reviewed in Lomax & Calder⁽⁶⁾) have been demonstrated in clinical trials, there are only a limited number of studies that have actually studied if these effects translate into clinically relevant benefits. Clinical trials targeting a paediatric population have thus far focused on the prevention or treatment of infections and allergic disease. The effects of prebiotics in the prevention of infections have been investigated in a few studies⁽⁵⁾. Bruzzese *et al.*⁽⁷⁾ reported a lower incidence of gastroenteritis and fewer antibiotic courses in a group of infants receiving formula supplemented with galacto- and fructo-oligosaccharides, compared with a group receiving a placebo formula. However, the design of that study was open and not double-blinded, which might unavoidably have introduced some biases to the results. In another study targeting a population at risk of allergic disease, galacto-oligosaccharides/fructo-oligosaccharides-supplemented infants had long-term preventative effects on infections and antibiotic prescriptions, when compared with placebo⁽⁸⁾. In this issue, van Stuijvenberg *et al.*⁽⁹⁾ report the results from the Multi-centre Infection Prevention Study, a multi-centre, randomised, controlled trial assessing the effects of prebiotic-supplemented formula on fever episodes in healthy infants. A total of 414 infants were randomised to a non-hydrolysed cows' milk protein-based infant formula supplemented with short-chain galacto-oligosaccharides and long-chain fructo-oligosaccharides (total amount of oligosaccharides 8 g/l) and 416 infants were randomised to the same formula without addition of oligosaccharides (control group). A group of 300 breastfed infants was included as a non-randomised reference group. Of 830 randomised infants, 361 and 374 in the prebiotic and control groups, respectively, completed the first year. As discussed by the authors, the reported overall incidence of fever episodes was low in all the groups. Somewhat surprisingly, the incidence of fever

episodes was slightly higher in the breastfed group. There was no difference in fever episodes or reported associated infectious symptoms or antibiotic treatment between the prebiotic and control groups. This is in contrast to previous studies that reported preventative effects on infections and antibiotic treatment^(7,8) by prebiotics. However, the study populations are not necessarily comparable as the study reported in this issue targeted infants at low risk of allergic disease, whereas one of the previous studies targeted a high-risk population⁽⁸⁾. Also, the effects of prebiotics are likely to be influenced by a range of host and environmental factors which might explain the inconsistency in results. Still, other factors need to be considered. In the study by van Stuijvenberg *et al.*⁽⁹⁾, mothers in the formula groups could continue breastfeeding following randomisation for ethical reasons. Since 20–30% of the mothers in the control group still breastfed their infants, the oligosaccharides present in breast milk might have acted as natural prebiotics, possibly affecting the outcome. Another open issue is optimal dosing and intake duration of prebiotics. As underlined in the position paper by the European Society of Gastroenterology, Hepatology and Nutrition Committee of Nutrition⁽⁵⁾, this still needs to be defined.

Earlier epidemiological studies suggested a protective link between dietary fibre and allergic conditions⁽¹⁰⁾ and there is preliminary evidence of protective effects on early allergic manifestations by neonatal supplementation with oligosaccharides in infants at high risk of allergic disease⁽⁹⁾. Notably, the Multicentre Infection Prevention Study group recently reported a reduction in the incidence of eczema in this study population with a low risk of allergic disease⁽¹¹⁾. These findings provide a strong basis to further explore the effects of prebiotics in allergic inflammatory conditions, both in high- and low-risk populations⁽¹²⁾.

In summary, oligosaccharides are the third largest fraction in human milk and confer many potential benefits in breastfed infants. Many of these are dependent on specific structures, some of which are genetically determined. Current commercially available prebiotics are much less complex and it is unlikely that they will provide the recipient infant with all the health benefits as provided by those in human milk. However, they seem to have the potential to promote gut colonisation with bifidobacteria; and some studies have also demonstrated immune-stimulating effects. Preliminary data suggest a role for commercially available prebiotics in the prevention of infections and allergic disease, but confirmatory clinical trials are needed before any recommendations can be given. With further development of oligosaccharides with greater similarity to those in human milk, more significant clinical outcomes can be anticipated. Future clinical trials are needed to provide a clearer message of the possible clinical benefits and limitations of current and future prebiotics.

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