

EDITORIAL

Clinical & Experimental Allergy

Probiotics, prebiotics and synbiotics: a hope or hype in allergy?

This editorial discusses the findings of the paper by van der Aa et al. [11] pp. 795–804.

M. Kalliomäki

Department of Paediatrics, Functional Foods Forum, University of Turku, Turku, Finland

In his landmark paper David Strachan demonstrated an association of hayfever with family size and position in the household in childhood. He suggested that declining family size, improvements in household facilities and in personal hygiene have reduced infection burden among families resulting in more widespread expression of atopic disease [1]. Thereafter vigorous epidemiological, clinical and experimental research emerged that has led to a revision of the original hygiene hypothesis. There is now a widely accepted theory that deficient exposure to non-pathogenic microbes, including those in gut microbiota, early in life is a crucial factor for development of allergy [2]. Several prospective follow-up studies have found that alterations in gut microbiota precede development of allergy. Changes have been quite variable, but they have been found most often in the amounts of bifidobacteria, clostridia and *Escherichia coli* [3]. Moreover, many cross-sectional studies have shown that there is different composition in gut microbiota between children with atopic eczema/eczema and healthy controls [3]. Antibiotic use in the first year of life has been shown to be associated with later symptoms of asthma, allergic rhinoconjunctivitis and eczema further supporting the hypothesis [4]. Considering these findings, it is not surprising that manipulation of gut microbiota composition has lately been a major target in clinical studies of allergy [5].

Probiotics, prebiotics and synbiotics are all capable of eliciting changes in the gut microbiota composition. Nowadays, they are increasingly found as ingredients in functional foods. A functional food is defined as 'a food that targets functions in the body, beyond adequate nutrition, in a way that improves health and well-being or reduces the risk of disease' [6]. According to an

independent market analyst, Datamonitor, the combined US, European and Asia-Pacific functional food market value in 2007 was worth US\$72.3 billion. The analyst forecasted the market to be growing at a compound annual growth rate of 5.7% between 2007 and 2012 [7]. The FAO/WHO has defined probiotics as 'live microorganisms which when administered in adequate amounts confer a health benefit on the host'. The most common probiotic strains belong to the genera *Lactobacillus* and *Bifidobacterium*. Prebiotics are non-digestible food ingredients that beneficially affect the host by selectively stimulating the growth and/or activity of one or a limited number of bacteria in the colon that can improve the host health [6]. They comprise non-digestible carbohydrates and include the oligosaccharides inulin, fructo-oligosaccharides (FOS), galacto-oligosaccharides (GOS) and lactulose. These oligosaccharides are bifidogenic, i.e. they stimulate bifidobacteria in the colon. Synbiotics are mixtures of probiotics and prebiotics [6].

Since the late 1990s over 30 randomized clinical trials (RCT) have been published where probiotics have been used either in the treatment or prevention of atopic disease, as reviewed recently by the international expert group [5]. Most success has been obtained in primary prevention of eczema/atopic eczema. A limited number of studies have also provided evidence for a beneficial effect of different probiotics in the management of eczema/atopic eczema and allergic rhinitis. However, as discussed in the paper, there are methodological and other deficiencies in most of the trials. That is to say, they are not compatible with the Consolidated Standards of Reporting Trials (CONSORT) statement, which is nowadays widely endorsed [8]. Moreover, the results are partly conflicting, even with the same probiotic strain, due to e.g. differences in target populations, intervention schemes, diagnostic criteria, regimens, additional treatments such as topical treatments and also different probiotic preparations or formulations. Therefore, no recommendations for use of any specific probiotic strains in clinical allergy practice can be given [5]. So far, there are only two RCT in which

Correspondence:

Marko Kalliomäki, Department of Paediatrics, Functional Foods Forum, University of Turku, PO Box 52, FI-20521 Turku, Finland.
E-mail: markal@utu.fi

Cite this as: M. Kalliomäki, *Clinical & Experimental Allergy*, 2010 (40) 694–696.

prebiotics has been studied in allergy. Kestose, a FOS, was found to decrease the severity of atopic eczema in a small cohort of infants [9]. A mixture of short-chain (sc)GOS and long-chain (lc)FOS during the first 6 months of life was shown to decrease cumulative incidences of atopic eczema, recurrent wheezing and allergic urticaria [10]. Despite these positive preliminary findings, it is far too early to draw any solid conclusions about the use of prebiotics in allergy.

In this issue of the journal, van der Aa et al. [11] report a well-designed and conducted contribution to the field. They have carried out the first RCT where the therapeutic effect of a synbiotic on the severity of atopic eczema in infants has been investigated. Ninety infants were randomly assigned to receive either an extensively hydrolyzed formula with *Bifidobacterium breve* M-16V (at a dose of 1.3×10^9 CFU/100 mL) and a mixture of 90% scGOS and 10% lcFOS (0.8 g/100 mL) or the same formula without synbiotic during 12 weeks. All the infants were exclusively formula-fed. The synbiotic mixture had no effect on eczema severity, the primary outcome measure, or atopic sensitization and inflammation, as measured by total serum IgE, specific IgE against food and inhalant allergens and serum eosinophilic granulocytes. Nevertheless, the mixture use was associated with increased percentages of bifidobacteria and decreased percentages of clostridia-related species in the gut microbiota. Again, the metabolic profile of fecal samples changed to resemble that of breastfed infants [11]. The synbiotic was well tolerated and it made stools softer but adverse events were comparable between the study groups. In a subgroup analysis it was found that infants with IgE-associated atopic eczema and supplemented with the synbiotic mixture had a greater reduction in the severity of atopic eczema after 12 weeks of intervention than those receiving placebo.

Albeit well-documented bifidogenic and metabolic effects, that is the signs of good compliance, the synbiotic mixture had no effect on the severity of atopic eczema. One explanation for ineffectiveness may be that, in fact, there have been other changes than decreased bifidobacteria counts (or no changes at all) in the most studies where fecal microbiota in patients with eczema/atopic eczema have been evaluated [3]. It is thus possible that stimulation of bifidobacteria is not at all an effective way to treat the disease. Alternatively, it is possible that the infants were treated too late. The mean age of the infants at the beginning of the intervention was approximately 5 months. Evidence from the literature suggests that the window of opportunity for bifidobacteria may lie earlier, both in terms of age and development of atopic disease. We found in a prospective follow-up study that a reduced ratio of bifidobacteria to clostridia at the age of 3 weeks in fecal microbiota, but not later, was associated with a higher risk for atopic sensitization at the age of 1 year

[12]. Moreover, a recent Finnish trial reported a preventive effect of an intervention by a combination of a probiotic mixture and GOS (actually a synbiotic) on a subgroup of IgE-associated eczema in caesarean-delivered children [13]. Interestingly, the authors demonstrated that the prevalence of fecal bifidobacteria was constantly lower from the first months of life on in the caesarean-delivered children who were supplemented with the placebo as compared with those caesarean-delivered children who were supplemented with the synbiotic or the children delivered vaginally regardless of the supplementation [13]. This implies that the restoration of early defective bifidogenic gut microbiota might decrease later risk for IgE-associated eczema.

However, these findings should be regarded so far only suggestive because they were based on the subgroup analysis for which the study was not powered to. Still, based on the above-mentioned, it would be of interest to know whether the synbiotic used by van der Aa et al. [11] had preventive potential in allergy. Similarly, as already suggested by the authors, the finding of the positive effect of synbiotic in the treatment of IgE-associated atopic eczema should be explored in future RCT addressed and adequately powered to this group of infants. Before that, no firm conclusion for either direction should be drawn.

The adoption of the revised recommendations of the CONSORT statement [7] as a requested standard for RCT also in the field of probiotics, prebiotics and synbiotics would assist to increase both quality and transparency of the research. Additionally, awareness about frequency of misquotation, probably even the more common problem in the probiotic field than in many other sectors of the biomedical literature [14], should be gained among authors, referees, editors and also readers. By running and reporting RCT of good quality, such as the one by van der Aa and colleagues, and by frank quotation of them, it is possible to avoid hype in the field of probiotics, prebiotics and synbiotics in relation to allergy. Together with modern technologies, such as metagenomics and metabolomics, new enhanced functional foods can be tailored [15] that presumably will convert a hope in the field into actual cures.

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