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REVIEW

# The Role of Probiotics in the Management of Allergic Disease

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**Summary**
Probiotics have recently been advocated for the prevention and treatment of allergic disease (AD). In clinical practice they are increasingly being used for these purposes. Here we review the evidence base for the use of probiotics in the management of AD. We find support for their use in the treatment of childhood eczema, but the clinical significance of any treatment effect is uncertain. There is also evidence to support the use of probiotics in the prevention of childhood eczema. However the available evidence suggests that probiotics are not an effective treatment for allergic airway diseases. Probiotics may be more effective when used early in life, and they may have a particular role in gastrointestinal AD. The relative efficacy of different probiotic strains in the management of AD is not well established, and further work is needed to establish their mechanisms of action. In summary probiotics are likely to play a part in the management of childhood eczema in the future, and further studies are warranted to precisely define their role.

**Keywords** allergic disease, eczema, *Lactobacillus*, probiotic
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## Introduction

Probiotics in the form of *Streptococcus thermophilus* and *Lactobacillus bulgaricus* in fermented milk have been ingested by humans for thousands of years, and fermented milk products have long been believed by some to have health benefits. For example Persian tradition has it that Abraham owed his fertility and longevity to the regular ingestion of yoghurt. In the early 20th century the Russian immunologist Elie Metchnikoff proposed that lactic acid bacilli may have beneficial health effects, and attributed his own longevity to regular ingestion of these. In recent years the belief that ingestion of bacteria may have health benefits has become more widely held, and has undergone increasingly rigorous scientific evaluation. Probiotics have become an important commercial commodity, and the probiotic market continues to grow – for example sales of probiotic products in Australia increased by 22% in 2 years to March 2005 [1]. The efficacy of probiotics in the treatment of gastroenteritis is now well established, and their role in AD is emerging [2]. In the light of recent studies, it is pertinent to review the role of probiotics in the management of AD.

### *Defining probiotics*

Probiotics are best defined as 'live microorganisms which when administered in adequate amounts confer a health benefit on the host' [3]. It is believed by many that the ideal probiotic should remain viable at the level of the intestine and should adhere to the intestinal epithelium in order to confer a significant health benefit. There is some evidence to support this assumption in human studies, with viable bacteria having greater immunological effects than non-viable bacteria [4]. Probiotics must also be resistant to gastric acid digestion and to bile salts in order to reach the intestine intact, and they should be non-pathogenic. Most probiotics are strains of *Bifidobacterium* or *Lactobacillus* species. Some are derived from the intestinal microbiota of healthy humans, others are non-human strains used in the fermentation of dairy products. Species from other bacterial genera such as *Streptococcus*, *Bacillus* and *Enterococcus* have also been used as probiotics, but there are concerns surrounding the safety of such probiotics as these genera contain many pathogenic species, particularly *Enterococcus* [3]. Non-bacterial microorganisms such as yeasts from the genus *Saccharomyces* are also used as probiotics. While the overall safety profile of probiotics is excellent, it should be noted that several case reports describe clinically significant sepsis related to their use, and the potential transfer of antibiotic resistance is also a concern [5]. Sepsis has more commonly occurred in those with gastrointestinal disease or immune compromise [6–9].

## The theoretical basis for using probiotics in allergic disease

### *Microbial Exposures in the Development of allergic disease*

There is evidence from a number of sources to suggest that microbial exposures are important in the development of AD. Reduced exposure to infectious organisms such as helminths and in particular hepatitis A is strongly associated with allergic sensitization [10–12]. Exposure to wild type measles infection has also been correlated with reduced risk of allergic sensitization [13]. Two separate studies have found that early child care is protective against the development of asthma and allergic sensitization, at least in those without an older sibling, and this may reflect exposure to specific or non-specific microbial components [14, 15]. The association of antibiotic use in early life with increased prevalence of allergic sensitization and bronchial hyperactivity may also reflect a more general alteration in microbial load [16]. Both allergic sensitization and allergic rhinitis (AR) are uncommon in those who spend their childhood on a farm [17, 18]. This may reflect increased exposure to specific farm-related organisms, or to less specific bacterial products such as the endotoxin lipopolysaccharide which is present at higher levels in the homes of farm children than other children [19]. While these studies support a role for microbial exposures in protecting against AD, the specific microbes that are important and the underlying mechanisms are not clear. The protective effect of microbial exposures against AD may be greatest in early life, as studies of birth order, of German reunification, and of specific environmental exposures all suggest that the environment in early life strongly affects one's subsequent risk of developing AD [15, 18, 20, 21].

### *The intestinal microbiota – our greatest microbial exposure*

The greatest microbial exposure throughout life, and the newborn infant's first major microbial challenge is the intestinal microbiota. The human intestinal microbiota contains up to 500 species of bacteria, as well as archaea and eukarya, and the bacterial density is particularly high in the large intestine (up to $10^{11}$ colony-forming units (CFU) per gram).

The species composition of the human intestinal microbiota is surprisingly restricted at the division and genus level, although there is considerable strain variation [22]. In adults, the species composition appears to be very stable for a given individual over time [23, 24]. Perhaps for this reason studies of probiotic supplementation in adults have generally not shown persistent changes in the bacterial strain composition of the adult intestinal microbiota [25, 26]. In contrast the newborn microbiota changes rapidly in the first weeks of life and at the time of weaning, and is not thought to reflect adult patterns until 2 years age [27, 28]. The intestinal microbiota of infants may therefore be more amenable to manipulation using probiotic supplementation than the intestinal microbiota of adults, and this concept is supported by clinical studies in humans [29].

### *The intestinal microbiota in allergic disease*

The intestinal microbiota is an important stimulus for both intestinal and immune development. Intestinal microbes promote both intestinal mucosal barrier function and intestinal maturation, and play an important part in host nutrient absorption. They stimulate development of the body's largest collection of lymphoid tissue (the gut associated lymphoid tissue), by providing constant microbial stimulation of local and systemic immune responses via pattern recognition molecules such as toll-like receptors. Studies in mice have demonstrated the importance of the intestinal microbiota for a range of immune functions including Ig production, the development and persistence of oral tolerance to food antigens and the formation of germinal centres within lymphoid follicles [22, 30]. These studies provide circumstantial evidence that alterations in immune stimulation by the intestinal microbiota are important in the development of AD.

Observational studies in humans also support the importance of the intestinal microbiota in immune development, and have found a relationship with the development of AD. Infants with AD have different intestinal microbiota to those without, and importantly the differences in infant microbiota *precede* the development of AD. In particular the numbers and species of *Bifidobacteria* appear to be important biomarkers for healthy microbiota development. In a prospective study children who later developed allergic sensitization to common allergens were shown to have lower numbers of *Bifidobacteria*, increased numbers of *Clostridia* and altered bacterial fatty acid profiles in feces from the first weeks of life [31]. Another prospective study also found that infants who will develop AD have lower levels of *Bifidobacterium* species in their feces from early life [32]. A separate case–control study in older children (age 2–12 years) with eczema found both the presence and severity of eczema to be correlated with lower levels of *Bifidobacterium* species in feces [33]. In addition to having lower numbers of *Bifidobacteria,* children with atopic eczema have also been shown to have altered composition of *Bifidobacteria* as compared with healthy infants – those with eczema have predominantly *B. adolescentis* (a strain more commonly found in adults) in their stools, whereas in healthy age-matched infants *B. bifidum* is more commonly found [34]. The *Bifidobacterium* species of allergic infants also have reduced adhesion to human intestinal mucus, a phenomenon which is likely to alter host–microbe interactions during the first months of life [35]. *In vitro* studies

show that *Bifidobacteria* from allergic infants induce less IL-10 production and more proinflammatory cytokine production than those from non-allergic infants [36]. So there is both observational and mechanistic data to support the importance of the early human intestinal microbiota (in particular the level and composition of intestinal *Bifidobacterium* species) in the development of AD. Interestingly these differences in load and species composition of *Bifidobacteria* may be exclusive to children with eczema, as they have not been found in young children with wheeze and allergic sensitization [37].

## Clinical studies of probiotics in allergic disorders

### *Probiotics for the treatment of allergic disease*

There have been several studies examining the use of probiotics to treat ADs. Eczema is the most widely investigated disease in this respect, and studies of probiotics in the treatment of eczema are summarized in Table 1. Below we describe significant studies of probiotics in the treatment of eczema, food allergy, AR and asthma individually.

*Probiotics for the treatment of atopic eczema*. The first randomized-controlled trial of a probiotic in the treatment of eczema was a study of 27 children aged 2.5–15.7 months with mild/moderate atopic eczema and challenge-confirmed cow's milk allergy [38]. Participants received an extensively hydrolysed whey formula (eHF) with or without *L. rhamnosus* strain GG (American Type Culture Collection (ATCC) 53103; LGG) at $5 \times 10^8$ CFU/g for 1 month. All cow's milk products were also excluded during the study period. Ten of the infants had positive RAST to cow's milk (ie IgE mediated or mixed cow's milk allergy). Median SCORAD scores improved significantly in the LGG-supplemented group (from 26 pre-treatment to 15 at 1 month) but not in the non-LGG-supplemented group (21 pre-treatment, 19 at 1 month). It was not reported whether this greater improvement in SCORAD in LGG- vs. non-LGG supplemented infants reached statistical significance. After a further month continuing to use eHF but without LGG supplementation, both groups had similar median SCORAD scores that were significantly improved from initial scores (16 in the LGG-treated group, 14 in the non-LGG treated group) [38]. In a second randomized-controlled study by the same group 27 exclusively breastfed infants with mild/moderate atopic eczema (median SCORAD 16) were weaned to eHF. The infants were randomized to eHF alone, eHF with *B. lactis* Bb-12 at $1 \times 10^9$ CFU/g and eHF with LGG at $3 \times 10^8$ CFU/g. Two months after weaning to the study formula there was no improvement in the SCORAD score of the non-probiotic treated infants (median SCORAD 10 at baseline, 13.4 at 2 months), but there was significant improvement in the SCORAD scores of both probiotic-treated groups. At 2 months follow-up the *B. lactis* treated group had a median SCORAD score of 0, and the LGG-treated group a median SCORAD score of 1. At 6 months follow-up all

**Table 1.** Probiotics for the treatment of atopic eczema

| Study | Mean Age (Range) | Probiotic (Dose) | Change in SCORAD |
|---|---|---|---|
| **Majamaa and Isolauri** [38] | N/A<br>(2.5–15.7 months) | LGG<br>($5 \times 10^8$ CFU/g in formula) | LGG: 11 points†<br>Placebo: 2 points |
| **Kirjavainen et al.** [40] | 5.5 months<br>(N/A) | LGG<br>($10^9$ CFU/g in formula) | LGG: 14 points‡<br>Placebo: 5 points |
| **Viljanen et al.** [43] | 6.4 months<br>(1.4–11.9 months) | LGG or probiotic mix§<br>($10^{10}$ CFU/day) | LGG: 16.6 points<br>Mix: 14 points<br>Placebo: 14.2 points |
| **Rosenfeldt et al.** [41] | 5.2 years<br>(1–13 years) | L.rhamnosus 19070-2<br>L.reuteri DSM12246<br>($2 \times 10^{10}$ CFU/day) | Probiotic: 4 points<br>Placebo: 0 points |
| **Weston et al.** [45] | 3.7 months<br>(6–18 months) | L.fermentum VRI-003 PCC<br>($2 \times 10^9$ CFU/day) | Probiotic: 16 points*<br>Placebo: 8.7 points |
| **Isolauri et al.** [39] | 4.6 months<br>(N/A) | LGG or B.lactis Bb12<br>($3 \times 10^8$ cfu/g or $10^9$ CFU/g in formula) | SCORAD after 2 months treatment<br>Placebo: 13.4<br>LGG: 1†<br>*B.lactis*: 0† |

*$P < 0.05$.

†$P < 0.01$ for improvement in eczema score in actively treated group over time.

‡$P < 0.05$ for greater improvement in eczema score in treatment compared to placebo group.

§Probiotic mix = $5 \times 10^9$ CFU LGG, $5 \times 10^9$ CFU *Lactobacillus rhamnosus* LC705, $2 \times 10^8$ CFU *Bifidobacterium breve* Bbi99 and $2 \times 10^9$ CFU *Propionibacterium freudenreichii* ssp. *shermanii* JS given twice daily.

CFU, colony-forming units.

 

three groups had similar improvement in SCORAD score, with an overall median SCORAD score of 0 [39]. Both this study and the previous work by the same authors suggest that probiotic supplementation leads to acceleration in the improvement of infant atopic eczema seen with conventional management. Moreover such supplementation may only be required in the short term. In their most recent study this group investigated viable and heat-killed LGG preparations in the treatment of 35 infants with atopic dermatitis and suspected cow's milk allergy [40]. Ten of the 25 infants in this study who underwent formal challenge were found not to be allergic to cow's milk. All infants were changed to eHF at entry to the study, and were randomized to three groups. A 'viable' group had eHF supplemented with LGG at $1 \times 10^9$ CFU/g, a 'non-viable' group had eHF supplemented with heat inactivated LGG at the same concentration, and a 'placebo' group had no LGG added. The study was terminated early because of adverse gastrointestinal effects in the 'non-viable' group. Perhaps for this reason the length of treatment varied from less than a week to over 10 months, although most infants were treated for a period of several weeks. There was significantly greater reduction in SCORAD score in the 'viable' group than in the placebo group (mean 14- point vs. 5-point reduction, $P = 0.02$). Given the premature termination of this study and the great variation in length of treatment conclusions from this investigation must be guarded, but it again suggests a role for probiotics in the treatment of infant eczema.

In a study by a second group using different probiotics, 43 children aged 1 to 13 years with moderate/severe atopic eczema took part in a randomized placebo-controlled crossover trial [41]. Participants were given *L. rhamnosus* 19070–2 and *L. reuteri* DSM12246 at a dose of $10^{10}$ CFU each twice daily, or placebo. Each treatment was given for 6 weeks, with a 6-week washout period in between. Fifty-six percent of participants or their parents felt that the eczema had improved after the combined probiotic treatment, but only 15% reported improvement after placebo treatment ($P = 0.01$). The mean SCORAD score improved from 35.6 to 31.6 ($P = 0.06$) after probiotic treatment, but did not improve after placebo treatment. In a subgroup analysis the authors found that the relative improvement in SCORAD score was greater in those children with an allergic diathesis, (defined by raised total IgE and a positive skin prick test (SPT), or a history of IgE mediated food allergy, allergic rhinoconjunctivitis or asthma). However this improvement of 2.4 points (vs. a worsening of 3.2 points in the placebo group; $P = 0.04$) is of only minor clinical significance. They make the point that studies such as this should ideally investigate a well-defined age group. There are several possible explanations for the reduced efficacy of probiotics in this study. First, the probiotics were administered in water rather than in milk or with food, and this may increase their susceptibility to gastric acid digestion and reduce the numbers of viable bacteria reaching the intestine. Fecal recovery rates of probiotic bacteria were not reported in this study. Second, there was a wide age range (1–13 years) included in this study – it may be that the more stable intestinal microbiota of older children and adults makes them less susceptible to the treatment effects of probiotics than young infants. Third, the participants in this study were both older and had more severe eczema than those in the studies of Isolauri and Majamaa. These studies of infant eczema found significant improvement in eczema in placebo-treated groups as well as probiotic-treated groups, with the main benefit of probiotics being to accelerate the improvement in eczema seen with conventional management. Rosenfeldt's study population was quite different – older children with more severe eczema are less likely to improve spontaneously, and although gastrointestinal symptoms were common in this study, food allergy with associated intestinal inflammation less commonly plays a significant part in eczema in this age group [42]. Finally the probiotics used in this study may be antagonistic to each other, reducing their potency, or may have reduced efficacy compared with those used in other studies.

In the largest randomized double-blind placebo-controlled study of probiotics in eczema treatment to date, Viljanen et al. treated 230 infants with moderate/severe eczema with either $5 \times 10^9$ CFU LGG, a probiotic mixture ($5 \times 10^9$ CFU LGG, $5 \times 10^9$ CFU *L. rhamnosus* LC705, $2 \times 10^8$ CFU *B. breve* Bbi99 and $2 \times 10^9$ CFU *Propionibacterium freudenreichii* ssp. *shermanii* JS) or cellulose placebo, in each case mixed with food twice daily [43]. One hundred and twenty of these infants had challenge-proven cow's milk allergy. Interestingly *before* randomization LGG was detected using culture-based methods at a level of at least $10^3$ CFU/g feces in the stools of 11 of 52 infants analysed. This was despite the exclusion of infants who had been reported to receive probiotics for more than 1 week at a time within 6 weeks of enrolment in the study. This may reflect the high use of LGG products in Finland [44]. Infants were treated for 4 weeks, and SCORAD assessed at the beginning and end of this period, and again 4 weeks after treatment finished. Disappointingly there was no significant difference in the change in SCORAD score between the probiotic groups and placebo group. However a subgroup analysis of those sensitized to at least one allergen did find a greater improvement in the LGG group (but not the probiotic mix group) compared with placebo at 8-week follow-up (mean SCORAD improvement 26.1 points in the LGG group, 19.8 points in the placebo group; $P = 0.036$). In a further subgroup analysis the authors excluded all infants who had received antibiotics during the study, as almost 30% of infants received antibiotics during the 8-week study period and this may interfere with probiotic effects on the infant

intestine. In this analysis those infants with atopic eczema and evidence of allergic sensitization again responded better to LGG than to placebo (mean SCORAD improvement 38.4 points LGG vs. 28.5 points placebo; $P = 0.008$). Again this treatment effect was not noted for those infants treated with a mix containing LGG and other probiotics, suggesting a detrimental interaction between the particular probiotics present in this mix. It is interesting that this study replicates Rosenfeldt's finding that those children with allergic sensitization benefit most from probiotic treatment of their eczema. One possible explanation for the small treatment effect of LGG in this study is the large overall benefit from inclusion in the study, with placebo-treated infants having a mean reduction in SCORAD score of 20.3 points over the first 4 weeks of the study. This may be attributable to concomitant cow's milk exclusion and optimum topical treatment during the study. A second possible explanation is the high prevalence of LGG present in infant stools at the commencement of the study. This reduces the power of the study to detect an LGG-related benefit in eczema severity.

The most recent study of probiotics in the treatment of eczema was a randomized double-blind placebo-controlled trial of $1 \times 10^9$ CFU *L. fermentum* VRI-003 PCC or maltodextran placebo twice daily for 8 weeks [45]. Fifty-six infants with moderate or severe eczema (modified SCORAD at least 25) were enrolled. At 16 week follow-up the probiotic treated children had a significant improvement in SCORAD score, and the placebo treated group had a non-significant improvement in SCORAD score (median improvement 17 and 12 points, respectively). Ninety-two per cent of probiotic treated children had an improvement in SCORAD score over the 16-week period, but only 63% of placebo treated children ($P = 0.01$). However there was no significant improvement in parental perception of eczema or in impact of eczema on the family, no difference in topical corticosteroid use, and no significant difference in reduction in SCORAD score between treatment and placebo groups. As with some previous studies, the power of this study to detect clinically significant improvements in probiotic treated infants may have been reduced by both the improvement in SCORAD score in the placebo-treated infants, and by the small number of study participants. While no single study has shown a clearcut role for probiotics in treating eczema, all studies described at least show a trend to a beneficial effect or a benefit in certain subgroups. This therefore represents an important area for further study.

*Probiotics for the treatment of food allergy.* Probiotics have been studied in the treatment of eczema where patients also have food allergy (e.g. [38]), but a specific effect of probiotics promoting resolution of food allergy has not been investigated. Nevertheless there is mechanistic data to suggest that probiotics may have a role in the treatment of food allergy. For example Majamaa et al. found LGG supplementation of eHF to reduce fecal α-1antitrypsin levels and fecal TNF-α levels, suggesting a beneficial effect on intestinal inflammation and integrity [38]. In a placebo-controlled study of cow's milk allergic adults, LGG supplementation of cow's milk (at $2.6 \times 10^8$ CFU/day) during challenge was found to prevent the increase in expression of phagocytosis receptors seen in those challenged with unsupplemented cow's milk [46]. Finally in the crossover study by Rosenfeldt et al described above probiotic treatment of children aged 1–13 for 6 weeks reduced the number with gastrointestinal symptoms such as diarrhoea and abdominal pain (39% had symptoms during the last 2 weeks of placebo treatment; 10% during the last 2 weeks of probiotic treatment, $P = 0.02$), and led to a decrease in intestinal permeability [47]. These gastrointestinal symptoms may relate to food allergies as food allergies are common in those with atopic eczema [42]. So one might propose that probiotics can reduce food allergy symptoms by reducing systemic exposure to allergenic foods as a result of reduced intestinal permeability. However this hypothesis remains to be formally tested.

*Probiotics for the treatment of allergic rhinitis.* The first randomized double-blind placebo-controlled study of probiotics in the treatment of AR evaluated 33 adults and adolescents with birch pollen allergy, as defined by a positive SPT to birch pollen, no other pollen allergy and symptoms of seasonal rhinoconjunctivitis +/− asthma. All participants also had symptoms suggestive of the oral allergy syndrome in relation to apple. Participants took $10^{10}$ CFU LGG twice daily or placebo for 5.5 months. The treatment commenced 2.5 months before and finished 2 months after one birch pollen season. Outcome measures were symptom and medication diaries, and open apple challenges before, during and after the pollen season [48]. There was no benefit shown in any outcome measure from LGG supplementation, and no significant trend in favour of a benefit. The authors therefore felt it unlikely that a larger study would have revealed a significant treatment benefit. In a second study Wang et al. treated children over 5 years age (median age 15.8 years) with AR and house dust mite sensitization in a randomized controlled trial. Eighty participants were randomized to receive 200–400 mL daily of fermented milk containing *S. thermophilus* and *L. bulgaricus* (placebo group), or the same formula with *L. paracasei-33* added at $1 \times 10^7$ CFU/mL (probiotic group) for 30 days [49]. In both groups there was a significant improvement in a number of parameters on a modified Paediatric Rhinoconjunctivitis Quality-of-Life Questionnaire score. The improvement in 3 parameters of the score was greater in the probiotic supplemented group, however this increased treatment effect was entirely accounted for by

 

higher scores in the probiotic group at baseline; scores in the probiotic and placebo groups were very similar at the end of the treatment period. The implication of this study is that *L. paracasei-33* is not effective in the treatment of AR, but the study's power to detect a treatment effect may have been reduced by including the probiotics *S. thermophilus* and *L. bulgaricus* in the placebo group. In fact the design of this study must be strongly questioned given the previous suggestion that regular ingestion of yoghurt containing *S. thermophilus* and *L. bulgaricus* for a year may improve nasal allergy symptoms in adults [50]. In this latter study Trapp et al treated 80 adults in a randomized-controlled trial of live vs. heat killed *S. thermophilus* and *L. bulgaricus* (at unspecified levels) taken in 200 g yoghurt daily for 1 year. They also included a non-blinded placebo group who consumed no yoghurt. Overall 80% of participants were successfully retained in the study to 1 year, and they completed a health questionnaire each week. There were reduced levels of self-reported nasal allergy symptoms in those consuming live yoghurt compared with those consuming heat-killed yoghurt. There was no *a priori* hypothesis in this study regarding effects on allergic symptoms however, and nasal allergy symptoms were one of over 40 parameters compared between groups. The details of nasal allergy questionnaires are not described, and no analysis is made of possible confounding factors such as an imbalance of nasal allergies in the randomized groups at recruitment [50]. In what appears to be a repeat publication of part of the same study, Van der Water et al. report treating 60 healthy adults in a placebo-controlled trial. Twenty took 200 g live yoghurt daily for a year, 20 took 200 g pasteurised yoghurt and 20 refrained from ingesting fermented milk products for the year. They again report a decrease in nasal allergy symptoms in the live yoghurt-treated group but the report suffers the same methodological deficits as the original publication [51]. Overall the studies of probiotic in the treatment of AR are conflicting, but the best-designed study to date suggests that probiotics are ineffective in the treatment of this condition [48].

*Probiotics for the treatment of asthma.* In a randomized controlled crossover trial Wheeler et al. studied the use of probiotics to treat 15 adolescents and adults with asthma who were sensitized to inhalant allergens [52]. Placebo treatment was 450 g yoghurt daily containing *S. thermophilus* $3.4 \times 10^8$ CFU/g and *L. bulgaricus* $3.2 \times 10^8$ CFU/g for 1 month; active treatment was the same yoghurt with *L. acidophilus* added at $7.6 \times 10^8$ CFU/g for 1 month. There was a washout period of 4 weeks between treatments. They found no significant difference in clinical parameters of asthma control, nor in laboratory markers of inflammation between the two treatments. Again one might argue that the use of a probiotic preparation as a placebo risked a positive effect in both groups, but neither active treatment nor placebo led to any improvement in lung function. There is therefore no evidence at present to suggest a role for probiotics in the treatment of asthma.

### Probiotics for the prevention of allergic disease

The use of probiotics in the prevention of AD has not been widely investigated to date, although a number of studies are currently underway. The first randomized placebo-controlled prevention study was a trial of LGG in the primary prevention of AD. One hundred and fifty-nine pregnant women were recruited with a history of AR, asthma or atopic eczema in themselves, their partner or a previous child. They received $2 \times 10^{10}$ CFU of LGG daily for the last 2–4 weeks of pregnancy, and then continued postnatally. Postnatally those mothers who were breastfeeding continued to take the same dose themselves, and those who formula fed their infants gave a lower dose of $1 \times 10^{10}$ CFU daily directly to their infants. The supplementation was continued in all cases until 6 months postnatal age [53]. One hundred and thirty-two of the 159 study participants completed the study to 2 years, and 107 (67%) to 4 years. There was a 50% reduction in chronic relapsing atopic eczema at 2 year follow-up, with 4.5 (95% confidence interval 2.6–15.6) mothers needing to be treated to avoid one child developing eczema. At 4-year follow-up there was a 43% reduction in the risk of chronic relapsing eczema in the treatment group, no difference in the rate of atopic sensitization, but a reduction in exhaled nitric oxide production (from 14.5 to 10.8 p.p.b) suggesting a reduction in airway inflammation. However, a direct effect on the development of AR or asthma was not shown [54]. Subgroup analysis showed the reduction in risk of eczema to be greatest in breastfed infants who did not receive the supplement directly postnatally (the supplement was given to their mothers postnatally) for at least the first 3 months of life. In an analysis of the 57 such infants followed to 2 years there was a 68% reduction in the risk of chronic relapsing atopic eczema in the treatment group compared with the placebo group [55]. One can therefore deduce that there was a 34% relative risk reduction for the infants who received LGG directly (rather than via maternal supplementation and breastfeeding) in the postnatal period, with 11 of 37 developing eczema in the first 2 years of life, compared with 17 of 38 infants receiving placebo directly. So the relative risk reduction for breastfed babies who's mother received LGG was twice that of formula fed babies receiving LGG directly. Some tentative conclusions may be drawn from this small study. First that a combined regimen of pre- and postnatal supplementation with LGG may offer the potential of a simple preventive measure against atopic eczema in high-risk families. Second that direct supplementation of the infant postnatally may not be

 

necessary for the preventive effect of LGG. Third that the effect of LGG supplementation may be enhanced by exclusive breastfeeding for the first 3 months of life, as the protective effect of LGG over placebo was greatest in the breastfeeding group (relative risk reduction 68% breastfeeding group; 34% formula feeding group). The mechanisms through which LGG might act in preventing eczema are not clear, although the authors have shown an increase in breast milk TGF-β2 levels in those women who received LGG while breastfeeding compared with placebo-treated breastfeeding mothers [55]. TGF-β is an important regulatory cytokine which has been shown to suppress some forms of intestinal inflammation, so the increased levels in breast milk in this study may have led to the down-regulation of intestinal allergic inflammation [56]. In contrast it should be noted that eczema treatment studies have suggested LGG may act by *inducing* inflammation – these conflicting results suggest that the mechanisms of action of probiotics merit further study [57].

## Conclusions

There is strong evidence that probiotics are effective in the treatment and prevention of a number of non-allergic conditions. These include the prevention of flares of chronic pouchitis in those with inflammatory bowel disease, the treatment of infective diarrhoea and the prevention of antibiotic-associated diarrhoea [2, 58, 59]. We have found evidence to support their efficacy in treating eczema in children, however the effect size seen in treatment studies may not be of great clinical significance. Further studies are needed to clarify their role in eczema treatment. The limited data available regarding probiotics in the prevention of eczema suggests a clinically significant benefit, and a number of ongoing studies are exploring their potential in this regard. Probiotic treatment can also lead to improvements in markers of intestinal inflammation and permeability in infants with atopic eczema, suggesting that it may hasten the resolution of food-allergic disorders. This again warrants further study. However the studies suggest that probiotics do not have a role in the treatment of allergic airway diseases such as rhinoconjunctivitis and asthma. This is consistent with recent findings that probiotic supplementation can protect infants attending childcare against episodes of diarrhoeal illness and fever, but does not protect against respiratory illness [60]. The effects of probiotic supplementation are likely to be most marked in gastrointestinal disorders, or in related allergic diseases such as atopic eczema associated with food allergy. The heterogeneity of probiotic studies hampers interpretation – in particular the diversity of probiotic strains, dosing regimens and forms of administration used and the varied patient groups recruited in the available studies makes interpretation difficult. Moreover our understanding of the immunological and microbiological mechanisms of probiotic actions is limited at this time. In summary probiotics are promising agents for the control and prevention of allergic disease. Given the relative instability of the composition of the infant intestinal microbiota, and the importance of food allergy in infants with atopic eczema, the role of probiotics in AD treatment may be limited to eczema and food allergy in young children. However the role of probiotics in *preventing* AD may be wider than this. They are likely to have an important place in the management of AD in the future, and further studies are clearly warranted to better define their role.

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