The worldwide prevalence of allergic diseases such as asthma, eczema, food allergy and allergic rhinitis has increased considerably in the past few decades.\(^1,2\) The hygiene hypothesis suggests that this rise is associated with reduced microbial exposure during early life, leading to aberrant intestinal microbiota and subsequent immune dysregulation.\(^3\) It is believed that Western life-style factors such as small family size, increased antibiotic usage, vaccination and improved hygiene have all contributed to this reduced microbial exposure.\(^3\) The most important post-natal source of microbial stimulation comes from the gastrointestinal microbiota, which plays a vital role in immune regulation as well as in the induction and maintenance of immune tolerance to food and self-antigens. Differences in the intestinal microbiota have been reported in individuals living in countries with high and low prevalence of allergic diseases\(^3,4\) and between allergic and non-allergic children.\(^5,6\) Infants with eczema are more often colonised with an adult-type *Bifidobacterium*, *B. adolescentis*, while infant-type species such as *B. longum* (including *B. longum* biotypes *infantis* and *longum*, and *B. bifidum*) and *B. breve* are most abundant in non-atopic infants.\(^7,8\) Moreover, these differences were observed prior to the onset of disease,\(^4,5,9\) suggesting that a healthy intestinal microbiota is crucial for normal development of the immune system. Manipulation of the intestinal microbiota during infancy offers an attractive approach for management of allergic disease. Probiotics can modulate early development of intestinal microbiota\(^10,11\) and have been proposed for the prevention or treatment of allergic disorders. Here, the clinical effects of probiotics in the treatment and prevention of allergic disease are reviewed.

### Definition of Probiotics, Prebiotics and Synbiotics

Probiotics are defined as ‘live microorganisms that, when administered in adequate amounts, confer a health benefit on the host’.\(^1,2\) The most widely used probiotic bacteria are from the
genera *Lactobacillus* and *Bifidobacterium*. Probiotics are defined as 'a selectively fermented ingredient that allows specific changes, both in the composition and/or activity in the gastrointestinal microbiota that confers benefits upon host wellbeing and health'. The term 'symbiotic' refers to a combination of probiotics and prebiotics.

**Probiotics for the Treatment of Allergic Disease**

**Atopic dermatitis or eczema**

Eczema is frequently the first manifestation of allergic disease in infancy, and most studies evaluating probiotics have focused on eczema as the primary outcome measure. *Lactobacillus* species, either alone or in combination with other probiotic bacteria, and *Bifidobacterium* species are the most common probiotics that have been evaluated in the treatment of eczema. Initial small studies using *L. rhamnosus* GG (LGG) or *B. lactis* Bb-12 for 4–8 weeks have reported eczema improvement (SCORAD or SCORAD i) with fructo-oligosaccharide for 8 weeks showed a greater reduction in SCORAD than the placebo group (33.7% vs. 19.4%, P = 0.03), although the difference between the two groups did not reach statistical significance (P = 0.06).

However, more recent and/or larger trials have failed to confirm beneficial effects of probiotics for the treatment of eczema. Interestingly, in three studies, subgroup analyses revealed improvements in SCORAD following probiotic treatment in children with atopy (increased IgE levels), and in combination with probiotic but not those treated with placebo (P = 0.03), making the interpretation of results difficult; however, this magnitude of effect is of uncertain clinical significance. The combination of *L. rhamnosus* LC705, *B. breve* BB99 and *Propionibacterium freudenreichii* spp. *shermanii* JS given to infants with IgE-associated eczema had no effect on SCORAD.

Nevertheless, promising results were observed in the two most recent studies evaluating probiotic and/or prebiotic preparations. One study in 90 children aged 1–3 years with moderate to severe eczema who were randomised to receive a probiotic/prebiotic mixture (*L. acidophilus* DDS-1 and *B. lactis* UABLA-12 with fructo-oligosaccharide) for 8 weeks showed a greater reduction in SCORAD than the placebo group (33.7% vs. 19.4%, P = 0.001). In another study, a 12-week treatment with *L. sakei* KCTC 10755BP given to 88 children aged 2–10 years with eczema demonstrated a significantly lower pretreatment-adjusted SCORAD (P = 0.01) and improved mean disease activity (31% vs. 13%, P = 0.008) compared with the placebo-treated group.

Three small studies investigated the effect of probiotic treatments on eczema in adults. A crossover study by Roessler et al. reported a trend towards reduced SCORAD (15.5%) in 15 adults with eczema treated with a probiotic combination containing *L. paracasei* Lpc-37, *B. animalis* subsp. *lactis* DGCC 420 and *L. acidophilus* 74-2, but this change was not significantly different to that observed in the placebo-treated group. Similarly, Matsumoto et al. studied the effect of a probiotic yoghurt containing *B. animalis* subsp. *lactis* LKM512 in 10 adults with moderate eczema and reported no significant difference in the number of symptoms with subjective improvement compared with placebo. It is of note that these patients were also receiving Japanese traditional herbal medicines during the study period, making the interpretation of results difficult. In contrast, 34 adults with eczema treated with heat-killed *L. paracasei* K71 had a significant reduction in skin scores compared with the placebo treatment.

Systematic reviews and meta-analyses of studies evaluating the use of probiotics for the treatment of eczema have concluded that there is insufficient evidence to support their use in the treatment of this condition. Our Cochrane systematic review, which included 12 studies but not the recent adult studies by Roessler et al. and Matsumoto et al., found no significant reduction in eczema symptoms with probiotic treatment compared with placebo. Subgroup analysis by eczema severity or presence of atopy did not identify a specific population in which probiotic treatment was effective. A recent meta-analysis by Michail et al. reported a significant reduction in SCORAD by probiotics (mean change from baseline −3.01; 95% confidence interval: −5.36 to −0.66; P = 0.01), and children with moderately severe disease were more likely to benefit; however, this magnitude of effect is of uncertain clinical significance.

Topical application of probiotic *Vitreoscilla filiformis* lysate cream was recently reported to significantly reduce SCORAD and pruritus compared with placebo, as well as minimising loss of sleep compared with the start of treatment. Future studies evaluating topical approaches would be of interest.

Overall, the role of probiotics in the treatment of eczema remains controversial. Trials that recruited older children and adults generally demonstrated minimal or no beneficial effects. Significant heterogeneity exists between studies, which may be explained by the use of different probiotic strains. Therefore, lack of effect based on pooled data from different probiotics does not exclude the possibility that a certain strain or strain combination could still be effective.

**Food allergy**

Induction and maintenance of oral tolerance to food antigens during infancy is critical for normal immune system development. Available data suggest that probiotics may have a role in the treatment of food allergy by maintaining the intestinal epithelial barrier integrity, suppressing intestinal inflammatory responses and inducing mucosal IgA production and tolerogenic immune responses. However, evidence that probiotics can induce tolerance in the clinical setting is currently lacking. A study of 119 infants with challenge-confirmed cows milk allergy found no effect of *L. casei* CRL431 and *B. lactis* Bb-12 supplementation for 12 months on the acquisition of cows milk tolerance. In children sensitised to egg, peanut or cows milk with clinical symptoms, treatment with a probiotic mix (predominantly *Lactobacillus* spp. and *Bifidobacterium* spp.) for 3 months failed to influence sensitisation or *ex vivo* immune responses.
Taken together, current evidence indicates that probiotic treatment does not modify the natural course of food allergy.

**Allergic rhinitis and asthma**

Published randomised control trials (RCTs) evaluating the role of probiotics in the treatment of allergic rhinitis and asthma provide conflicting results. Several double-blind placebo-controlled (DBPC) studies reported improved quality-of-life scores following treatment with *L. paracasei* 33 or *Bacillus clausii* in adolescents with allergic rhinitis.50–58 Such an effect was not observed in children given *Tetragenococcus halophilus* Th221 or a combination of *L. acidophilus* NCFM and *B. lactis* Bl-04.39,40 Despite *L. acidophilus* NCFM/B. lactis Bl-04 reducing eosinophil infiltration into the nasal mucosa,50 Adults with Japanese cedar pollen seasonal allergic rhinitis treated with *B. longum* BB536, *L. casei* strain Shirotai, *L. acidophilus* L-92 or a fermented milk containing LGG and *L. gasseri* TMC1551 did not show any clinical benefit,41–44 although other studies reported improved nasal blockage,44 nasal symptom–medication scores,44 eye symptoms45 or eye symptom–medication scores.45 Nevertheless, three recent studies have reported encouraging results. In adults with allergic rhinitis, supplementation with *L. acidophilus* strain L-92 resulted in significantly improved nasal symptom–medication scores.45 Short-term treatment with *L. paracasei* ST11 also demonstrated improved nasal symptoms in adults with allergic rhinitis and was associated with downregulation of interleukin-5 and Immunoglobulin G4.46 Similarly, a significant improvement in ocular symptom–medication score was observed in adults with allergic rhinitis following *L. plantarum* No.14 treatment.47 Several DBPC studies have included mixed patient populations of children and/or adults with allergic rhinitis and/or asthma rather than either condition alone. No beneficial effects were found in children with allergic asthma and/or allergic rhinitis treated with *L. casei*.48 Likewise, young adults and teenagers with birch pollen allergy and oral allergy syndrome with or without asthma treated with LGG demonstrated no improvement in oral allergy and lung symptoms.49 However, a recent study of 105 school children with asthma and allergic rhinitis had significantly reduced clinical symptoms and improved pulmonary function and peak expiratory flow rate (PEFR) following *L. gasseri* treatment, with significant reductions in production of tumor necrosis factor-α, interferon-γ, interleukin-12 and interleukin-13.50

Only a few studies have evaluated the role of probiotics in the treatment of asthma. A crossover study of 15 adults with moderate asthma had no beneficial effects on clinical parameters following consumption of *L. acidophilus*.31 Treatment with non-pathogenic *Enterococcus faecalis* in children with intermittent or mild persistent asthma also showed no improvement in FEV1, quality of life or use of rescue medication.32 In addition, in adults with allergic asthma, treatment with *B. breve* M-16V and a probiotic mixture (galacto-oligosaccharides and fructo-oligosaccharides) did not modulate bronchial inflammation or lung function, despite reduced IL-5 and improved PEFR.33 Probiotics for the treatment of allergic rhinitis and asthma have produced inconsistent results. There is currently insufficient evidence to suggest a role for probiotics in the treatment of allergic rhinitis and asthma.

**Probiotics for the Prevention of Allergic Disease**

To date, 14 RCTs evaluating various probiotic bacteria, alone or in combination with other probiotics (and also prebiotics in one study), have been published (summarised in Table 1).54–67 Nine studies involved combined pre-natal (last 2–6 weeks of pregnancy) and post-natal (6–24 months) treatments.54–61,65 Four studies evaluated post-natal-only therapy62–66 and one study investigated pre-natal therapy alone.67

Of the nine combined pre-natal and post-natal studies (evaluating 10 interventions), eight assessed various probiotic interventions34,35,57–61,65 and one assessed a symbiotic intervention.56 All except two studies recruited pregnant mothers carrying children at increased risk for allergy (first-degree relative with allergic disease), while the studies by Huurre et al.58 and Dotterud et al.60 recruited an unselected population of mothers. Six of the nine studies reported a significantly reduced cumulative incidence of eczema,54,60,64 IgE-associated eczema57 or both56,57 during the first 2 years of life, while the remaining three studies demonstrated no beneficial effects on these parameters.58,59,65 One treatment led to a reduced cumulative incidence of parent-reported and doctor-diagnosed eczema at age 3 months but not at 1 or 2 years of age.59 Apart from two studies,55,58 the majority of combined pre- and post-natal treatments failed to modify infant sensitisation. Treatment with *L. reuteri*59 or a combination of *B. lactis* BB12/LGG58 significantly reduced sensitisation in infants. Five studies also evaluated other allergic disease outcomes such as recurrent wheeze, asthma, allergic rhinitis and food allergy. Kukkonen et al.56 found no effect on the cumulative incidence of all allergic diseases or atopic sensitisation with a synbiotic treatment. Similarly, no differences in asthma or allergic rhinitis at age 2 years were reported by Dotterud et al.60 In contrast, Kopp et al.58 demonstrated an almost threefold increased risk of recurrent wheezing bronchitis at age 2 years following pre-natal/post-natal LGG treatment. A trend to increased respiratory allergic disease at age 7 years following combined pre-natal/post-natal LGG was reported by Kalliomaki et al., although the beneficial effect on eczema persisted.56 Additional data on asthma and allergic rhinitis outcomes will become available as further follow-up analyses from the above studies have been concluded.

Three of the four post-natal treatments demonstrated no beneficial effects on eczema, IgE-associated eczema or sensitisation at 12 months.62–64 Rather, treatment with *L. acidophilus* LAVRI-A1 was associated with an increased risk of IgE-associated eczema and atopic sensitisation at 1 year of age.62 One study, however, reported a reduced cumulative incidence of eczema at 13 months following post-natal treatment with *L. paracasei* F19 during weaning (4–13 months of age).66 Again, a mixture of study designs was noted, with two studies recruiting high-risk infants with a family history of atopic disease,62,64 while the other two studies included formula-fed infants irrespective of allergic disease family history.55,56 Findings from these four studies suggest that post-natal treatment alone may be insufficient to reduce the risk of allergic disease in high-risk infants. It is also possible that the lack of effect observed with post-natal probiotic supplementation studies relates to the administration of probiotic directly to the infant rather than to


<table>
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<tr>
<th>Study</th>
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<tr>
<td>Kalliomaki et al. 2001</td>
<td>132 infants with at least one first-degree relative with allergic disease</td>
<td>2 groups: LGG (1 x 10^10 CFU/day) or placebo</td>
<td>Reduction in eczema (OR 0.74, ( P = 0.01 )) and IgE-associated eczema (OR 0.66, ( P = 0.008 )).</td>
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<td>Kukkonen et al. 2007</td>
<td>195 infants with at least one first-degree relative with allergic disease</td>
<td>2 groups: prebiotic mixture + probiotic mixture daily to mothers and daily to infants or placebo</td>
<td>Reduction in eczema (hazard ratio 0.51, ( P = 0.013 )) at 2 years; no difference in other allergic disease or sensitisation. Subgroup analysis: less sensitisation in infants of allergic mothers.</td>
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<tr>
<td>Abrahamsson et al. 2005</td>
<td>101 infants with at least one first-degree relative with allergic disease</td>
<td>3 groups: ATCC 55730 (1 x 10^9 CFU/day) or placebo</td>
<td>No effect on eczema at 1 year; higher sensitisation rate in LGG group.</td>
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<tr>
<td>Kopp et al. 2008</td>
<td>140 infants with at least one first-degree relative with allergic disease</td>
<td>2 groups: a mixture of probiotics (LGG, B. lactis Bb12, each 1 x 10^9 CFU/day) or placebo</td>
<td>Reduction in eczema at 1 year (36.4% vs. 62.9%, ( P = 0.029 )); no difference in total IgE or sensitisation.</td>
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<tr>
<td>Wickens et al. 2009</td>
<td>278 infants with at least one first-degree relative with allergic disease</td>
<td>2 groups: a mixture of probiotics (LGG, L. acidophilus LA-5 and Bb12, each 10^7 CFU/day), L. acidophilus AD031, each 10^10 CFU/day) or placebo</td>
<td>Reduction in eczema at 13 months (111% vs. 22%, ( P &gt; 0.05 )); no effect on sensitisation.</td>
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<td>Rautava et al. 2009</td>
<td>178 infants with atopic mothers</td>
<td>2 groups: infant formula with LGG and infant cereal with AD031, each 10^9 CFU/day) or placebo</td>
<td>No effect on eczema, IgE-associated eczema and sensitisation at 1 year.</td>
</tr>
<tr>
<td>Soh et al. 2009</td>
<td>245 infants with at least one first-degree relative with allergic disease</td>
<td>2 groups: infant formula with LL24, each 10^9 CFU/day) or placebo</td>
<td>Reduction in eczema at 1 year (57% vs. 62%, ( P = 0.03 )); no difference in total IgE or sensitisation.</td>
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<tr>
<td>Kim et al. 2010</td>
<td>68 infants with at least one first-degree relative with allergic disease</td>
<td>2 groups: infant formula with LGG and infant cereal with Propionibacterium freudenreichii BL999, each 10^7 CFU/day) or placebo</td>
<td>Reduction in eczema at 1 year (36.4% vs. 62.9%, ( P = 0.029 )); no difference in total IgE or sensitisation.</td>
</tr>
<tr>
<td>Wulff et al. 2010</td>
<td>46 infants with at least one first-degree relative with allergic disease</td>
<td>2 groups: LGG (1 x 10^10 CFU/day) or placebo</td>
<td>Reduction in eczema and sensitisation at 1 year after 3 months.</td>
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<td>Nors et al. 2009</td>
<td>96 infants with at least one first-degree relative with allergic disease</td>
<td>2 groups: prebiotic mixture + probiotic mixture daily to mothers and daily to infants or placebo</td>
<td>Reduction in parent-reported eczema during the first 3 months, but similar in both groups after 3 months.</td>
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<tr>
<td>Boyle et al. 2011</td>
<td>212 infants with at least one first-degree relative with allergic disease</td>
<td>2 groups: prebiotic mixture + probiotic mixture daily to mothers and daily to infants or placebo</td>
<td>No effect on eczema or sensitisation at 1 year.</td>
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the breastfeeding mother. Nevertheless, the study by West et al. reported beneficial effects with post-natal probiotic administration direct to infants during weaning.66

We have recently reported the only study evaluating pre-natal (without post-natal) probiotic treatment for the prevention of eczema and showed that pre-natal LGG administered to mothers in the last 4 weeks of pregnancy provided no beneficial effect on the cumulative incidence of eczema or infant sensitisation at 12 months.67 These findings, together with those by Kopp et al.63 and Kalliomaki et al.,64 suggest that post-natal therapy may also be required or that LGG may not be effective for prevention of eczema in some populations.

Importantly, the cumulative findings from these studies suggest that the most profound effects were observed in breastfed infants in whom probiotics were administered to their mother during pregnancy and breastfeeding, without direct infant supplementation.68 When LGG was given to pregnant mothers 2–4 weeks before delivery and post-natally for 6 months, the greatest effect was observed in the subgroup of breastfed, compared with formula-fed, infants.69 These beneficial effects may be related to increased breast milk transforming growth factor β2 levels in breastfeeding mothers treated with LGG.70 Taken together, these findings indicate that direct infant probiotic supplementation in early life may not be an absolute requirement for protective effects. Another key consideration is the important concept of species and strain specificity. Wickens et al.71 evaluated two different probiotic treatments and found that L. rhamnosus HN001 reduced eczema at age 2 years, while B. animalis subsp. lactis HN019 did not. Furthermore, the immune mechanisms responsible for beneficial clinical effects remain poorly understood.72

Gene–environment interactions are important factors influencing probiotic effects. Kopp et al.63 evaluated pre-natal and post-natal LGG treatment using the same dose and a similar protocol to the original study by Kalliomaki et al.,64 but were not able to demonstrate similar beneficial effects on infant eczema. It has been reported that gene polymorphisms in innate receptors can result in differential downstream effects following receptor signalling.73 It is therefore likely that the ability for microorganisms to modulate immune responses and protect against the development of allergic disease is influenced by genetic factors in the individual.

In summary, probiotics may be effective in the prevention of eczema and/or IgE-associated eczema during the first 2 years of life, particularly if treatment is administered both pre- and post-natally. Despite these promising effects, a Cochrane systematic review concluded that further studies are required to determine whether these findings are reproducible.72

Conclusion

Studies examining the use of probiotics for the treatment of allergic disease have not confirmed beneficial effects. However, a potential role for certain probiotics in the prevention of eczema or IgE-associated eczema is suggested. While pre-natal treatment is critical,72 continuation into the post-natal period may also be important. However, post-natal probiotic supplementation alone does not appear to be effective. Furthermore, indirect administration to breastfeeding mothers may be insufficient for beneficial effects. Strain- and species-specificity of probiotic effects is an important factor contributing to the variable results obtained in these studies. Further work is needed to clarify the optimal dose, bacterial strain(s), timing for intervention and patient populations that would provide optimal effects for allergy prevention.

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References

Probiotics in allergy


