Probiotics for the Treatment or Prevention of Atopic Dermatitis
A Review of the Evidence from Randomized Controlled Trials

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Abstract

Probiotics are defined as live microorganisms which, when administered in adequate amounts, confer a health benefit on the host. To synthesize the evidence for the effectiveness of probiotics in the treatment or prevention of atopic dermatitis (AD) in children, we reviewed the results of 13 relevant randomized (placebo)-controlled trials (RCTs), 10 of which evaluated probiotics as treatment and 3 for prevention of AD. The main outcome measure in 9 RCTs was the change in SCORAD (SCORing Atopic Dermatitis).

Four RCTs suggested that there was a statistically significant decrease in SCORAD after probiotic administration to infants or children with AD for 1 or 2 months compared with that after placebo, while in two RCTs SCORAD was significantly reduced after treatment with lactobacilli only in children with IgE-associated AD. In four of these six RCTs, clinical improvement was associated with a change in some inflammatory markers. In three RCTs, the change in SCORAD was not statistically significant between probiotic- and placebo-treated children, although in one of these trials SCORAD was significantly lower after probiotic than with placebo treatment in food-sensitized children. In most RCTs, probiotics did not cause a statistically significant change in interferon-γ, interleukin-4, tumor necrosis factor-α, eosinophil cationic protein or transforming growth factor-β compared with placebo.

Regarding the effectiveness of probiotics in the prevention of AD, in two RCTs, infants at high risk for atopy who received probiotics developed AD significantly less frequently during the first 2 years of life than infants who received placebo. In these studies, mothers were administered Lactobacillus rhamnosus GG with or without other probiotics perinatally, followed by treatment of the infants with the same probiotics for the first 6 months of life. However, in another trial, neither the frequency nor the severity of AD during the first year of life were
significantly different between infants with atopic mothers who received *L. acidophilus* for the first 6 months of life compared with infants who received placebo.

Probiotics, especially *L. rhamnosus* GG, seem to be effective for the prevention of AD. They were also found to reduce the severity of AD in approximately half of the RCTs evaluated, although they were not found to change significantly most of the inflammatory markers measured in the majority of the RCTs evaluated. More RCTs need to be conducted to elucidate whether probiotics are useful for the treatment or prevention of AD.

Atopic dermatitis (AD) is an inflammatory disease of the skin characterized by pruritus, facial and/or extensor extremity surface involvement, and a chronic course. Local corticosteroids are the main treatment for AD. Tacrolimus or pimecrolimus ointment, doxepin cream, emollients, refined-coal cream, systemic anti-histamines, oral anti-staphylococcal β-lactams, and UV light are also used for the treatment of AD, together with systemic corticosteroids for severe acute exacerbations.[1] Probiotics have also been tested as possible agents for the treatment or prevention of AD.

Probiotics are defined as live microorganisms which, when administered in adequate amounts, confer a health benefit on the host.[2] The main probiotics are lactobacilli and bifidobacteria. Stool samples from infants and children with AD have significantly less lactobacilli and bifidobacteria than samples from healthy individuals.[3] Probiotics that produce l-lactic acid may reduce the increased leakage of allergens from the intestine to blood by reducing d-lactic acid and ethanol, which are produced by some *Lactobacillus* species and enterobacteria and are toxic to the gut wall, in infants with AD.[4] Moreover, probiotics have been found to modulate specific and nonspecific immune responses to allergens by affecting phagocytosis and production of proinflammatory cytokines and IgA.[5]

In this article we investigate whether administration of probiotics can reduce the severity or inflammatory process of AD and whether it can prevent the development of AD in infants at high risk for atopy.

### 1. Search Methodology

We searched the PubMed, Cochrane, and EMBASE databases (1997–2007) for randomized, double-blind, placebo-controlled trials that compared the effectiveness of probiotics with that of placebo for the prevention or treatment of AD. The search terms used were ‘probiotics’, ‘*Lactobacillus*’, ‘*Bifidobacterium*’, ‘atopic dermatitis’, ‘atopic eczema’, and ‘SCORAD’.

### 2. Outcomes

With respect to treatment, the primary outcomes of our review were whether probiotic administration significantly reduced the severity of AD and whether there were any significant changes compared with placebo in cytokines involved in the pathogenesis of AD at the end of probiotic administration and 4 or 8 weeks after discontinuation of treatment in children with AD. With respect to prevention, we investigated whether administration of probiotics to pregnant women and/or infants at high risk for atopy prevented infants from developing AD. Secondary outcomes were changes in fecal numbers of lactobacilli, markers of intestinal barrier function, and plasma lipids in *Lactobacillus*-treated children with AD compared with placebo-treated children. Subgroup analyses, such as in children with IgE-associated AD, were not pre-planned but arose during data analysis.

### 3. Results

Tables I and II present the characteristics and outcomes of 13 randomized controlled trials (RCTs) investigating whether various probiotics are beneficial for the management or prophylaxis of AD in comparison with placebo. Ten RCTs[6-19] studied the effectiveness of probiotics in the treatment of infants or older children with AD, while three RCTs[20-23] studied whether probiotics can prevent the development of AD.

#### 3.1 Clinical Effectiveness of Probiotics in the Treatment of Atopic Dermatitis (AD)

In nine RCTs[6-14] of treatment of children with AD, the effect of probiotics on the severity of AD was evaluated by assessing the change in SCORAD (SCORing Atopic Dermatitis) after probiotic administration and comparing this with the change in SCORAD after placebo administration. Some of these trials[6-8] suggested that the decrease in SCORAD in infants with AD with or without cow’s milk allergy (CMA) after administration of *L. rhamnosus* GG or *Bifidobacterium lactis* Bb-12 for 1 or 2 months was statistically significantly higher than that seen after administration of placebo. Weston et al.[9] found that, although the reduction in SCORAD was statistically significant for children with moderate-to-severe AD treated with *L. fermentum* VRI-033 PCC for 8 weeks (but not for those taking placebo), there was no statistically significant difference in the SCORAD index between *Lactobacillus*- and placebo-treated children 8 weeks after the end of treatment.
Table I  Randomized controlled trials comparing the effectiveness of probiotics with that of placebo for the treatment of atopic dermatitis (AD)

<table>
<thead>
<tr>
<th>Authors</th>
<th>No. of pts</th>
<th>Age</th>
<th>Study population</th>
<th>Treatment</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Folster-Holst et al.</td>
<td>53</td>
<td>1–55 mo</td>
<td>Moderate-to-severe AD</td>
<td>LGG 5 × 10^9 cfu PO twice daily for 8 wk (n = 26) n = 27</td>
<td>Mean SCORAD: wk 0: 43.3 (LGG group), 41.4 (placebo); wk 8: 35.3 (LGG group), 31.6 (placebo); wk 12: 32.8 (LGG group), 30.1 (placebo). Change in SCORAD from wk 0 to wk 8: LGG: p &lt; 0.001, placebo: p &lt; 0.001, LGG vs placebo: p &gt; 0.05. Fecal ECP: statistically significant decrease in the whole study population (p &lt; 0.04); no statistically significant difference between LGG and placebo groups</td>
</tr>
<tr>
<td>(2006)</td>
<td></td>
<td>(median: 19 mo)</td>
<td></td>
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<tr>
<td>Holst et al.</td>
<td>19 mo</td>
<td>Infants AD and suspected CMA</td>
<td>Group 1 (n = 17): L. rhamnosus for 3 mo; group 2 (n = 16): LGG for 3 mo</td>
<td>n = 17</td>
<td>SCORAD at randomization; not significantly different between the 3 groups (29.7 [placebo], 24.23 [group 1], 29.4 [group 2]). Decrease in SCORAD at 1, 2, and 3 mo: not significantly different between the 3 groups (2.6 every month [placebo], 0.05 more than placebo every month [group 1], 0.2 more than placebo every month [group 2]). No statistically significant difference in blood eosinophils, urinary eosinophil protein X, fecal α1-antitrypsin. No statistically significant difference between lactobacilli- and placebo-treated pts in changes in IL-4, IL-5, and IFNγ in the supernatants of cultured PBMCs stimulated with Con A or anti-CD3/anti-CD28</td>
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<tr>
<td>(2006)</td>
<td></td>
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<tr>
<td>Sistek et al.</td>
<td>59</td>
<td>1–10 y</td>
<td>AD (IgE associated)</td>
<td>2 × 10^10 cfu/g L. rhamnosus and Bifidobacterium lactis daily for 12 wk (n = 29)</td>
<td>Geometric mean SCORAD at baseline: 26 in probiotic group vs 35.1 in placebo group (p = 0.02). Change (compared with baseline) in geometric mean SCORAD at the end of treatment (12 wk) and 4 wk after the end of treatment (16 wk): significant reduction in probiotic-treated and in food-sensitized probiotic-treated pts, no significant change in placebo-treated pts. Geometric mean SCORAD after adjustment for baseline differences: not significantly different between probiotic- and placebo-treated pts (at 12 and 16 wk), significantly lower in probiotic- than in placebo-treated, food-sensitized children at 12 wk (not at 16 wk)</td>
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<tr>
<td>(2006)</td>
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<tr>
<td>Weston et al.</td>
<td>53</td>
<td>6–18 mo</td>
<td>Moderate or severe AD</td>
<td>10^9 L. fermentum VRI 033 PCC™ PO twice daily for 8 wk (n = 26) n = 27</td>
<td>Reduction in SCORAD: statistically significant in the probiotic group (p = 0.03), not in the placebo group (p = 0.83). No statistically significant difference in SCORAD between probiotic- and placebo-treated pts at wk 16 (change from baseline –17 vs –12, respectively; p = 0.06). SCORAD better than baseline at wk 16: 92% of probiotic-treated (n = 24) vs 63% of placebo-treated (n = 17) pts (p = 0.01). Mild AD at end of study: 54% of probiotic-treated (n = 14) vs 30% of placebo-treated (n = 8) pts (p = 0.066)</td>
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<tr>
<td>(2005)</td>
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<tr>
<td>Authors</td>
<td>No. of pts</td>
<td>Age</td>
<td>Study population</td>
<td>Treatment</td>
<td>Outcome</td>
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<tr>
<td>Prescott et al.</td>
<td>53</td>
<td>6–18 mo</td>
<td>Moderate-to-severe AD</td>
<td>probiotic L. fermentum VRI 033 PCC™ PO for 8 wk (n = 26)</td>
<td>IFNγ responses to PHA and SEB at wk 8 and 16 (compared with wk 0): significant increase (p = 0.004 and p = 0.046, respectively) in lactobacilli-treated pts, no significant change in placebo-treated pts. Increase in IFNγ response to SEB at wk 8 (not at wk 16) directly proportional to decrease in severity of AD (r = −0.445, p = 0.026). TNFα responses to HKLB and to HKSA in lactobacilli-treated children: significantly higher at wk 8 (p = 0.018, p = 0.011, respectively), no significant difference at wk 16 (compared with placebo). IL-13 responses to OVA in lactobacilli-treated children: significant decrease at wk 8 (p = 0.008), no significant difference at wk 16. No significant effect of probiotics on TGFβ response to PHA, SEB, HKLB, HKSA, OVA</td>
</tr>
<tr>
<td>Viljanen et al.</td>
<td>230 Infants</td>
<td>AEDS ± suspected CMA</td>
<td>Group 1 (n = 80): LGG (5 × 10⁹ cfu) twice daily for 4 wk (n = 80); Group 2 (n = 76): 5 × 10⁹ cfu LGG + 5 × 10⁹ cfu L. rhamnosus LC705 + 2 × 10⁸ cfu B. breve Bb99 + 2 × 10⁹ cfu Propionibacterium freudenreichii ssp. shermanii JS twice daily for 4 wk (n = 76)</td>
<td>n = 74</td>
<td>No statistically significant difference in mean SCORAD between probiotic- and placebo-treated groups 4 and 8 wk after start of treatment. IgE-associated AEDS: reduction in SCORAD 4 wk after end of treatment higher in group 1 than in placebo group (−26.1 vs −19.8, respectively; p = 0.036) Change in total (median) lactobacilli counts in feces (from start of treatment to 4 wk later): significantly higher for group 1 and group 2 vs placebo group (p = 0.029 and p = 0.002, respectively)</td>
</tr>
<tr>
<td>Viljanen et al.</td>
<td>230 Infants</td>
<td>AEDS and suspected CMA</td>
<td>Group 1: LGG (5 × 10⁹ cfu) twice daily for 4 wk (n = 80); Group 2: 5 × 10⁹ cfu LGG + 5 × 10⁹ cfu L. rhamnosus LC705 + 2 × 10⁸ cfu B. breve Bb99 + 2 × 10⁹ cfu P. freudenreichii ssp. shermanii JS twice daily for 4 wk (n = 76)</td>
<td>n = 74</td>
<td>Post-treatment values (adjusted by pre-treatment values): fecal IgA: group 1 vs placebo p = 0.064, group 2 vs placebo p = 0.064; TNFα: group 1 vs placebo p = 0.71, group 2 vs placebo p = 0.76; α1-antitrypsin: group 1 vs placebo p = 0.9, group 2 vs placebo p = 0.5, ECP: group 1 vs placebo p = 0.3, group 2 vs placebo p = 0.92; IgE-associated CMA: fecal IgA: group 1 vs placebo p = 0.014</td>
</tr>
<tr>
<td>Požijavuori et al.</td>
<td>119 Infants</td>
<td>AD and suspected CMA</td>
<td>Group 1: 5 × 10⁹ cfu LGG (ATCC 53103) twice daily for 4 wk (n = 42); Group 2: 5 × 10⁹ cfu LGG + 5 × 10⁹ cfu L. rhamnosus LC705 + 2 × 10⁸ cfu B. breve Bb99 + 2 × 10⁹ cfu P. freudenreichii ssp. shermanii JS twice daily for 4 wk (n = 41)</td>
<td>Group 3: n = 36</td>
<td>Change in IFNγ, IL-4, and IL-5 secretion (from stimulated PBMCs): group 1 vs group 3 p &gt; 0.05, group 2 vs group 3 p &gt; 0.05; increase in IFNγ in infants with CMA (n = 65) and in infants with IgE-associated dermatitis*: higher in group 1 than in group 3 (p = 0.006 and p = 0.017, respectively) [group 2 vs group 3 p = 0.058 and p = 0.32, respectively]; increase in IL-4 in infants with CMA: higher in group 2 than in group 3 (p = 0.028), group 1 vs group 3 p &gt; 0.05 (change in IL-4 in infants with IgE-associated dermatitis: group 1 or group 2 vs group 3, p &gt; 0.05)</td>
</tr>
<tr>
<td>Authors</td>
<td>No. of pts</td>
<td>Age</td>
<td>Study population</td>
<td>Treatment probiotic</td>
<td>Placebo</td>
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<tr>
<td>Rosenfeldt et al. (2003)</td>
<td>43</td>
<td>1–13 y</td>
<td>AD</td>
<td>Group A (n = 20): placebo twice daily for 6 wk, no intervention for the following 6 wk, then 10^10 cfu L. rhamnosus 19070-2 + 10^10 cfu L. reuteri DSM 122460 twice daily for the last 6 wk; group B (n = 23): 10^10 cfu L. rhamnosus 19070-2 + 10^10 cfu L. reuteri DSM 122460 twice daily for 6 wk, no intervention for the following 6 wk, finally placebo twice daily for 6 wk</td>
<td>Improvement in eczema 56% after lactobacillus vs 15% after placebo, p = 0.001</td>
</tr>
<tr>
<td>Rosenfeldt et al. (2004)</td>
<td>41</td>
<td>1–13 y</td>
<td>Moderate or severe AD</td>
<td>Group A: placebo twice daily for 6 wk, no intervention for the following 6 wk, then 10^10 cfu L. rhamnosus 19070-2 + 10^10 cfu L. reuteri DSM 122460 twice daily for the last 6 wk; group B: 10^10 cfu L. rhamnosus 19070-2 + 10^10 cfu L. reuteri DSM 122460 twice daily for 6 wk, no intervention for the following 6 wk, finally placebo twice daily for 6 wk</td>
<td>Frequency of gastrointestinal symptoms: during the last 14 d of lactobacillus treatment &lt; during the last 14 d of placebo treatment (10% vs 39%, respectively; p = 0.002)</td>
</tr>
<tr>
<td>Kirjavainen et al. (2003)</td>
<td>35 Infants (mean age: 5.5 mo)</td>
<td>Atopic eczema and suspected CMA</td>
<td>Viable LGG (n = 14) or heat-inactivated LGG (n = 13) for 7.5 wk (mean)</td>
<td>Placebo (n = 8)</td>
<td>Heat-inactivated LGG: adverse gastrointestinal symptoms (diarrhea) [5/13]</td>
</tr>
<tr>
<td>Isolauri et al. (2000)</td>
<td>27 Infants (mean age: 4.6 mo)</td>
<td>Atopic eczema (during exclusive breast feeding)</td>
<td>Group 1: 1 × 10^9 cfu/g B. lactis Bb-12 for 2 mo (n = 9); group 2: 3 × 10^8 cfu/g LGG (ATCC 53103) for 2 mo (n = 9)</td>
<td>Group 3: n = 9</td>
<td>At 2 mo: change in SCORAD: group 1: 12→0, group 2: 14→1, placebo: 10→13.4. Significant change in SCORAD: 9/9 group 1, 9/9 group 2, 4/9 placebo, p = 0.002 Serum soluble CD4: statistically significant decrease in groups 1 and 2 (not in group 3). TGF-β1: statistically significant decrease (p = 0.04) in group 1 (not in groups 2 and 3). Urinary eosinophilic protein X: statistically significant decrease in group 1 (p = 0.01) and group 2 (p = 0.04). TNFα: not modified by probiotics</td>
</tr>
</tbody>
</table>
Table I.

<table>
<thead>
<tr>
<th>Authors</th>
<th>No. of pts</th>
<th>Age</th>
<th>Study population</th>
<th>Treatment</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Majamaa et al.</td>
<td>15</td>
<td>Infants</td>
<td>Atopic eczema</td>
<td>Milk with 5 × 10^8 cfu/mg LGG and suspected CMA (ATCC 53103) for 1 mo LGG (n = 16) placebo treated: p = 0.89, Decrease in α1-antitrypsin: LGG: p = 0.03, no LGG: p = 0.89. Fecal ECP no significant change (from stimulated PBMCs); no significant differences between LGG and no LGG after placebo administration.</td>
<td></td>
</tr>
<tr>
<td>Isolauri, et al.</td>
<td>15</td>
<td>Infants</td>
<td>Atopic eczema</td>
<td>Milk with 5 × 10^8 cfu/mg LGG and suspected CMA (ATCC 53103) for 1 mo LGG (n = 16) placebo treated: p = 0.89, Decrease in α1-antitrypsin: LGG: p = 0.03, no LGG: p = 0.89. Fecal ECP no significant change (from stimulated PBMCs); no significant differences between LGG and no LGG after placebo administration.</td>
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</table>

Some other trials reported a statistically nonsignificant change in SCORAD in infants or children aged 1–13 years with AD after probiotic administration as compared with placebo administration for 1–3 months. In two of these trials the reduction in SCORAD was significantly higher 1 month after the end of treatment with *L. rhamnosus* GG for 4 weeks or during treatment with *L. rhamnosus* 19070-2 and *L. reuteri* DSM 122460 for 6 weeks among children with at least one positive skin prick test response and/or high total or allergen-specific IgE in comparison with those who took placebo. Finally, in the trial by Sistek et al. after adjustment for baseline differences, the geometric mean SCORAD was significantly lower after 12 weeks of treatment with *L. rhamnosus* and *B. lactis* than after placebo only in food-sensitized children.

3.2 Laboratory Outcomes in the Reviewed Randomized Controlled Trials

Some trials have compared the change in secretion of selected cytokines after treatment of young children with probiotics with that after placebo. Four studies showed that serum interferon (IFN)-γ and interleukin (IL)-4 levels did not change significantly after administration of *L. rhamnosus* GG or other strains of *L. rhamnosus* with or without *L. reuteri* or *B. breve* Bh99 and *Propionibacterium freudenreichii* spp. *shermanii* for 1–3 months as compared with placebo administration. However, Poljavuori et al. showed that IFNγ increased significantly in infants with AD or CMA or with IgE-associated AD who received *L. rhamnosus* GG and that IL-4 increased significantly in infants with AD and CMA treated with a mixture of four probiotics as compared with those receiving placebo. Another RCT showed that IFNγ responses to phytohemagglutinin and *Staphylococcus aureus* enterotoxin B increased significantly in children with AD 8 and 16 weeks after start of treatment with *L. fermentum* VRI-033 PCC for 8 weeks, while there was no significant change in placebo-treated children.

After administration of *L. rhamnosus* GG for 1 month, fecal tumor necrosis factor (TNF-α) was found to be significantly lower in infants with AD and CMA compared with those taking placebo in a trial by Majamaa and Isolauri. However, in another trial of infants with atopic eczema/dermatitis syndrome, values of fecal TNFα after administration of *L. rhamnosus* GG or of a combination of four probiotics for 1 month (adjusted to pre-treatment values) were not significantly different compared with such values after placebo administration. In the study by Majamaa and Isolauri, TNFα production by peripheral blood mononuclear cells (PBMCs) was not significantly different at the end of the 1-month study period either for infants taking *L. rhamnosus* GG or
Table II. Randomized controlled trials comparing the effectiveness of probiotics with that of placebo for the prevention of atopic dermatitis (AD)

<table>
<thead>
<tr>
<th>Authors</th>
<th>No. of pts</th>
<th>Age (mo)</th>
<th>Study population</th>
<th>Treatment</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Taylor et al.</td>
<td>178</td>
<td>Infants</td>
<td>Infants of atopic mothers (asthma, allergic rhinitis, AD, and positive skin prick test to one or more common allergens)</td>
<td><em>Lactobacillus acidophilus</em></td>
<td>Rates of AD not significantly different between probiotic- and placebo-treated pts at 6 mo (n = 23/89 [25.8%] vs 20/88 [22.7%], respectively; p = 0.629) and at 12 mo (38/88 [43%] vs 34/87 [39%], respectively; p = 0.581) Severity of AD (SCORAD) not significantly different between probiotic- and placebo-treated pts at 12 mo (p = 0.995) AD with positive skin prick test: significantly more common in probiotic- than in placebo-treated pts at 12 mo (23/88 [26%] vs 12/87 [14%], respectively; p = 0.045) Positive stool cultures for <em>Lactobacillus</em>: not significantly different between probiotic- and placebo-treated pts at 1 mo (p = 0.123), significantly more common in probiotic- than in placebo-treated pts at 6 mo (p = 0.039), not associated with frequency of AD</td>
</tr>
<tr>
<td>Kukkonen et al.</td>
<td>925</td>
<td>Pregnant and their infants (one or both parents with allergic disease)</td>
<td><em>L. rhamnosus</em> LC705 + <em>Bifidobacterium breve</em> BS99 + <em>Propionibacterium freudenreichii</em> sp. <em>shermanii</em> JS; twice daily for 2–4 wk before delivery (mothers) + 0.8 g galacto-oligosaccharides (prebiotic) once daily for 6 mo after birth (infants) (n = 461)</td>
<td>5 × 10⁹ cfu <em>LGG</em> + 5 × 10⁹ cfu <em>L. rhamnosus</em> LC705 + 2 × 10⁸ cfu <em>B. breve</em> BS99 + 2 × 10⁹ cfu <em>P. freudenreichii</em> sp. <em>shermanii</em> JS; twice daily for 2–4 wk before delivery (mothers), + 0.8 g galacto-oligosaccharides (prebiotic) once daily for 6 mo after birth (infants) (n = 461)</td>
<td>AD in infants aged 2 y: 57/459 (12.4%) probiotic group vs 82/463 (17.7%) placebo group, p = 0.025 (multivariable analysis, p = 0.012) Prevalence (and median log counts) of lactobacilli, bifidobacteria, and administered probiotics in feces: significantly higher in the probiotic than in the placebo group at age 6 mo, no statistically significant (p &gt; 0.05) difference at age 2 y</td>
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<tr>
<td>Rautava et al.</td>
<td>62</td>
<td>Pregnant and lactating women with a family history of atopy and their infants</td>
<td>LGG (ATCC 53103): 2 × 10¹⁰ cfu/l/day during 4 wk before labor and during the first 3 mo of breast feeding (n = 30)</td>
<td>TGFβ2 in breast milk: mothers receiving probiotics &gt; mothers receiving placebo (2885 vs 1340 pg/mL, respectively; p = 0.018) Risk for development of chronic relapsing AD in infants during their first 2 y of life: significantly lower in infants whose mothers received probiotics than in infants whose mothers received placebo (4/27 [15%] vs 14/30 [47%], respectively; relative risk 0.32, p = 0.01) Infants with cord blood IgE ≥0.5 kU/L: TGFβ2 in milk: significantly higher in mothers receiving probiotics than in mothers receiving placebo (5085 vs 1136 pg/mL, respectively; p = 0.021)</td>
<td></td>
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<tr>
<td>Kalliomaki et al.</td>
<td>264</td>
<td>Pregnant women with a family history of atopic disease [one or more first-degree relative(s) or partner with atopic eczema, allergic rhinitis, or asthma] and their infants</td>
<td>LGG 10¹⁰ cfu/day for 2–4 wk</td>
<td>Atopic eczema: 46/132 (35%) of children aged 2 y Frequency of chronic relapsing AD at 2 y of life significantly lower in the probiotic than in the placebo group (15/64 [23%] vs 31/68 [46%], respectively, p = 0.008) Geometric mean SCORAD (in infants with AD) at 24 mo: 9.8 (Lactobacillus-treated) vs 10.4 (placebo-treated), p = 0.6 Total serum IgE, frequency of infants with serum antigen-specific IgE &gt;0.35 kU/L, frequency of infants with one positive skin prick test at 3, 12, 24 mo: not statistically different between Lactobacillus- and placebo-treated pts</td>
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</table>

*cfu* = colony forming units; *LGG* = *Lactobacillus rhamnosus* GG; *PO* = orally; *pts* = patients; *SCORAD* = SCORing Atopic Dermatitis; *TGF* = transforming growth factor.
between infants receiving *L. rhamnosus* GG and those taking placebo. In another study by Isolauri et al., serum levels of TNFα also did not change significantly after 2 months’ administration of *B. lactis* Bb-12 or *L. rhamnosus* GG to infants with AD during exclusive breast feeding. On the other hand, Prescott et al.[16] found that TNFα responses to heat-killed *Lactobacillus* and to heat-killed *S. aureus* by PBMCs increased significantly after 2 months of *L. fermentum* administration, but not 2 months after the end of treatment.

Changes in the levels of eosinophil cationic protein (ECP) in serum or feces after treatment of young children with AD with probiotics have been evaluated in some studies. Majamaa and Isolauri[8] found that ECP levels in serum and in feces did not change significantly after 1 month of *L. rhamnosus* GG administration. However, Rosenfeldt et al.[11] found that the mean change in serum ECP was significantly different after administration of *L. reuteri* and *L. rhamnosus* 19070-2 than after placebo (~6.2 vs 2 µg/L, respectively; p = 0.03). In two other studies,[14,17] fecal ECP in infants with AD did not change significantly after treatment with *L. rhamnosus* GG or a mixture of four probiotics for 4 or 8 weeks compared with placebo treatment, but did decrease significantly in the whole study population.

The effect of probiotics on the concentration of transforming growth factor (TGF)-β has also been studied. Isolauri et al.[8] found that, in infants with AD during exclusive breast feeding treated with *B. lactis* Bb-12 for 2 months, serum TGFβ1 decreased statistically significantly (p = 0.04), while in infants treated with *L. rhamnosus* GG there was a statistically nonsignificant increase (p = 0.07). Viljanen et al.[24] found that administration of *L. rhamnosus* GG or of four probiotics to infants with atopic eczema/dermatitis syndrome did not significantly affect plasma concentrations of TGFβ1 and TGFβ2. In the trial by Prescott et al.,[16] TGFβ responses to various stimuli in cultures of PBMCs from children with AD also did not change significantly after treatment with *L. fermentum* for 8 weeks. Rautava et al.[20] found that TGFβ2 in the breast milk of mothers with a family history of atopy who consumed *L. rhamnosus* GG for the month before labor and for the following 3 months during breast feeding was significantly higher and development of AD during the first 2 years of life of their infants was significantly less common as compared with mothers taking placebo (p = 0.018).

### 3.3 Effectiveness of Probiotics in the Prevention of AD

Three RCTs[20-22] found that administration of *L. rhamnosus* GG alone or combined with three other probiotics to pregnant women with atopy or a family history of atopy (or with atopic husbands) for 2–4 weeks before labor, followed by treatment of the mothers over the first 3 or 6 months of breast feeding or of their infants with the same probiotics alone or together with probiotics for the first 6 months of life, resulted in significantly less frequent development of AD during the first 2 years of life in these infants compared with infants whose mothers received placebo. However, AD severity and serum IgE measurements were not significantly different between probiotic- and placebo-treated infants in one of these RCTs.[21]

A more recent RCT[23] found that neither the frequency nor the severity of AD during the first year of life were significantly different between infants with atopic mothers who received *L. acidophilus* LAVRI-A1 for the first 6 months of life compared with infants who took placebo, although positive stool cultures for lactobacilli were significantly more common at 6 months in lactobacillus-treated infants compared with those treated with placebo.

### 4. Interpretation of the Reviewed Evidence

All RCTs examining the effect of probiotics on SCORAD used Hanifin and Rajka[25] or modified UK diagnostic criteria for AD,[26] except for two RCTs[7,10] in which AD was not defined. SCORAD has been proposed as a means of evaluating the severity of AD based on its extent, its intensity (erythema, edema/papulation, oozing/crusting, excoriation, and lichenification), and two common subjective symptoms (pruritus and insomnia). Three RCTs[12-14] suggested that the effect of probiotics on the severity of AD is not statistically significant, although in one of these trials,[12] SCORAD decreased significantly in food-sensitized children. SCORAD was significantly reduced after probiotic administration in four RCTs[6-9] in two other trials, SCORAD decreased significantly only in children with IgE-associated AD.[10,11] Four of these six RCTs[6,8,10,15,16] associated the observed clinical improvement with changes in some inflammatory markers in infants with AD treated with *L. rhamnosus* GG, *L. fermentum* VRI-033 PCC, or *B. lactis* Bb-12.

However, most of the ‘positive’ RCTs had serious limitations. In the RCT by Kirjavainen et al.,[7] no significant changes in fecal bacterial numbers were measured after probiotic treatment, despite the clinical improvement. This trial was discontinued prematurely because of adverse gastrointestinal effects in 38.5% of infants treated with heat-inactivated *L. rhamnosus* GG. Another limitation was that the duration of treatment varied widely (0.4–45.3 weeks) in the trials evaluated. Furthermore, in two RCTs[9,10] the difference in SCORAD of five to six points between probiotic- and placebo-treated children was statistically significant but the clinical significance of such a difference (on a scale of 1–103) is possibly small.[27] In the trial by Viljanen et al.,[10] cow’s milk was eliminated from infants’ diets during the trial and this might have
affected the results. In the trial by Weston et al.,[9] there were more severe cases of AD in placebo- than Lactobacillus-treated children before intervention (25% vs 7%, respectively) and no adjustment was made for severity of AD in the analysis of the results.[27] In most of the RCTs evaluated, probiotics did not have a significant effect on IFNγ or IL-4 production in children with AD treated with probiotics. However, in one RCT,[16] the increase in IFNγ response to S. aureus enterotoxin B after 8 weeks of treatment with L. fermentum VRI-033 PCC was directly proportional to the decrease in the severity of AD. Moreover, the results of another trial suggested that, in infants with IgE-associated AD, the increase in IFNγ[15] was significantly higher in infants treated with L. rhamnosus GG for 4 weeks than in those taking placebo.

T helper-2 (Th2)-mediated immunity becomes stronger during the first 2 years of life in atopic infants[28] but gradually weakens and deviates toward Th1-mediated immunity in non-atopic infants. Patients with AD,[29] especially infants with severe AD,[30,31] have decreased numbers of CD4+ T cells that are spontaneously IFNγ producers. Some studies[29,32] have found lower numbers of CD4+ T cells that express IL-4 in patients with AD compared with non-atopic patients, whereas other studies[30] have reported them to be higher in AD patients. IL-4 stimulates IgE production by lymphocytes, while IFNγ has the opposite effect. L. casei GG-derived enzymes hydrolyse in vitro bovine caseins, which suppress proliferation of lymphocytes and reduce production of IL-4 by PBMCs.[33,34]

Probiotics also did not have a significant effect on TNFα levels in the feces or sera of infants with AD in most of the studied trials. However, in the study by Majamaa and Isolauri,[6] the decreases in median fecal TNFα and in median SCORAD were statistically significant in infants with AD and CMA treated with L. rhamnosus GG for 1 month but not in those treated with placebo. Live lactobacilli have been found to induce production of TNFα by human PBMCs.[35] Production of TNFα in patients with AD has been found to be significantly lower compared with that in non-allergic patients in some studies,[31,36,37] while TNFα levels in patients with chronic AD or after stimulation with phorbol-12-myristate 13-acetate and ionomycin were not significantly different from that of control patients in other studies.[32,38,39] However, in some other studies,[38,40] TNFα production from CD4+ T cells was found to be significantly higher in patients with severe or acute AD than in non-atopic patients and the increase in TNFα has been correlated with the severity of AD.[41,42] TNFα increases the expression of adhesion molecules (vascular cell adhesion molecule-1, E-selectin, endothelial leukocyte adhesion molecule-1)[43] and stimulates keratinocytes to produce substances (Regulated upon Activation, Normal T cell-Expressed and Secreted [RANTES] chemokine, granulocyte macrophage-colony stimulat-
tory markers measured. More RCTs should be carried out in order to elucidate whether and which probiotics are effective for the treatment or prevention of AD.

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