

# 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- $\gamma$ , interleukin-4, tumor necrosis factor- $\alpha$ , eosinophil cationic protein or transforming growth factor- $\beta$  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 antihistamines, oral anti-staphylococcal  $\beta$ -lactams, and UV light are also used for the treatment of AD, together with systemic corticosteroids for severe acute exacerbations.<sup>[1]</sup> 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.<sup>[2]</sup> 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.<sup>[3]</sup> 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.<sup>[4]</sup> Moreover, probiotics have been found to modulate specific and nonspecific immune responses to allergens by affecting phagocytosis and production of proinflammatory cytokines and IgA.<sup>[5]</sup>

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<sup>[6-19]</sup> studied the effectiveness of probiotics in the treatment of infants or older children with AD, while three RCTs<sup>[20-23]</sup> 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<sup>[6-14]</sup> 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<sup>[6-8]</sup> 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.<sup>[9]</sup> 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 1.** Randomized controlled trials comparing the effectiveness of probiotics with that of placebo for the treatment of atopic dermatitis (AD)

Authors (year)	No. of pts	Age	Study population	Treatment	Outcome
Folster-Holst et al. <sup>[14]</sup> (2006)	53	1–55 mo (median: 19 mo)	Moderate-to-severe AD	probiotic LGG 5 × 10 <sup>9</sup> cfu PO twice daily for 8 wk (n = 26)	placebo n = 27 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 < 0.001, placebo: p < 0.001, LGG vs placebo: p > 0.05 Fecal ECP: statistically significant decrease in the whole study population (p < 0.04); no statistically significant difference between LGG and placebo groups
Brouwer et al. <sup>[13]</sup> (2006)	50	Infants <5 mo	AD and suspected CMA	Group 1 (n = 17): <i>L. rhamnosus</i> for 3 mo; group 2 (n = 16): LGG for 3 mo	n = 17 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
Sistek et al. <sup>[12]</sup> (2006)	59	1–10 y	AD (IgE associated <sup>45</sup> )	2 × 10 <sup>10</sup> cfu/g <i>L. rhamnosus</i> and <i>Bifidobacterium lactis</i> daily for 12 wk (n = 29)	n = 30 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)
Weston et al. <sup>[9]</sup> (2005)	53	6–18 mo	Moderate or severe AD	10 <sup>9</sup> <i>L. fermentum</i> VRI 033 PCC™ PO twice daily for 8 wk (n = 26)	n = 27 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)

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Table 1. Contd

Authors (year)	No. of pts	Age	Study population	Treatment	Outcome
Prescott et al. <sup>[16]</sup> (2005)	53	6–18 mo	Moderate-to-severe AD	probiotic 10 <sup>9</sup> <i>L. fermentum</i> VRI 033 PCC™ PO for 8 wk (n = 26) placebo n = 27	IFN $\gamma$ 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 IFN $\gamma$ response to SEB at wk 8 (not at wk 16) directly proportional to decrease in severity of AD (r = -0.445, p = 0.026). TNF $\alpha$ 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 TGF $\beta$ response to PHA, SEB, HKLB, HKSA, OVA
Viljanen et al. <sup>[10]</sup> (2005)	230	Infants (1.4–11.9 mo)	AEDS $\pm$ suspected CMA	Group 1 (n = 80): LGG (5 $\times$ 10 <sup>8</sup> cfu) twice daily for 4 wk (n = 80); group 2 (n = 76): 5 $\times$ 10 <sup>9</sup> cfu LGG + 5 $\times$ 10 <sup>9</sup> cfu <i>L. rhamnosus</i> LC705 + 2 $\times$ 10 <sup>8</sup> cfu <i>B. breve</i> Bbi99 + 2 $\times$ 10 <sup>9</sup> cfu <i>Propionibacterium freudenreichii</i> ssp. <i>shermanii</i> JS twice daily for 4 wk (n = 76)	n = 74 No statistically significant difference in decrease in mean SCORAD between probiotic- and placebo-treated groups 4 and 8 wk after start of treatment. IgE-associated AEDS <sup>a</sup> : 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)
Viljanen et al. <sup>[17]</sup> (2005)	230	Infants	AEDS and suspected CMA	Group 1: LGG (5 $\times$ 10 <sup>8</sup> cfu) twice daily for 4 wk (n = 80); group 2: 5 $\times$ 10 <sup>9</sup> cfu LGG + 5 $\times$ 10 <sup>9</sup> cfu <i>L. rhamnosus</i> LC705 + 2 $\times$ 10 <sup>8</sup> cfu <i>B. breve</i> Bbi99 + 2 $\times$ 10 <sup>9</sup> cfu <i>P. freudenreichii</i> ssp. <i>shermanii</i> JS twice daily for 4 wk (n = 76)	n = 74 Post-treatment values (adjusted by pre-treatment values): fecal IgA $\downarrow$ : group 1 vs placebo p = 0.064, group 2 vs placebo p = 0.064; TNF $\alpha$ : group 1 vs placebo p = 0.71, group 2 vs placebo p = 0.76; $\alpha$ 1-antitrypsin $\downarrow$ : group 1 vs placebo p = 0.9, group 2 vs placebo p = 0.5; ECP $\downarrow$ : 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
Pohjavuori et al. <sup>[15]</sup> (2004)	119	Infants	AD and suspected CMA	Group 1: 5 $\times$ 10 <sup>9</sup> cfu LGG (ATCC 53103) twice daily for 4 wk (n = 42); group 2: 5 $\times$ 10 <sup>9</sup> cfu LGG + 5 $\times$ 10 <sup>9</sup> cfu <i>L. rhamnosus</i> LC705 + 2 $\times$ 10 <sup>8</sup> cfu <i>B. breve</i> Bbi99 + 2 $\times$ 10 <sup>9</sup> cfu <i>P. freudenreichii</i> ssp. <i>shermanii</i> JS twice daily for 4 wk (n = 41)	Group 3: n = 36 Change in IFN $\gamma$ , IL-4, and IL-5 secretion (from stimulated PBMCs): group 1 vs group 3 p > 0.05, group 2 vs group 3 p > 0.05; increase in IFN $\gamma$ in infants with CMA (n = 65) and in infants with IgE-associated dermatitis <sup>a</sup> : 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 > 0.05 (change in IL-4 in infants with IgE-associated dermatitis: group 1 or group 2 vs group 3, p > 0.05)

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Table 1. Contd

Authors (year)	No. of pts	Age	Study population	Treatment		Outcome
				probiotic	placebo	
Rosenfeldt et al. <sup>[11]</sup> (2003)	43	1–13 y	AD	Group A (n = 20): placebo twice daily for 6 wk, no intervention for the following 6 wk, then 10 <sup>10</sup> cfu <i>L. rhamnosus</i> 19070-2 + 10 <sup>10</sup> cfu <i>L. reuteri</i> DSM 122460 twice daily for the last 6 wk; group B (n = 23): 10 <sup>10</sup> cfu <i>L. rhamnosus</i> 19070-2 + 10 <sup>10</sup> cfu <i>L. reuteri</i> DSM 122460 twice daily for 6 wk, no intervention for the following 6 wk, finally placebo twice daily for 6 wk	placebo	Improvement in eczema 56% after lactobacillus vs 15% after placebo, p = 0.001 Change in mean SCORAD: -3.4 (after lactobacillus) vs 0.5 (after placebo), p = 0.12. Change in SCORAD in allergic pts (serum IgE ↑ and ≥1 positive skin prick test or history of asthma, allergic rhinitis, or food allergy): -2.4 (after lactobacillus) vs 3.2 (after placebo), p = 0.04 Change in extent of eczema: -4.4 (after lactobacillus) vs 2.4 (after placebo), p = 0.02 Mean change in serum ECP: -6.2 (after lactobacillus) vs 2 µg/L (after placebo), p = 0.03. IL-2, IL-4, IL-10, IFNγ: no significant changes
Rosenfeldt et al. <sup>[18]</sup> (2004)	41	1–13 y	Moderate or severe AD	Group A: placebo twice daily for 6 wk, no intervention for the following 6 wk, then 10 <sup>10</sup> cfu <i>L. rhamnosus</i> 19070-2 + 10 <sup>10</sup> cfu <i>L. reuteri</i> DSM 122460 twice daily for the last 6 wk; group B: 10 <sup>10</sup> cfu <i>L. rhamnosus</i> 19070-2 + 10 <sup>10</sup> cfu <i>L. reuteri</i> DSM 122460 twice daily for 6 wk, no intervention for the following 6 wk, finally placebo twice daily for 6 wk	placebo	Frequency of gastrointestinal symptoms: during the last 14 d of lactobacillus treatment < during the last 14 d of placebo treatment (10% vs 39%, respectively; p = 0.002) Lactulose-to-mannitol ratio (in urine): after probiotic < after placebo (0.073 vs 0.11, respectively; p = 0.001). => Small intestinal permeability: after probiotic < after placebo. Positive association between lactulose-to-mannitol ratio and SCORAD (r = 0.61, p = 0.02 after placebo and r = 0.53, p = 0.05 after lactobacillus treatment)
Kirjavainen et al. <sup>[7]</sup> (2003)	35	Infants (mean age: 5.5 mo)	Atopic eczema and suspected CMA	Viable LGG (n = 14) or heat-inactivated LGG (n = 13) for 7.5 wk (mean)	Placebo (n = 8)	Heat-inactivated LGG: adverse gastrointestinal symptoms (diarrhea) [5/13] Significant decrease in SCORAD in all groups: SCORAD: 13→8 (placebo), 19→5 (viable LGG), 15→7 (heat-inactivated LGG). Mean decrease in SCORAD: higher for the viable LGG group than for the placebo group (p = 0.02) No significant changes in fecal numbers of bifidobacteria, lactobacilli, <i>Bacteroides</i> , enterococci, clostridia after treatment in all groups
Isolaari et al. <sup>[8]</sup> (2000)	27	Infants (mean age: 4.6 mo)	Atopic eczema (during exclusive breast feeding)	Group 1: 1 × 10 <sup>9</sup> cfu/g <i>B. lactis</i> Bb-12 for 2 mo (n = 9); group 2: 3 × 10 <sup>8</sup> cfu/g LGG (ATCC 53103) for 2 mo (n = 9)	Group 3: n = 9	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). TGFB1: 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

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Table 1. Contd

Authors (year)	No. of pts	Age	Study population	Treatment	Outcome
Majamaa and Isolauri <sup>[6]</sup> (1997)	31	Infants	Atopic eczema and suspected CMA	probiotic Milk with $5 \times 10^8$ cfu/mg LGG (ATCC 53103) for 1 mo (n = 15) placebo Milk without LGG (n = 16)	Decrease in SCORAD after 1 mo: LGG treated: p = 0.008, placebo treated: p = 0.89 Decrease in $\alpha_1$ -antitrypsin: LGG: p = 0.03, no LGG: p = 0.68. Decrease in median fecal TNF $\alpha$ : LGG: p = 0.003, no LGG: p = 0.38. Fecal ECP: no significant change Change in IFN $\gamma$ and TNF $\alpha$ secretion (from stimulated PBMCs): no significant differences between LGG and no LGG
Kankaanpää et al. <sup>[19]</sup> (2002)	15	Infants	Atopic eczema	Group 1: 76 mL/kg/day of $3 \times 10^8$ cfu/g LGG ATCC 53103 for 4.4 mo (mean) [n = 5]; group 2: 73 mL/kg/day of $1 \times 10^9$ cfu/g <i>Bifidobacterium</i> Bb-12 for 7.3 mo (mean) [n = 5]	n = 5 $\alpha$ -Linolenic acid proportions: ↓ in plasma neutral lipids by probiotics, no effect in phospholipids by LGG, ↑ in phospholipids by <i>Bifidobacterium</i> Bb-12 (mean: 0.13→0.24, p = 0.002)

a IgE-associated AEDS-positive skin prick test or any antigen-specific IgE >0.7 kU/L.

**AEDS** = atopic eczema/dermatitis syndrome; **cfu** = colony forming units; **CMA** = cow's milk allergy; **ECP** = eosinophil cationic protein; **HKLB** = heat-killed *Lactobacillus*; **HKSA** = heat-killed *Staphylococcus aureus*; **IFN** = interferon; **IL** = interleukin; **LGG** = *Lactobacillus rhamnosus* GG; **OVA** = ovalbumin; **PBMCs** = peripheral blood mononuclear cells; **PHA** = phytohemagglutinin; **PO** = orally; **pts** = patients; **SEB** = *S. aureus* enterotoxin B; **SCORAD** = SCORing Atopic Dermatitis; **TGF** = transforming growth factor; **TNF** = tumor necrosis factor; ↓ indicates decrease; ↑ indicates increase; → indicates movement to; ⇒ indicates conclusively.

Some other trials<sup>[10-14]</sup> 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<sup>[10,11]</sup> 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 serum IgE in comparison with those who took placebo. Finally, in the trial by Sistek et al.,<sup>[12]</sup> 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<sup>[6,11,13,24]</sup> showed that serum interferon (IFN)- $\gamma$  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* Bbi99 and *Propionibacterium freudenreichii* ssp. *shermanii* for 1–3 months as compared with placebo administration. However, Pohjavuori et al.<sup>[15]</sup> showed that IFN $\gamma$  increased significantly in infants with AD and 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<sup>[16]</sup> showed that IFN $\gamma$  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)- $\alpha$  was found to be significantly lower in infants with AD and CMA compared with those taking placebo in a trial by Majamaa and Isolauri.<sup>[6]</sup> However, in another trial of infants with atopic eczema/dermatitis syndrome, values of fecal TNF $\alpha$  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.<sup>[17]</sup> In the study by Majamaa and Isolauri,<sup>[6]</sup> TNF $\alpha$  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)

Authors (year)	No. of pts	Age (mo)	Study population	Treatment		Outcome
				probiotic	placebo	
Taylor et al. <sup>[23]</sup> (2007)	178	Infants (0–12)	Infants of atopic mothers (asthma, allergic rhinitis, AD, and positive skin prick test to one or more common allergens)	<i>Lactobacillus acidophilus</i> LAVRI-A1 (3 × 10 <sup>9</sup> ) PO daily from birth to age 6 mo (n = 89)	n = 89	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 <i>Lactobacillus</i> : 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 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 (p < 0.05) higher in the probiotic than in the placebo group at age 6 mo, no statistically significant (p > 0.05) difference at age 2 y
Kukkonen et al. <sup>[22]</sup> (2007)	925		Pregnant women and their infants (one or both parents with allergic disease)	5 × 10 <sup>9</sup> cfu LGG + 5 × 10 <sup>9</sup> cfu <i>L. rhamnosus</i> LC705 + 2 × 10 <sup>8</sup> cfu <i>Bifidobacterium breve</i> Bbi99 + 2 × 10 <sup>9</sup> cfu <i>Propionibacterium freudenreichii</i> ssp. <i>shermanii</i> 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]	n = 464	TGFβ2 in breast milk: mothers receiving probiotics > 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)
Rautava et al. <sup>[20]</sup> (2002)	62		Pregnant and lactating women with a family history of atopy and their infants	LGG (ATCC 53103) 2 × 10 <sup>10</sup> cfu/day during 4 wk before labor and during the first 3 mo of breast feeding (n = 30)	n = 32	
Kalliomaki et al. <sup>[21]</sup> (2001)	264		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	LGG 10 <sup>10</sup> cfu/day for 2–4 wk prenatally to 64 mothers and for 6 mo postnatally to 36 (of 64) infants or to 28 (of 64) breast-feeding mothers	68 mothers, 68 infants	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 ( <i>Lactobacillus</i> -treated) vs 10.4 (placebo-treated), p = 0.6 Total serum IgE, frequency of infants with serum antigen-specific IgE >0.35 kU/L, frequency of infants with one positive skin prick test at 3, 12, 24 mo: not statistically different between <i>Lactobacillus</i> - and placebo-treated pts

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.,<sup>[8]</sup> serum levels of TNF $\alpha$  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.<sup>[16]</sup> found that TNF $\alpha$  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<sup>[6]</sup> 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.<sup>[11]</sup> 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  $\mu\text{g/L}$ , respectively;  $p = 0.03$ ). In two other studies,<sup>[14,17]</sup> 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)- $\beta$  has also been studied. Isolauri et al.<sup>[8]</sup> found that, in infants with AD during exclusive breast feeding treated with *B. lactis* Bb-12 for 2 months, serum TGF $\beta$ 1 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.<sup>[24]</sup> 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 TGF $\beta$ 1 and TGF $\beta$ 2. In the trial by Prescott et al.,<sup>[16]</sup> TGF $\beta$  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.<sup>[20]</sup> found that TGF $\beta$ 2 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<sup>[20-22]</sup> 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 prebiotics 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.<sup>[21]</sup>

A more recent RCT<sup>[23]</sup> 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<sup>[25]</sup> or modified UK diagnostic criteria for AD,<sup>[26]</sup> except for two RCTs<sup>[7,10]</sup> 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<sup>[12-14]</sup> suggested that the effect of probiotics on the severity of AD is not statistically significant, although in one of these trials,<sup>[12]</sup> SCORAD decreased significantly in food-sensitized children. SCORAD was significantly reduced after probiotic administration in four RCTs;<sup>[6-9]</sup> in two other trials, SCORAD decreased significantly only in children with IgE-associated AD.<sup>[10,11]</sup> Four of these six RCTs<sup>[6,8-10,15,16]</sup> 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.,<sup>[7]</sup> 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,<sup>[9,10]</sup> 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.<sup>[27]</sup> In the trial by Viljanen et al.,<sup>[10]</sup> 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.,<sup>[9]</sup> 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.<sup>[27]</sup>

In most of the RCTs evaluated, probiotics did not have a significant effect on IFN $\gamma$  or IL-4 production in children with AD treated with probiotics. However, in one RCT,<sup>[16]</sup> the increase in IFN $\gamma$  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 IFN $\gamma$ <sup>[15]</sup> 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<sup>[28]</sup> but gradually weakens and deviates toward Th1-mediated immunity in non-atopic infants. Patients with AD,<sup>[29]</sup> especially infants with severe AD,<sup>[30,31]</sup> have decreased numbers of CD4+-Th1 cells that spontaneously express IFN $\gamma$ . Some studies<sup>[29,32]</sup> have found lower numbers of CD4+-Th2 cells that express IL-4 in patients with AD compared with non-atopic patients, whereas other studies<sup>[30]</sup> have reported them to be higher in AD patients. IL-4 stimulates IgE production by lymphocytes, while IFN $\gamma$  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.<sup>[33,34]</sup>

Probiotics also did not have a significant effect on TNF $\alpha$  levels in the feces or sera of infants with AD in most of the studied trials. However, in the study by Majamaa and Isolauri,<sup>[6]</sup> the decreases in median fecal TNF $\alpha$  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 TNF $\alpha$  by human PBMCs.<sup>[35]</sup> Production of TNF $\alpha$  in patients with AD has been found to be significantly lower compared with that in non-allergic patients in some studies,<sup>[31,36,37]</sup> while TNF $\alpha$  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.<sup>[32,38,39]</sup> However, in some other studies,<sup>[38,40]</sup> TNF $\alpha$  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 TNF $\alpha$  has been correlated with the severity of AD.<sup>[41,42]</sup> TNF $\alpha$  increases the expression of adhesion molecules (vascular cell adhesion molecule-1, E-selectin, endothelial leukocyte adhesion molecule-1)<sup>[43]</sup> and stimulates keratinocytes to produce substances (Regulated upon Activation, Normal T cell-Expressed and Secreted [RANTES] chemokine, granulocyte macrophage-colony stimulat-

ing factor) that attract eosinophils in the skin of patients with AD.<sup>[44,45]</sup>

In most of the RCTs evaluated, probiotics did not cause a statistically significant change in serum or fecal ECP in children with AD compared with placebo. Serum levels of ECP have been found to be statistically significantly higher in patients with AD in comparison with healthy control patients in many studies.<sup>[46-54]</sup> Majamaa et al.<sup>[55]</sup> found that fecal ECP was also significantly increased in infants with AD compared with healthy infants. Although most studies have suggested that there is a statistically significant association between serum levels of ECP and SCORAD,<sup>[46,47,52,56]</sup> a few have suggested that there is no statistically significant relationship.<sup>[57,58]</sup> Improvement in the clinical severity of AD has been accompanied by a decrease in serum ECP in some studies.<sup>[52,56]</sup>

TGF $\beta$  is considered to induce IgA production and oral tolerance and has been found to be lower in patients with AD compared with non-atopic patients.<sup>[59-61]</sup> One study<sup>[59]</sup> has suggested that children with moderately severe, chronic AD are more likely to have a low TGF $\beta$ 1 producer genotype than non-atopic children. Similarly, in another study,<sup>[60]</sup> spontaneous messenger RNA expression of TGF $\beta$  in PBMCs was significantly lower in patients with AD compared with control patients. However, serum TGF $\beta$  levels were not found to be significantly elevated by treatment with probiotics in infants with AD in the RCTs studied. TGF $\beta$ 2 in breast milk has been found to be significantly lower in mothers with AD compared with mothers without AD.<sup>[61]</sup> In one RCT,<sup>[20]</sup> a statistically significant increase in TGF $\beta$ 2 in the breast milk of mothers with a family history of atopy was found after *L. rhamnosus* GG administration compared with placebo, which probably protected their infants from developing AD.

The RCTs of the effectiveness of probiotics in the prevention of AD also had some limitations. In two studies,<sup>[20,21]</sup> the prevalence of AD in placebo-treated infants was very high<sup>[62]</sup> and fecal lactobacilli counts were not measured. Thus, evidence as to whether the administered probiotics colonized the intestine was lacking.<sup>[63]</sup>

## 5. Conclusion

Administration of probiotics, especially *L. rhamnosus* GG to infants at high risk for atopy and/or to their mothers, seems to be effective for preventing infants from developing AD. Treatment with probiotics for 1 or 2 months was also found to reduce the severity of AD in approximately half of the RCTs evaluated, with children with high total or allergen-specific serum IgE, especially those with food allergy, being most likely to benefit. However, use of probiotics did not significantly change most of the inflamma-

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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## References

- Williams HC. Atopic dermatitis. *N Engl J Med* 2005; 352: 2314-24
- Reid G, Jass J, Sebulsky T, et al. Potential uses of probiotics in clinical practice. *Clin Microbiol Rev* 2003; 16: 658-72
- Bjorksten B, Sepp E, Julge K, et al. Allergy development and the intestinal microflora during the first year of life. *J Allergy Clin Immunol* 2001; 108 (4): 516-20
- Bongaerts GPA, Severijnen RSVM. Preventive and curative effects of probiotics in atopic patients. *Med Hypotheses* 2005; 64: 1089-92
- Isolauri E, Sutas Y, Kankaanpaa P, et al. Probiotics: effects on immunity. *Am J Clin Nutr* 2001; 73: 444-50
- Majamaa H, Isolauri E. Probiotics: a novel approach in the management of food allergy. *J Allergy Clin Immunol* 1997; 99 (2): 179-85
- Kirjavainen PV, Salminen SJ, Isolauri E. Probiotic bacteria in the management of atopic disease: underscoring the importance of viability. *J Pediatr Gastroenterol Nutr* 2003; 36: 223-7
- Isolauri E, Arvola T, Sutas Y, et al. Probiotics in the management of atopic eczema. *Clin Exp Allergy* 2000; 30 (11): 1604-10
- Weston S, Halbert A, Richmond P, et al. Effects of probiotics on atopic dermatitis: a randomised controlled trial. *Arch Dis Child* 2005 Sep; 90 (9): 892-7
- Viljanen M, Savilahti E, Haahtela T, et al. Probiotics in the treatment of atopic eczema/dermatitis syndrome in infants: a double-blind placebo-controlled trial. *Allergy* 2005; 60 (4): 494-500
- Rosenfeldt V, Benfeldt E, Nielsen SD, et al. Effect of probiotic *Lactobacillus* strains in children with atopic dermatitis. *J Allergy Clin Immunol* 2003; 111: 389-95
- Sistek D, Kelly R, Wickens K, et al. Is the effect of probiotics on atopic dermatitis confined to food sensitized children? *Clin Exp Allergy* 2006; 36 (5): 629-33
- Brouwer ML, Wolt-Plompen SA, Dubois AE, et al. No effects of probiotics on atopic dermatitis in infancy: a randomized placebo-controlled trial. *Clin Exp Allergy* 2006 Jul; 36 (7): 899-906
- Folster-Holst R, Muller F, Schnopp N, et al. Prospective, randomised controlled trial on *Lactobacillus rhamnosus* in infants with moderate to severe atopic dermatitis. *Br J Dermatol* 2006; 155: 1256-61
- Pohjavuori E, Viljanen M, Korpela R, et al. *Lactobacillus* GG effect in increasing IFN-gamma production in infants with cow's milk allergy. *J Allergy Clin Immunol* 2004; 114: 131-6
- Prescott SL, Dunstan JA, Hale J, et al. Clinical effects of probiotics are associated with increased interferon-gamma responses in very young children with atopic dermatitis. *Clin Exp Allergy* 2005 Dec; 35 (12): 1557-64
- Viljanen M, Kuitunen M, Haahtela T, et al. Probiotic effects on faecal inflammatory markers and on faecal IgA in food allergic atopic eczema/dermatitis syndrome infants. *Pediatr Allergy Immunol* 2005; 16: 65-71
- Rosenfeldt V, Benfeldt E, Valerius NH, et al. Effect of probiotics on gastrointestinal symptoms and small intestinal permeability in children with atopic dermatitis. *J Pediatr* 2004; 145: 612-6
- Kankaanpaa PE, Yang B, Kallio HP, et al. Influence of probiotic supplemented infant formula on composition of plasma lipids in atopic infants. *J Nutr Biochem* 2002; 13 (6): 364-9
- Rautava S, Kalliomaki M, Isolauri E. Probiotics during pregnancy and breastfeeding might confer immunomodulatory protection against atopic disease in the infant. *J Allergy Clin Immunol* 2002; 109 (1): 119-21
- Kalliomaki M, Salminen S, Arvilommi H, et al. Probiotics in primary prevention of atopic disease: a randomised placebo-controlled trial. *Lancet* 2001; 357 (9262): 1076-9
- Kukkonen K, Savilahti E, Haahtela T, et al. Probiotics and prebiotic galacto-oligosaccharides in the prevention of allergic diseases: a randomised, double-blind, placebo-controlled trial. *J Allergy Clin Immunol* 2007; 119: 192-8
- Taylor A, Dunstan J, Prescott S. Probiotic supplementation for the first 6 months of life fails to reduce the risk of atopic dermatitis and increases the risk of allergen sensitisation in high-risk children: a randomised controlled trial. *J Allergy Clin Immunol* 2007; 119: 184-91
- Viljanen M, Pohjavuori E, Haahtela T, et al. Induction of inflammation as a possible mechanism of probiotic effect in atopic eczema-dermatitis syndrome. *J Allergy Clin Immunol* 2005; 115 (6): 1254-9
- Hanifin JM, Rajka G. Diagnostic features of atopic dermatitis. *Acta Derm Venereol* 1980; 92: 44-7
- Williams HC, Burney PG, Pembroke AC, et al. The U.K. Working Party's diagnostic criteria for atopic dermatitis: III. Independent hospital validation. *Br J Dermatol* 1994; 131: 406-16
- Williams HC. Two positive studies of probiotics for atopic dermatitis. *Arch Dermatol* 2006; 142: 1201-3
- Kawamoto N, Kaneko H, Takemura M, et al. Age-related changes in intracellular cytokine profiles and Th2 dominance in allergic children. *Pediatr Allergy Immunol* 2006; 17 (2): 125-33
- Kallstrom E, Roscher I, Andreasson A, et al. Decreased frequency of intracellular IFN-gamma producing T cells in whole blood preparations from patients with atopic dermatitis. *Exp Dermatol* 2002; 11 (6): 556-63
- Tang M, Kemp A, Varigos G. IL-4 and interferon-gamma production in children with atopic disease. *Clin Exp Immunol* 1993; 92 (1): 120-4
- Dunstan JA, Hale J, Breckler L, et al. Atopic dermatitis in young children is associated with impaired interleukin-10 and interferon-gamma responses to allergens, vaccines and colonizing skin and gut bacteria. *Clin Exp Allergy* 2005; 35 (10): 1309-17
- Machura E, Mazur B, Kwicencin J, et al. Intracellular production of IL-2, IL-4, IFN-gamma, and TNF-alpha by peripheral blood CD3+ and CD4+ T cells in children with atopic dermatitis. *Eur J Pediatr* 2007; 166 (8): 789-95
- Sutas Y, Soppi E, Korhonen H, et al. Suppression of lymphocyte proliferation in vitro by bovine caseins hydrolyzed with *Lactobacillus casei* GG-derived enzymes. *J Allergy Clin Immunol* 1996; 98 (1): 216-24
- Sutas Y, Hurme M, Isolauri E. Down-regulation of anti-CD3 antibody-induced IL-4 production by bovine caseins hydrolysed with *Lactobacillus* GG-derived enzymes. *Scand J Immunol* 1996; 43 (6): 687-9
- Miettinen M, Vuopio-Varkila J, Varkila K. Production of human tumor necrosis factor alpha, interleukin-6 and interleukin-10 is induced by lactic acid bacteria. *Infect Immun* 1996; 64: 5403-5
- Poulsen LK, Bindslev-Jensen C, Diamant M, et al. Biomolecular regulation of the IgE immune response: III. Cytokine profiles in atopic dermatitis, inhalant allergy and non-allergic donors. *Cytokine* 1996; 8 (8): 651-7
- Takahashi T, Sasaki Y, Hama K, et al. Production of IL-4, IL-2, IFN-gamma, and TNF-alpha by peripheral blood mononuclear cells of patients with atopic dermatitis. *J Dermatol Sci* 1992; 3 (3): 172-80
- Antunez C, Torres MJ, Mayorga C, et al. Different cytokine production and activation marker profiles in circulating cutaneous-lymphocyte-associated antigen T cells from patients with acute or chronic atopic dermatitis. *Clin Exp Allergy* 2004; 34 (4): 559-66
- Reinhold U, Pawelec G, Wehrmann W, et al. Cytokine release from cultured peripheral blood mononuclear cells of patients with severe atopic dermatitis. *Acta Derm Venereol* 1989; 69 (6): 497-502
- Seneviratne SL, Jones L, Bailey AS, et al. Severe atopic dermatitis is associated with a reduced frequency of IL-10 producing allergen-specific CD4+ T cells. *Clin Exp Dermatol* 2006; 31 (5): 689-94
- Pellegrino M, Minervini B, Musto P, et al. Tumor necrosis factor-alpha and interleukin-1 beta: two possible mediators of allergic inflammation. *Minerva Pediatr* 1996; 48 (7-8): 309-12
- Sumimoto S, Kawai M, Kasajima Y, et al. Increased plasma tumour necrosis factor-alpha concentration in atopic dermatitis. *Arch Dis Child* 1992; 67 (3): 277-9

43. de Vries IJ, Langeveld-Wildschut EG, van Reijssen FC, et al. Adhesion molecule expression on skin endothelia in atopic dermatitis: effects of TNF-alpha and IL-4. *J Allergy Clin Immunol* 1998; 102 (3): 461-8
44. Noso N, Sticherling M, Bartels J, et al. Identification of an N-terminally truncated form of the chemokine RANTES and granulocyte-macrophage colony-stimulating factor as major eosinophil attractants released by cytokine-stimulated dermal fibroblasts. *J Immunol* 1996; 156 (5): 1946-53
45. Yamada H, Matsukura M, Yodate T, et al. Enhanced production of RANTES, an eosinophil chemoattractant factor, by cytokine-stimulated epidermal keratinocytes. *Int Arch Allergy Immunol* 1997; 114 Suppl. 1: 28-32
46. Angelova-Fischer I, Hipler UC, Bauer A, et al. Significance of interleukin-16, macrophage-derived chemokine, eosinophil cationic protein and soluble E-selectin in reflecting disease activity of atopic dermatitis: from laboratory parameters to clinical scores. *Br J Dermatol* 2006; 154 (6): 1112-7
47. Pucci N, Lombardi E, Novembre E, et al. Urinary eosinophil protein X and serum eosinophil cationic protein in infants and young children with atopic dermatitis: correlation with disease activity. *J Allergy Clin Immunol* 2000; 105 (2 Pt 1): 353-7
48. Gebhardt M, Wenzel HC, Hipler UC, et al. Monitoring of serologic immune parameters in inflammatory skin diseases. *Allergy* 1997; 52 (11): 1087-94
49. Miyasato M, Tsuda S, Nakama T, et al. Serum levels of eosinophil cationic protein reflect the state of in vitro degranulation of blood hypodense eosinophils in atopic dermatitis. *J Dermatol* 1996; 23 (6): 382-8
50. Nakama T. Relationships between eosinophil-associated parameters and disease severity in atopic dermatitis. *Kurume Med J* 1995; 42 (2): 95-106
51. Kristjansson S, Shimizu T, Strannegard IL, et al. Eosinophil cationic protein, myeloperoxidase and tryptase in children with asthma and atopic dermatitis. *Pediatr Allergy Immunol* 1994; 5 (4): 223-9
52. Czech W, Krutmann J, Schopf E, et al. Serum eosinophil cationic protein (ECP) is a sensitive measure for disease activity in atopic dermatitis. *Br J Dermatol* 1992; 126 (4): 351-5
53. Sugai T, Sakiyama Y, Matumoto S. Eosinophil cationic protein in peripheral blood of pediatric patients with allergic diseases. *Clin Exp Allergy* 1992; 22 (2): 275-81
54. Paganelli R, Fanales-Belasio E, Carmini D, et al. Serum eosinophil cationic protein in patients with atopic dermatitis. *Int Arch Allergy Appl Immunol* 1991; 96 (2): 175-8
55. Majamaa H, Laine S, Miettinen A. Eosinophil protein X and eosinophil cationic protein as indicators of intestinal inflammation in infants with atopic eczema and food allergy. *Clin Exp Allergy* 1999; 29 (11): 1502-6
56. Tsuda S, Kato K, Miyasato M, et al. Eosinophil involvement in atopic dermatitis as reflected by elevated serum levels of eosinophil cationic protein. *J Dermatol* 1992; 19 (4): 208-13
57. Slobodna MS, Jasna L, Vesna Z, et al. Serum eosinophil cationic protein in children with atopic dermatitis. *Int J Dermatol* 2006; 45 (10): 1156-60
58. Wolkerstorfer A, Laan MP, Savelkoul HF, et al. Soluble E-selectin, other markers of inflammation and disease severity in children with atopic dermatitis. *Br J Dermatol* 1998; 138 (3): 431-5
59. Arkwright PD, Chase JM, Babbage S, et al. Atopic dermatitis is associated with a low-producer transforming growth factor beta(1) cytokine genotype. *J Allergy Clin Immunol* 2001; 108 (2): 281-4
60. Lee HJ, Lee HP, Ha SJ, et al. Spontaneous expression of mRNA for IL-10, GM-CSF, TGF-beta, TGF-alpha, and IL-6 in peripheral blood mononuclear cells from atopic dermatitis. *Ann Allergy Asthma Immunol* 2000; 84 (5): 553-8
61. Laiho K, Lampi AM, Hamalainen M, et al. Breast milk fatty acids, eicosanoids, and cytokines in mothers with and without allergic disease. *Pediatr Res* 2003; 53 (4): 642-7
62. Nowak-Wegrzyn A. Future approaches to food allergy. *Pediatrics* 2003; 111: 1672-80
63. Matricardi PM, Bjorksten B, Bonini S, et al. Microbial products in allergy prevention and therapy. *Allergy* 2003; 58: 461-71

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