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Probiotics for the Prevention of Childhood Eczema

A review of the literature

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Abstract

The prevalence of eczema has increased during the past few decades and continues to rise. Furthermore, childhood eczema is associated with the development of allergy later in life. As a result, there is considerable interest in identifying effective treatments to prevent eczema and, possibly, halt the progression of allergic disease. One such preventive treatment option is probiotic therapy; however, the results from clinical trials have been inconsistent due, in part, to differences in probiotic strains. The Probiotics and Allergy (PandA) trial was the first study of a multistrain probiotic for the prevention of childhood eczema in which strains were selected based on *in vitro* cytokine production. The results of this trial are discussed in the context of other published clinical trials on probiotics for the prevention of childhood eczema, along with a discussion of the hygiene hypothesis and a review of Th1/Th2 immune balance.

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Introduction

Eczema is a chronic, inflammatory skin condition characterized by varying degrees of erythema and pruritis, mainly affecting the face, neck, and flexural folds of the knees and elbows. The terms eczema and atopic dermatitis (AD) are often used interchangeably, although this lack of distinction is technically incorrect. A diagnosis of AD is more specific and excludes non-atopic pathologies, such as contact dermatitis.[1] Atopy is distinguished by IgE sensitization or a positive skin test to environmental or food allergens, although these studies are not often utilized in the clinical setting. In practice, the distinction between eczema and AD is a predominately clinical one and is often based on symptoms, age of onset, and family history of allergic disease. For the purposes of this review, both terms will be utilized, and the choice of terms will be based on the preference of the primary reference.

Eczema is the most common inflammatory skin condition in children and contributes significantly to childhood morbidity. Eczema affects children throughout the world, although prevalence varies widely by region. In the United States, northern Europe, and Australia, up to 20% of children are affected.[1,2] By contrast, only 2% to 5% of children in China and the Middle East are estimated to have eczema. The age of onset for more severe or chronic eczema is typically before 2 years and often within the first 6 months of life. Most children "outgrow" eczema by their teens, although this is not definitive and relapse may occur. While eczema can present at any time throughout life, adult onset of true AD is rare. According to one study, 10.7% of the total U.S. population, or 31.6 million Americans, meet the broad symptoms criteria for eczema, and the direct costs associated with AD alone may be as high as $1–4 billion.[3] Such estimates are difficult to confirm, however, as many cutaneous eruptions with an unclear etiology are labeled as eczema.

> Eczema is the most common inflammatory skin

> condition in children and contributes significantly to childhood morbidity.

The prevalence of allergic diseases among children, including eczema, has more than doubled during the past few decades and continues to rise.[4] Furthermore, childhood eczema is associated with the development of other allergic diseases later in life, including asthma,[5] a phenomenon referred to as the *allergic march*. The risk of developing asthma is nearly twice as high in people with childhood eczema compared to people with no history of eczema.[5] As a result, there is considerable interest in identifying effective treatments for the primary prevention of childhood eczema in an effort to alter the progression of allergic disease. One proposed treatment option is probiotics, defined as live microorganisms that, when administered in adequate amounts, confer a health benefit on the host.[6] Probiotics are generally regarded as safe, and so far no differences in gastrointestinal adverse event rates between probiotic and treatment groups have been reported.[7] However, the safety and effectiveness of probiotics in childhood eczema remains under investigation, and the mechanisms by which they might exert positive effects on eczema are not completely understood.

Randomized Controlled Trials

Probiotics have been studied for both the primary prevention and treatment of childhood eczema. Primary prevention studies, the subject of this review, often employ a perinatal supplementation protocol in which pregnant women are supplemented during the final weeks of pregnancy, followed by direct supplementation of the infant. Such studies enroll mothers at high risk for delivering an infant likely to develop atopic dermatitis, with the risk factor determined by family history. In some prevention studies, at-risk infants are enrolled and supplemented within hours of birth.

To date, 10 distinct randomized controlled trials assessing different probiotics or probiotic combinations have been published on the primary prevention of eczema, and these trials have produced conflicting results (see Table 1). Among these studies, 7 have reported a decreased incidence of eczema in probiotic-supplemented infants,[8,14,18,20-23] with a maximum risk reduction of 58% (the PandA trial).[20] One study reported no decrease in the overall incidence of eczema, but a decrease in eczema in children with a positive IgE titer or skin prick test (SPT).[11] Only one study has reported a decrease in the severity of eczema, as determined by the scoring of atopic disease (SCORAD) method.[18] Three studies reported no change in the incidence of eczema,[17-19] and one study reported an increased incidence in eczema in children with a positive SPT.[12] Furthermore, 2 studies reported significant increases in sensitization or incidence of wheezing.[12,17] This is in contrast to 2 reports of decreased sensitization in the breastfed infants of atopic mothers when the mothers were supplemented with probiotics.[13,22] No preventive effects of probiotics on the development of other allergic diseases have yet been reported.

Table 1. Summary of randomized controlled trials on probiotics for the primary prevention of eczema.

Reference(s) / Location	Strain(s) / Dosage[a]	n[b]	Duration of Supplementation		Follow up	Results
			Prenatal	Postnatal		
Kalliomaki 2001[8]; 2003[9]; 2007[10] / Finland	*Lactobacillus rhamnosus* GG (ATCC 53103) / 1 x 10^{10} CFU/d	159	2-4 wks	6 mos[c]	2, 4, and 7 yrs	? incidence of eczema No difference in severity (SCORAD)
						No difference in incidence of eczema ? IgE-associated eczema (IgE or

About the Author

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Abrahamsson 2007 / Sweden[11]	*Lactobacillus reuteri* (ATCC 55730) / 1 x 10^8 CFU/d (in coconut oil)	232	4 wks	12 mos	2 yrs	positive SPT) No difference in severity (SCORAD) Trend toward ? sensitization, significant only in children with atopic mothers (positive SPT)
Taylor 2007[12] / Bottcher 2008[13] Australia	*Lactobacillus acidophilus* (LAVRI-A1) / 3 x 10^9 CFU/d	226	N/Ad	6 mos	1 yr	No difference in incidence of eczema ? incidence of atopic eczema (positive SPT) ? rate of sensitization (positive SPT) ? overall incidence of wheezing (26% vs. 13%) ? *Lactobacillus* colonization confirmed
Kukkonen 2007[14]; Marschan 2008[15]; Kuitunen 2009[16] / Finland	*Lactobacillus rhamnosus* GG (ATCC 53103) / 5 x 10^9 CFU/d *Lactobacillus rhamnosus* LC705 (DSM 7061) / 5 x 10^9 CFU/d *Bifidobacterium breve* Bb99 (DSM 13692) / 2 x 10^8 CFU/d *Propionibacterium freudenreichii ssp. shermanii* JS (DSM 7076) / 2 x 10^9 CFU/d + 0.8 g galacto-oligosaccharides	1223	2-4 wks	6 mos	2 and 5 yrs	No difference in cumulative incidence of allergic diseases ? incidence of eczema (2 yrs) ? incidence of atopic eczema (IgE or positive SPT) (2 yrs) ? incidence of atopic eczema (IgE or positive SPT) in cesarean-delivered children (5 yrs) No difference in severity (SCORAD) ? CRP, IgA, IgE, and IL-10 (subgroup analysis, n=98) ? *Lactobacillus* and *Bifidobacterium* colonization confirmed
Kopp 2008[17] / Germany	*Lactobacillus rhamnosus* GG (ATCC 53103) / 5 x 10^9 CFU/d	105	4-6 wks	6 mos[e]	2 yrs	No difference in incidence of eczema No difference in severity (SCORAD) ? rate of recurrent episodes of wheezing bronchitis (26% vs. 9.1%)
						? incidence of eczema (*L. rhamnosus*) ? IgE-associated eczema

Wickens 2008[18] / New Zealand	*Lactobacillus rhamnosus* (HN001) / 6×10^9 CFU/d or *Bifidobacterium animalis ssp. lactis* (HN019) / 9×10^9 CFU/d	474	5 wks	6 mos (mother) 2 yrs (infant)	2 yrs	(positive SPT) (*L. rhamnosus*) ? severity (SCORAD = 10) (*L. rhamnosus*) No difference in incidence of eczema or severity (*B. lactis*) ? *Lactobacillus* and *Bifidobacterium* colonization confirmed
Soh 2009[19] / Singapore	*Bifidobacterium longum* (BL999) *Lactobacillus rhamnosus* (LPR) / ~2.8×10^8 CFU/d combined (in infant formula)	253	N/A[d]	6 mos	1 yr	No difference in incidence of eczema No difference in IgE-associated eczema (IgE or positive SPT) No difference in severity (SCORAD)
Niers 2009[20] / The Netherlands	*Bifidobacterium bifidum* (W23) *Bifidobacterium lactis* (W52) *Lactococcus lactis* (W58) / 3×10^9 CFU/d combined (as Ecologic® Panda)	156	6 wks	12 mos	2 yrs	? incidence of eczema (both parent-reported and physician-diagnosed) No difference in IgE-associated eczema (IgE or positive SPT) No difference in severity (SCORAD) ? *in vitro* production of IL-5 (?IL-13, ns) ?*Lactococcus* and *Bifidobacterium* colonization confirmed
Kim 2009[21] / Korea	*Bifidobacterium bifidum* (BGN4) *Bifidobacterium lactis* (AD011) *Lactobacillus acidophilus* (AD031) / 4.8×10^9 CFU/d combined	112	8 wks	6 mos[e]	1 yr	? incidence of eczema No difference in IgE-associated eczema (IgE) No difference in severity (SASSAD)
West 2009[22] / Sweden	*Lactobacillus* F-19 1×10^8 CFU (as cereal)	180		4-13 mos	13 mos	? incidence of eczema (physician diagnosed), No difference in atopic sensitization (IgE), Higher Th1/Th2 ratio (PBMC)
	Lactobacillus rhamnosus 5 10					? incidence of atopic dermatitis (NESS)

Dotterud 2010[23] / Norway	x10 CFU/d, *Bifidobacterium animalis ssp. Lactis* 5 x10^{10} CFU/d, *L. acidophilus* La-5 5 x10^{10} CFU/d combined (as Probiotic Milk Biola®)	415	1 mos	3 mos	2 yr	No difference in incidence of asthma (physician diagnosed) or atopic sensitization (IgE or positive SPT)

[a] *Provided as a powder mixed in water, breast milk, or formula unless otherwise indicated.*

[b] *At time of randomization.*

[c] *Mothers could choose to administer the probiotic directly to the infant (56%) or to consume the probiotic and deliver via breast milk.*

[d] *Supplementation was begun within 12 hours (Soh 2009) or 48 hours of birth (Taylor 2007).*

[e] *Mothers supplemented with the probiotic for 3 months , exposing infant via breast milk, followed by 3 months of direct supplementation of the infant.*

The large heterogeneity in results might be explained by several factors. First, it is apparent that different probiotic strains or combinations of probiotics would be expected to elicit different effects. This explanation is insufficient, however, based on the observation that studies on the same single strain of Lactobacillus rhamnosus GG (LGG) have reported dramatically different results.[8,17] Next, differences in outcomes may be due, in part, to differences in doses or routes of administration. While most studies of primary prevention have administered probiotics to both the pregnant mother and infant, some supplemented only the infant[12,19,22] and others relied on supplementation of the mother and the administration of protective factors to the infant via breast milk.[8,17, 21,23] Interestingly, supplementing pregnant and breastfeeding mothers with probiotics has been reported to alter immune factors in cord blood and breast milk and decrease the incidence of eczema, even without administration of probiotics to the child.[13,25,26] Finally, no studies have confirmed the colonization of probiotic bacteria in the intestine, and some studies have reported alterations in the microflora not reflective of the administered bacteria. Prenatal administration with LGG, for example, did not result in infant colonization with LGG, but rather an increase in the percentage of infants with detectable *Bifidobacterium longum*.[27] Clearly, the interactions between different probiotic strains or between probiotic bacteria and the resident microflora are still not fully understood.

Probiotics and the Hygiene Hypothesis

The mechanisms of action by which probiotic supplementation might reduce allergic diseases have not been elucidated but could be related to changes in the gut microbiota, immunological effects, or a combination of the two. Differences in the intestinal flora between allergic and nonallergic infants and children have been described, which predicate the development of allergic disease, including eczema, suggesting a potential causal relationship.[27-30] Specifically, *bifidobacteria* and *lactobacilli* are more often found in the microbiota of nonallergic children.[28,30] The hygiene hypothesis provides a framework for understanding the increased incidence of allergic diseases in the context of microbial and immune interactions.

According to the hygiene hypothesis, the increased prevalence of allergic diseases in children may be associated with reduced exposure to microbial components early in life. Although not so termed, the hygiene hypothesis was proposed by David Strachan, Department of Epidemiology and Population Sciences, London School of Hygiene and Tropical Medicine, in a landmark paper in the *British Medical Journal* in 1989.[31] In an entry just over a page in length, the epidemiologist provided data from a sample of approximately 17,000 people in Britain, demonstrating that parent-recalled eczema in the first year of life and the prevalence of hay fever later in life were both inversely and independently associated with the number of older children in the household. The author proposed that these observations could be explained if “allergic diseases were prevented by infection in early childhood, transmitted by unhygienic contact with older siblings, or acquired prenatally from a mother infected by contact with her older children … Later infection or reinfection by younger siblings,” he reasoned, “might confer additional protection…” Furthermore, he concluded, “Over the past century declining family size, improvements in household amenities, and higher standards of personal cleanliness have reduced the opportunity for cross infection in young families. This may have resulted in more widespread clinical expression of atopic disease…”

Extending these observations, the hygiene hypothesis suggests, in part, that a lack of early microbial exposure is associated with an imbalance in the neonatal development of T helper (Th)1, Th2 cells, and regulatory T cells (Treg), contributing to the increased prevalence of Th2-associated allergic diseases. Indeed, children at high risk of developing allergic disease early in life are characterized by a Th2-polarized cytokine profile.[32] As their name suggests, Th cells help to orchestrate the immune response by driving both cell-mediated responses and antibody responses, depending on the antigenic stimulus. Although not fully understood, the stimulating environment established by innate and accessory immune cells, such as natural killer cells, macrophages, and dendritic cells, along with the type and amount of antigen presented by the antigen presenting cell to the Th cell, determines the functional phenotype of the Th cell (Figure 1). Naïve Th0 cells can differentiate upon stimulation into either a Th1, a Th2, a Th17, or a Treg cell lineage, which differ in the cytokines, or chemical signaling molecules, they produce. Different cytokine profiles trigger different effects. In general, a Th1-dominant cytokine profile is characterized by interferon (IFN)-? and is associated with the activation of cellular immunity. In contrast, a Th2 cytokine profile, characterized by IL-4, IL-5, and IL-13, is associated with humoral immunity, or antibody production. Tregs are less well defined but are characterized by the production of IL-10, a cytokine involved in immune cell regulation and self-tolerance, as well as IL-6 and TGF-ß. Of course, no immune response is absolute but is the result of complex interactions between multiple cell types and activating and inhibitory molecules. Thus, it is important to recognize that a robust and controlled immune system requires the balanced and continuous interplay of Th1, Th2, and Treg activities.

It is important to note that the hygiene hypothesis has been revised several times and merely constitutes a theory to explain much more complicated immunologic functioning.

Figure 1

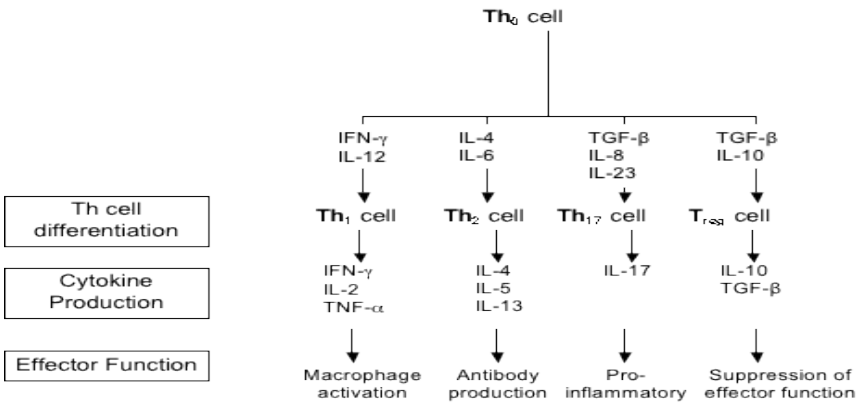

Figure 1. A schematic review of Th1 and Th2 immunity. Naïve Th0 cells differentiate into either Th1, Th2 , Th17 or Treg cells depending, in part, on the predominant cytokines in the activating environment. T helper subset dominant responses are then characterized by subsequent cytokine production and specific associated effector functions.

Probiotics and Infant Immunity

Several observations suggest that probiotics might be an effective means of supporting Th1/Th2 balance in neonates in the absence of sufficient natural microbial exposures, thus preventing the development of Th2-dominant allergic diseases. The basic requirement for the intestinal microbiota in the development, maturation, and functionality of the immune system has been clearly demonstrated in studies using gnotobiotic, (ie, germ-free) rodents.[33,34] *In vitro* studies have also shown that certain probiotic strains can modulate cytokine production and polarize toward Th1-dominant responses in both adult human peripheral blood mononuclear cells (PBMCs) and cord blood cells from neonates;[22,35-38] however, less is known about the strain-specific effects of probiotics on cytokine production *in vivo*, especially in human infants.

Recently, 3 publications have assessed *in vivo* immune modulation in infants in the context of the primary prevention of eczema.[14,20,22] In a subgroup analysis of Kukkonen et al.,[14] Marschan and colleagues

reported increased CRP, IgA, IgE, and IL-10 in infants supplemented with a combination of probiotics.[15] These results support the hypothesis that some probiotics may induce a systemic low-grade inflammation typical of a Th1-type immune response that could be beneficial for lowering the Th2 dominant profile seen in eczema.[39] In a separate study, T-cell mediated response was assessed in at-risk infants supplemented with probiotic-enhanced cereals during weaning.[22] Analysis of PBMCs showed a higher IFN-?/IL-4 ratio in infants supplemented with probiotics, indicative of a higher Th1/Th2 ratio, in conjunction with a lower incidence of eczema. The third study assessing immune modulation in infants is the PandA (Probiotics and Allergy) trial.[20] This study is unique in that probiotic strains were selected from an original pool of 69 strains in a multistage process. Candidate strains were selected based on stability and resistance to gastric acid, bile salts, and pancreatic enzymes[40] and then further selected according to *in vitro* cytokine production in adult human PBMCs and infant cord blood cells.[37,38] In the end, *Bifidobacterium bifidum* W23, *Bifidobacterium lactis* W52, and *Lactococcus lactis* W58, were selected based on their capacity to induce the production of regulatory IL-10 and a reduction in IL-5 and IL-13. Among these strains, *B. bifidum* most consistently modulated immune responses in neonatal cells, including a polarization toward Th1, as demonstrated by an increase in IFN-? producing T cells and a decrease in IL-4.[38]

The PandA Study

As summarized in Table 1, supplementation with combined *B. bifidum*, *B. lactis*, and *Lc. lactis* reduced the incidence of infant eczema at 3 months of age (The PandA Trial).[20] The physican-reported incidence of eczema was 23% in the control group and 6% in the probiotic-treated group. Similarly, the parent-reported incidence of eczema was 29% and 12%, respectively, or a relative risk reduction of 58%. This effect persisted to a lesser degree through 1 and 2 years, with risk reductions of 26% and 22%, respectively. Early colonization with *Lc. lactis* and *Bifidobacterium spp.* was confirmed by qPCR, and although not conclusive, the authors proposed that the observed reduction in the incidence of eczema may have been related to altered immune signaling—specifically a decrease in Th2-mediated immunity. A subgroup analysis of infants in the study demonstrated a 2- to 3-fold increase in IL-13 in infants in the placebo group who developed eczema compared to those who did not develop eczema, suggesting an important role for this Th2-associated cytokine in the development of eczema. Moreover, the production of IL-13 and IL-5 was lower in the probiotic-treated group whether or not those infants developed eczema. Cytokine profiles were further assessed by an *ex vivo* analysis in which whole blood samples obtained from study infants at age 3 months were stimulated with anti-CD2/CD28 antibodies for 48–72 hours in culture. Despite a large heterogeneity in cytokine production between subjects, the production of IL-5 was significantly reduced in the probiotic-treated group. There was a trend toward decreased IL-13 production, but this was not significant. No differences in the production of IL-10 were found.

The PandA trial was the first study of a combination probiotic intervention for the primary prevention of childhood eczema in which strains were selected based on *in vitro* cytokine production. Importantly, certain immunomodulatory effects demonstrated *in vitro*, such as the reduction in the Th2-associated cytokines IL-5 and IL-13, were subsequently observed *in vivo* and *ex vivo* in whole blood cells obtained from probiotic-supplemented infants who were also at a lower risk of developing eczema. Future studies need to continue this trend toward identifying the immune activities of probiotics *in vivo* in the context of clinical outcomes.

Conclusion

Several studies have now demonstrated the positive effects of probiotics on reducing the incidence of infant eczema by approximately 50%.[20,22] Perinatal supplementation with probiotics holds promise for the prevention of childhood eczema; however, more studies are needed to examine the effects of specific probiotic strains or combinations of strains, as well as potential interactions. Furthermore, although the concept that early prevention of eczema might halt the progression of allergic disease into adulthood is highly intriguing, it remains to be demonstrated. Future studies should address this significant question. Importantly, the concept of strain selection based on *in vitro* cytokine profiles has been tested and has resulted in a multistrain probiotic with a positive clinical outcome. Additional studies conducted in this manner could identify probiotic strains or combinations of strains that are safe and effective in the prevention and treatment of childhood eczema, as well as the prevention of other allergic diseases.

Disclosure

Dr. Ritz works for Atrium Innovations, which sells a variety of probiotic products, including some of those

mentioned in this paper.

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