

Probiotics, Prebiotics, and Allergy in Children

What's New in the Last Year?

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Abstract: Recent studies have confirmed immunomodulatory and anti-inflammatory properties of probiotics. There are clinical evidences suggesting that probiotics and prebiotics treatment is effective and had a protective effect in the development of atopic dermatitis and the mechanism may be related to local effect on the gastrointestinal tract. About the effect of probiotics on the allergic airway response, the beneficial effects seem to be strain specific, and other studies will be needed to understand the mechanisms involved. Recent data suggests that probiotics may have immunomodulatory effects on vaccine responses, but the significance and clinical relevance of this need to be determined too.

Key Words: probiotic, prebiotic, allergy, children

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Allergic diseases have increased significantly in recent years in all western countries and the cause of this increase should be sought between changes that have taken place in the environment and lifestyle. In the early ages of life, a reduction in the intestinal microbial colonization, resulting in improvement of health conditions, is one of the most accredited hypotheses in explaining this phenomenon. Microbial exposure is important in the development of allergic disease. Reduced exposure to infectious organisms is strongly associated with allergic sensitization that is uncommon in children who spend their childhood on a farm. This may reflect increased exposure to specific bacterial products such as endotoxin lipopolysaccharide. The protective effect of microbial exposure against allergic disease may be the greatest in early life. Intestinal microbiota promote both intestinal mucosal barrier functions and immune development.

Bacterial intestinal flora plays an important role not only in the maturation of humoral responses, especially

the IgA, but also in the polarization of the immune system by promoting the development of T_H1 or T_H2 cytokines. The T_H2 “allergic” phenotype is associated with an increased production of IgE and eosinophils, whereas T_H1 immune response mainly induces a function of intracellular killing.

The underlying mechanisms are not completely clear and probably for these reasons the role of probiotic has been emerging in the last year.

PROBIOTICS AND PREBIOTICS IN THE PREVENTION OF ALLERGIC DISEASES

Primary prevention is the possibility of preventing the beginning of allergic disease in high-risk children. In a recent study¹ in evaluating the cumulative effect of probiotic intervention during the first 7 years of life, we reexamined the study cohort at the age of 7. In 159 mothers who were randomly assigned to receive placebo or *Lactobacillus rhamnosus* strain GG daily for 4 weeks before expected delivery and after delivery, *Lactobacillus* GG or placebo was taken postnatally for 6 months. Children completing the 2-year follow-up were invited to the 7-year follow-up visit.

The cumulative risk for developing eczema during the first 7 years of life was significantly lower in the *Lactobacillus* GG group than in the placebo group. Atopic sensitization was similar between the groups, suggesting that the preventive effect on eczema was not IgE-mediated.

In another double blind, randomized, placebo-controlled trial² the aim was to prevent eczema and sensitization in infants with a family history of allergic disease by oral supplementation with the *Lactobacillus reuteri*. In 232 pregnant women with allergic disease, *L. reuteri* were given to gestational week 36 until delivery. The newborn continued with the same product from birth until 12 months of age and were followed-up for another year. The results showed that the cumulative incidence of eczema was similar but the *L. reuteri* group had less IgE-associated eczema during the second year. SPT reactivity was also less common in the treated than in the placebo group, significantly so for infants with mothers with allergies, 14% versus 31% ($P = 0.02$). Wheeze and other potentially allergic diseases were not affected.

In conclusion, no preventive effect on infant eczema occurred in this study and there was less IgE-associated eczema at 2 years of age in infants receiving *L. reuteri*.

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The different results between this and the Kalliomäki trial raise questions over whether different probiotic strains might have different properties for an effect on allergic diseases.

On the other hand, Taylor et al³ recruited 231 high-risk newborn babies of women with an allergy and gave either *Lactobacillus acidophilus* or placebo daily for the first 6 months of life. Children were assessed for atopic dermatitis (AD) and skin prick tests (SPTs) at 12 months of age. The proportion of children with SPT+AD was significantly higher in the probiotic group. At 12 months, the rate of sensitization was significantly higher in the probiotic group and the presence of *Lactobacillus* at 6 months of age was associated with the increased risk of subsequent cow's milk sensitization. Besides the use of a different bacterial strain, this study design differed from Abrahamsson's study and the Finnish study in that the mothers were not supplemented with probiotic during pregnancy. The results may therefore suggest that the supplementation with probiotic to the mothers in late pregnancy is of crucial importance.

Concerning probiotics plus prebiotic in primary prevention, Kukkonen et al⁴ randomized 1223 pregnant women carrying high-risk children and gave a probiotic preparation or a placebo for 2 to 4 weeks before delivery. Their infants received the same probiotics plus galactooligosaccharides (GOS) or a placebo for 6 months. Results showed at age 2 years that: (a) probiotic plus prebiotic treatment compared with placebo had no effect on the cumulative incidence of any allergic disease; (b) IgE-associated (atopic) diseases tended to occur less frequently in the probiotic plus prebiotic group; (c) eczema occurred less frequently in the probiotic plus prebiotic group; (d) probiotic plus prebiotic treatment more pronouncedly reduced the incidence of atopic eczema; (e) probiotic plus prebiotic treatment compared with placebo had no effect on sensitization at 2 years. In human milk, oligosaccharides are an important factor that promotes an intestinal flora that is dominated by bifidobacteria and lactobacilli.⁵

Moro et al⁶ investigated the effect of a prebiotic mixture of GOS and long chain fructo-oligosaccharides on the incidence of AD during the first 6 months of life in formula-fed infants with a high risk of atopy. Two hundred fifty-nine infants were enrolled at risk for atopy in a prospective, double blind, randomized, placebo-controlled trial. Results showed that the cumulative incidence of AD during the first 6 months of life was significantly reduced by supplementation of a hypoallergenic formula with GOS/fructo-oligosaccharides. Prebiotic supplements were associated with a significantly higher number of fecal bifidobacteria compared with controls but there was no significant difference in lactobacilli counts.

Prebiotics might modulate the postnatal development of the immune system by altering intestinal flora. The results of this study do not allow conclusions to be drawn about the mechanism of the effect that was observed on AD.

The relationship regarding the intestinal microflora and the development of immediate type hypersensitivity to food allergens were investigated by Kendler et al⁷ in children with eczema/dermatitis. In this study, there were no differences in the composition of intestinal microflora in children with food allergy and in children without food allergy.

PROBIOTICS IN THE TREATMENT OF ALLERGIC DISEASES

The use of probiotics in the treatment of allergic disease has been widely investigated by several studies principally for AD therapy, but also for food allergy, allergic rhinitis, and asthma.

Brouwer et al⁸ had the aim of evaluating the clinical and immunologic effects of supplementation of a hydrolyzed formula with 2 probiotic strains of bacteria on symptoms of AD in infancy. To do so, they conducted a randomized, double blind, placebo-controlled study and after 4 to 6 weeks of baseline and double-blind, placebo-controlled challenges for diagnosis of cow's milk allergy, infants less than 5 months old with AD received a hydrolyzed whey-based formula as placebo or supplemented with either *L. rhamnosus* or *Lactobacillus* GG for 3 months. Results showed that the Scoring Index Atopic Dermatitis (SCORAD) decreased significantly in all treatment groups ($P < 0.0001$). The change in SCORAD is not affected by the use of probiotics. No significant changes in sensitization and in cytokine production (eosinophil X protein in urine, fecal α -1-antitrypsin, IL-4, IL-5, and IFN- γ by polymorphonuclear leukocytes after polyclonal stimulation) were observed. In practice, the results indicate that oral supplementation with these probiotic bacterial strains will not have a significant impact on the symptoms of infantile AD.

The severity of AD may influence the outcome; milder AD seems to be more responsive to the effects of probiotics than more severe disease.⁹

On the contrary, Sistik et al¹⁰ examined the effect of *L. rhamnosus* and *Bifidobacteria lactis* on established AD in children. Children with current AD were allocated to receive probiotics or placebo. SCORAD score was assessed at baseline, 2, and 12 weeks after starting treatment and 4 weeks after treatment was discontinued.

There was a significant improvement in AD at 12 weeks only in food-sensitized children who had been treated with probiotics but not in children who had been sensitized to environmental allergens. These effects were not sustained 1 month after treatment ceased. These data suggest that the beneficial effect of probiotics in AD may probably be related to local effects on the gastrointestinal tract.

PROBIOTICS AND THE IMMUNE RESPONSE IN INFANCY

Activation of the innate immune system by microbial stimulation seems to be critical for normal immune

maturation, and thus this concept could be very important for inhibiting allergic-immune responses.

To assess innate immune function after a supplementation with probiotic, Taylor et al¹¹ recruited 231 allergic, pregnant women into a randomized, controlled trial. The infants received either *L. acidophilus* or placebo daily for the first 6 months of life. Functional responses to toll-like receptor (TLR) were assessed using ligands for TLR2 (Pansorbin) and TLR4/CD14 (lipopolysaccharide) and measuring cytokine responses in the supernatants. The results showed that probiotic supplementation with *L. acidophilus* did not alter early innate immune responses in this population who were at high risk of developing allergic diseases.

In addition, Taylor et al¹² determined whether probiotic dietary supplementation in the first 6 months of life could modify allergen-specific and vaccine-specific immune responses in 231 pregnant women with a history of allergic disease and positive SPT. The results show that administration of *L. acidophilus* was associated with significant attenuation of IL-10 responses to tetanus antigen at 6 months of age compared with the placebo group.

In conclusion, probiotics did not show any consistent effects on allergen-specific responses but these findings suggest that probiotics may have immunomodulatory effects during this “critical early window.”

PROBIOTICS IN ALLERGIC AIRWAY INFLAMMATION

Actually, there have been few reports of therapeutic effects of oral probiotics outside the gastrointestinal tract. Forsythe et al¹³ investigated the effect of 2 probiotic organisms on the response to antigen challenge in a mouse model of allergic airway inflammation. In doing so, an ovalbumin-sensitized asthma model in TLR9-deficient mice was used. Animals received live, heat-killed, or irradiated *L. reuteri*, *Lactobacillus salivarius*, or equivalent isolated *L. reuteri* DNA via gavage for 9 consecutive days before antigen challenge. After antigen challenge, airway responsiveness to methacholine, influx of inflammatory cells to the lung and cytokine levels in bronchoalveolar lavage fluid were assessed.

The results showed that cytokine levels were significantly increased in bronchoalveolar lavage fluid after ovalbumin challenge compared with saline-challenged animals. Treatment with *L. reuteri* significantly attenuated the increase in the tumor necrosis factor, monocyte chemoattractant protein-1 (MCP-1), IL-5, and IL-13. Treatment with either heat-killed or irradiated *L. reuteri* also significantly attenuated the increase in MCP-1, tumor necrosis factor, and IL-5 after antigen challenge but did not significantly alter levels of IL-13.

In conclusion, *L. reuteri* but not *L. salivarius* also decreased allergen-induced airway hyperresponsiveness. These responses were dependent on TLR9.

Oral treatment with live *L. reuteri* can attenuate major characteristics of an asthmatic response in a mouse

model of allergic airway inflammation. Oral treatment with specific live probiotic strains may have therapeutic potential in the treatment of allergic airway disease.

Xiao et al¹⁴ evaluated the effects of oral administration of *Bifidobacterium longum* on Japanese cedar pollinosis (JCP) that affects nearly 1 in 6 Japanese during the pollen season. In a randomized, double blind, placebo-controlled trial, 44 JCP subjects received *B. longum* or placebo for 13 weeks during the pollen season. Recording daily subjective symptoms and self-care measures, comparison of subjective symptom scores indicated significant decreases in rhinorrhea, nasal blockage, itching, and sneezing in the *B. longum* group compared with the placebo group.

In addition, Xiao et al¹⁵ had also demonstrated in a randomized, double-blind, placebo controlled trial, where 40 subjects with a clinical history of JCP were given yoghurt either containing *B. longum* (BB536 yoghurt) or without BB536 (placebo yoghurt) at 2 × 100 g/d for 14 weeks during the pollen season. Yoghurt supplemented with BB536 significantly alleviated eye symptoms compared with placebo yoghurt. Although no statistically significant differences were detected, nasal symptoms such as itching, rhinorrhea, and blockage, as well as throat symptoms. BB536 tended to suppress the decreasing blood levels of interferon- γ and the increasing blood eosinophil rates. A significantly higher interferon- γ level was observed for the difference from baseline at week 4 and a decreased trend in the difference from baseline levels of JCP-specific IgE levels was also observed at week 4 in the BB536 group. In conclusion, intake of BB536-supplemented yoghurt may relieve JCP symptoms, probably through a modulating effect on the T_H balance.

CONCLUSIONS

Recent studies have confirmed immunomodulatory and anti-inflammatory properties of probiotics. There is clinical evidence that suggests that probiotics and prebiotics treatment is effective and had a protective effect in the development of AD. The mechanism maybe related to a local effect on the gastrointestinal tract.

Regarding the effect of probiotics on the allergic airway response, in ovalbumin-sensitized mice, *L. reuteri* induced significant attenuation of inflammatory cell influx to the lung and airway responsiveness to methacholine. These beneficial effects seem to be strain-specific and other studies will be needed to understand the mechanisms involved.

Finally, recent data suggest that probiotics may have immunomodulatory effects on vaccine responses but the significance and clinical relevance of this need to be determined too.

In summary, probiotics are likely to play a part in the management of allergy in children but further studies are necessary to define their role more precisely.

REFERENCES

1. Kalliomaki M, Salminen S, Poussa T, et al. Probiotics during the first 7 years of life: a cumulative risk reduction of eczema in a

- randomized, placebo-controlled trial. *J Allergy Clin Immunol*. 2007;119:1019–1021.
2. Abrahamsson TR, Jakobsson T, Bottcher MF, et al. Probiotics in prevention of IgE-associated eczema: a double-blind, randomized, placebo-controlled trial. *J Allergy Clin Immunol*. 2007;119:1174–1180.
 3. Taylor AL, Dunstan JA, Prescott SL. Probiotic supplementation for the first 6 months of life fails to reduce the risk of atopic dermatitis and increases the risk of allergen sensitization in high-risk children: a randomized controlled trial. *J Allergy Clin Immunol*. 2007;119:184–191.
 4. Kukkonen K, Savilahti E, Haahtela T, et al. Probiotics and prebiotic galactooligosaccharides in the prevention of allergic diseases: a randomized, double-blind, placebo-controlled trial. *J Allergy Clin Immunol*. 2007;119:192–198.
 5. Kunz C, Rudloff S, Baier W, et al. Oligosaccharides in human milk: structural, functional, and metabolic aspects. *Ann Rev Nutr*. 2000;20:699–722.
 6. Moro G, Arslanoglu S, Stahl B, et al. A mixture of prebiotic oligosaccharides reduces incidence of atopic dermatitis during the first six months of age. *Arch Dis Child*. 2006;91:814–819.
 7. Kendler M, Uter W, Rueffer A, et al. Comparison of fecal microflora in children with atopic eczema/dermatitis syndrome according to IgE sensitization to food. *Pediatr Allergy Immunol*. 2006;17:141–147.
 8. Brouwer ML, Wolt-Plompen SAA, Dubois AEJ, et al. No effects of probiotics on atopic dermatitis in infancy: a randomized placebo-controlled trial. *Clin Exp Allergy*. 2006;36:899–906.
 9. Isolauri E, Arvola T, Sutas Y, et al. Probiotics in the management of atopic eczema. *Clin Exp Allergy*. 2000;30:1604–1610.
 10. Sistek R, Kelly K, Wickens T, et al. Is the effect of probiotics on atopic dermatitis confined to food sensitized children? *Clin Exp Allergy*. 2006;36:629–633.
 11. Taylor A, Hale J, Wiltschut J, et al. Evaluation of the effects of probiotic supplementation from the neonatal period on innate immune development in infancy. *Clin Exp Allergy*. 2006;36:1218–1226.
 12. Taylor A, Hale J, Wiltschut J, et al. Effects of probiotic supplementation for the first 6 months of life on allergen and vaccine specific immune responses. *Clin Exp Allergy*. 2006;36:1227–1235.
 13. Forsythe P, Inman MD, Bienenstock J. Oral treatment with live lactobacillus reuteri inhibits the allergic airway response in mice. *Am J Resp Crit Care Med*. 2007;175:561–569.
 14. Xiao J-Z, Kondo S, Yanagisawaw N, et al. Probiotics in the treatment of Japanese cedar pollinosis: a double-blind placebo-controlled trial. *Clin Exp Allergy*. 2006;36:1425–1435.
 15. Xiao JZ, Kondo S, Yanagisawa N, et al. Effect of Probiotic Bifidobacterium longum BBS36 in relieving clinical symptoms and modulating plasma cytokine levels of japanese cedar pollinosis during the pollen season. A randomized double-blind, placebo controlled trial J investgation. *Allergol Clin Immunol*. 2006;16:86.