

Probiotics and Prebiotics in the Prevention and Treatment of Atopic Dermatitis

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Atopic dermatitis (AD) is a highly prevalent condition. Recent evidence suggests a link between the altered gut microbiome and the development of AD. Probiotics and/or prebiotics have been used in the treatment and prevention of AD with the intention of correcting the aberrant gut microbiome. As of now, data from meta-analyses show some promise in the use of probiotics for the prevention of AD with the effect being seen only when administered both prenatally and postnatally. Prebiotics and synbiotics have less compelling evidence to support their effectiveness in AD prevention or treatment, mainly due to the discrepancies of results. Explanations for the variations in the results may come from environmental factors, probiotic/prebiotic factors, and host factors that affect efficacy of the probiotic/prebiotic. More studies are needed to understand the mechanisms of action of probiotics/prebiotics and also to identify their true benefits in the prevention and treatment of AD.

Keywords: atopic dermatitis, probiotics, prebiotics, synbiotics

Introduction

ALLERGIC DISEASES ARE ON the increase in all parts of the world with an estimated 30%–40% of the world's population being affected by at least one.¹ Atopic dermatitis (AD), food allergy, allergic rhinitis, and asthma are a quartet of allergic conditions that are seen sequentially and which may start from AD during early childhood and then progressively develop during the lifetime.²

AD affects 10%–20% of children in developed countries, with 60% of the cases starting during the first year of life.^{3,4} AD has been described as a disease that is mainly caused by the skewing of the immune response toward a type 2 T helper cell (Th2) response and an exaggerated IgE response to allergens. It is now being recognized as a disease mainly caused by abnormal epidermal barrier structure and function and inflammation of the skin caused by aberrant immunological responses to cutaneous antigens.³ In addition to defective skin, recent evidence revealed a close relationship between the aberrant gut microbiome and AD.

Gut Microbiota and AD

The gut harbors $\sim 10^{14}$ bacteria of 400–500 different species in an adult human.⁵ The hygiene hypothesis explains the rise in allergic diseases, including AD, as a consequence of reduced exposure to microbes and infec-

tions during childhood.^{6–9} In 1998, Wold suggested that an altered intestinal colonization pattern in infancy, rather than a decrease in bacterial or viral infections, fails to induce immunological tolerance, thus causing an increase in allergic diseases.¹⁰

Many studies describe a close relationship between gut microbiota and AD: Watanabe et al. showed that the counts of bifidobacterium were significantly lower in patients with AD than in healthy individuals in accordance with another study by Kalliomäki et al.^{11,12} A Swedish Estonian study comparing allergic (positive skin prick test for food antigens) and nonallergic children found lower counts of lactobacilli and bifidobacteria and higher counts of *Staphylococcus aureus* and enterobacteria in the allergic group.¹³ They also showed that differences in the gut microbial composition preceded the development of allergic diseases,¹⁴ suggesting the disturbed gut microbiota as a cause of AD. Accordingly, microbial exposure during pregnancy may be an important factor for allergy prevention.^{15,16}

Altering the intestinal microbiota in neonatal mice by use of kanamycin has shown to cause an increase in serum IgG1 and IgE and a decrease in serum IgG2a levels.¹⁷ Introducing intestinal bacteria into these antibiotic-treated mice prevented the upregulation of basal Th2 responses in the spleen. This shows that early-life exposure to antibiotics causes an adverse shift in the intestinal microbiota resulting in an imbalance in the T cell response, skewing it toward a Th2 one.

This evidence shows that changes in the gut microbial composition caused by prenatal, perinatal, and postnatal influences play a role in the development of AD. Modulating the gut microbiome by the use of probiotics and prebiotics has been attempted to rectify this difference.^{18–20}

Probiotics in AD

Probiotics, as defined by the World Health Organization (WHO), are live microorganisms that, when administered in adequate amounts, may confer a health benefit on the host.²¹ Probiotics have become one of the common approaches to modulating the gut microbiome and there have been numerous studies on the use of probiotics in AD. *Lactobacillus* and *bifidobacterium* are the 2 strains that have been widely used to this effect, the basis for which comes from early studies showing reduced colonization of the gut by these 2 species in those with allergic diseases, compared to those without.^{13,14} With evidence suggesting that an aberrant gut microbiome contributes to the development of AD, it is rational to use probiotics to recolonize or modulate the system.

Probiotics in the prevention of AD

As of yet and interestingly, of all allergic diseases studied, probiotics have mostly been beneficial in the prevention of AD. Most studies have concentrated on the effect of the lactic acid producer, *Lactobacillus*, alone or in combination with *bifidobacterium*.

A recent meta-analysis concluded that probiotic administration is indeed protective against the development of AD (Fig. 1).²² Through subgroup analysis they identified that probiotics are only effective when given pre- and postnatally

to both general and at-risk groups. This meta-analysis also concluded that *Lactobacilli* alone or in combination with *bifidobacteria* are protective.²² Two previous meta-analyses reached similar conclusions: Doege et al. found that probiotics significantly reduce the risk of developing AD, with 3 of the 7 studies that they included supporting this claim,²³ while Pelucchi et al. found an average decrease of 20% in the incidence of AD following probiotic treatment.²⁴

Contrary to the meta-analysis by Panduru et al., the former study²³ found that monotherapy was more beneficial than combination therapy although the bacterial load per strain was comparable in strain mixtures and monotherapy. They reasoned that this might be due to the competitive growth of the strains. The conclusions and recommendations from this meta-analysis were to administer *Lactobacillus* as a probiotic during pregnancy and lactation. The latter study by Pelucchi et al. found that monotherapy may be slightly more beneficial than combination therapy.²⁴

As seen by the general conclusions drawn by several groups, the consensus seems to be that the administration of probiotics is beneficial in decreasing the prevalence of AD. The World Allergy Organization—McMaster University Guidelines for Allergic Disease Prevention (GLAD-P): Probiotics, recommends the administration of probiotics to pregnant women with children at high risk for allergy, breastfeeding women with infants at high risk for allergy, and the infants themselves who are at high risk, with a high focus on the prevention of AD as the benefits of probiotics have shown the greatest benefit in this disease.²⁵ Nevertheless, the dose, duration of treatment, use of monotherapy or combination therapy, these are some of the factors that still need to be addressed before probiotics become standard preventive therapy for AD.

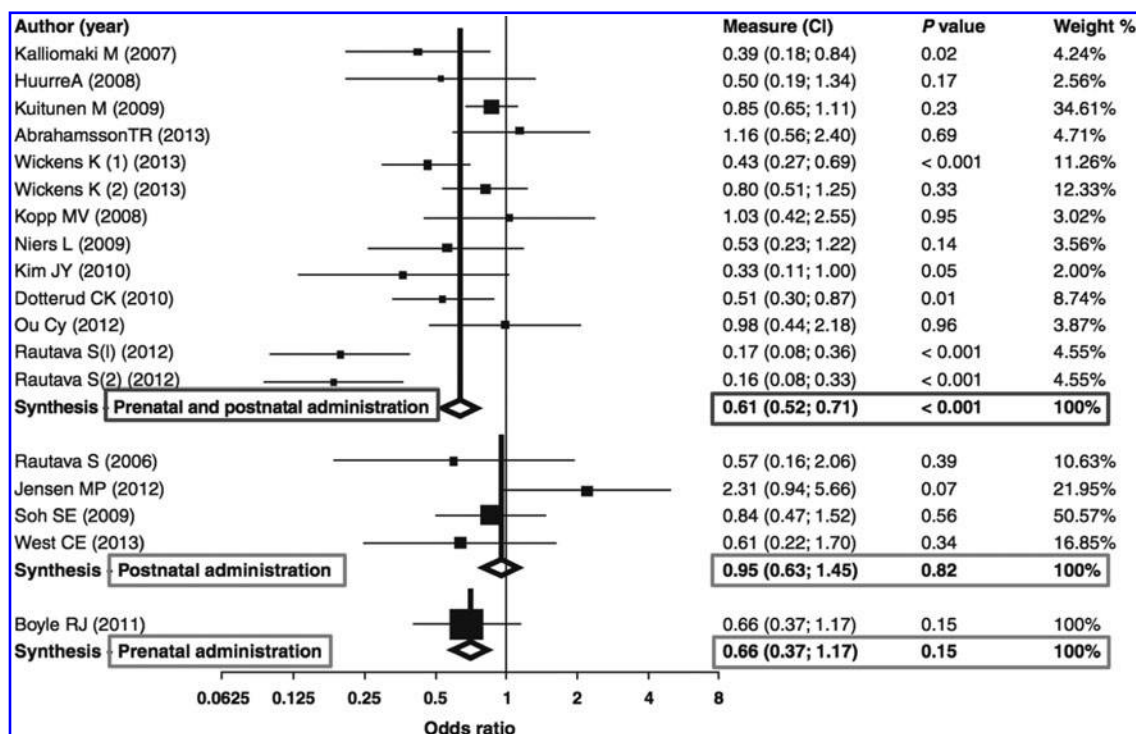


FIG. 1. Subgroup meta-analysis of studies on probiotics in the prevention of AD (modified from Panduru et al.²²). Prenatal and postnatal administration of probiotics has shown a beneficial effect on the prevention of AD, while prenatal- or postnatal-only administration is ineffective. AD, atopic dermatitis.

Probiotics in the treatment of AD

In contrast to prevention, fewer studies have looked at probiotics as treatment for established AD in children. The results from these studies are mixed, with only some studies showing a reduction of SCORAD (SCORing Atopic Dermatitis) value.

As of now, there are 3 meta-analyses that look at this topic.^{26–28} While 2 of these meta-analyses are skeptical about the efficacy of probiotics,^{26,27} the more recent meta-analysis by Kim et al. concluded that the probiotics show a significant decrease in SCORAD in children from 1 to 18 years and in adults.²⁸ An improved SCORAD score was also seen in the latest study, with decreased IgE and TNF- α , and increased IFN- γ and TGF- β in the probiotics group, although not significantly.²⁹ It is apparent that the evidence for the role of probiotics in the treatment of AD is scant and that at present the conclusions cannot be made with the current evidence.

Mechanisms of action

The beneficial effects of probiotics generally come from several possible immunological mechanisms, including modulation of Th cell activation and cytokine production, induction of the regulatory T cell (Treg) response, and improved recovery of barrier function.³⁰ Probiotic bacterial strains have been shown to inhibit the Th2 cell response and stimulate the production of type 1 T helper cell (Th1) cytokines.³¹ In addition, probiotic administration increases the Treg populations in experimental models of allergic diseases, including AD,^{32–34} most probably by inducing regulatory dendritic cells to exhibit immunological tolerance.³⁴

In a murine AD model, the migration of the Treg cells to the sites of inflammation also suppressed the disease.³⁴ To substantiate this, decreased Treg levels were found in patients with active AD compared to asymptomatic controls with similar IFN- γ , total IgE, and eosinophil levels in the serum.^{35,36}

The dysfunction of the skin barrier has been recognized as a leading causative factor in the development of AD. Using a *Lactobacillus paracasei* strain in an *ex vivo* experiment, Gueniche et al. showed that the lactobacillus was able to enhance the recovery of disrupted barrier function.³⁷ It has also been shown that *Bifidobacterium longum* lysates can improve skin reactivity, further supporting the ability of bacterial strains to relieve skin inflammation.³⁸ Nevertheless, as documented by Segers and Lebeer, *Lactobacillus rhamnosus* GG alone has been shown to have multiple mechanisms to interact with the host, with the same applying to the host response,³⁹ and more in-depth studies may need to be conducted to understand these mechanisms.

Prebiotics and AD

Prebiotics are nondigestible food ingredients that beneficially affect the host by stimulating the growth and/or the activity of a limited number of bacterial species in the colon.⁴⁰ Three criteria have been defined to consider a food ingredient a prebiotic: it should be hydrolyzed or absorbed in the upper part of the gastrointestinal tract, it has to be a selective substrate for beneficial commensal bacteria in the colon, and it should alter the intestinal microflora toward a healthier composition.⁴¹

The most widely used prebiotics are nondigestible carbohydrates such as fructooligosaccharides (FOS), oligofructose, and the long-chain inulin. Other prebiotics used less often include galactooligosaccharides (GOS), isomaltooligosaccharides, and soybean oligosaccharides. It has been observed that the type of prebiotic may have a differential effect on “bifidogenesis.” This is because short-chain prebiotics are mainly fermented in the cecum, while longer forms are fermented in the entire colon.⁴² Breastfed infants have a bifidobacteria-dominant gut flora that may be due to the naturally occurring prebiotic oligosaccharides, which are the third-most prevalent component in breast milk and are almost absent in cow’s milk.⁴³ A similar composition has been seen in infants receiving formula with various prebiotic mixtures, including FOS:GOS of 9:1 and GOS alone.^{18,44–46}

A recent meta-analysis of 4 studies found a significant reduction in AD with no statistically significant heterogeneity being observed between studies, but the upper confidence interval, including a benefit of unclear clinical importance.⁴⁷ Nevertheless, they did find some evidence for a possible dose effect with a larger risk decrease in high-risk infants compared to low-risk infants, although the difference was not statistically significant. Of 3 studies on low-atopy-risk infants included in this meta-analysis, 1 study from 5 European countries used a formula supplemented with pectin-derived acidic oligosaccharides, short-chain GOS, and long-chain FOS. This study showed that supplementation of infant formula/follow-on formula with this prebiotic mixture reduced the incidence of AD in low-risk infants up to 1 year of age. The levels were similar to those among breastfed infants. This effect was not seen on the severity of AD.⁴⁸

The only study that looked at the high-risk group of infants in this meta-analysis used a formula with an FOS/GOS and reported a borderline statistically significant decrease in AD. The supplemented group also showed a significant increase in the fecal bifidobacteria counts, while the lactobacilli were unaffected.⁴⁹ Using a GOS-supplemented infant formula on high-risk infants with AD, Boženský et al. reported no improvement of the manifestations of AD based on the SCORAD values.⁵⁰

Nevertheless, a recent study showed that while some bifidobacteria grew on long-chain inulin, most bifidobacteria preferred FOS.⁵¹ Of these, kestose, the smallest member of the FOS group, has shown the greatest bifidogenic effect.⁵² A small study to evaluate the effect of kestose on infants with AD found that the significant improvement in AD symptoms did not correlate with the fecal counts of bifidobacteria, suggesting that a different species may be responsible for the clinical improvement.⁵³ *Faecalibacterium prausnitzii*, a bacterium found in abundance in the adult gut, has been reported to be depleted in AD as well as in inflammatory bowel disease.^{54,55} This bacterium has also been shown to have an anti-inflammatory effect by being a major producer of butyrate, a short-chain fatty acid.⁵⁶ As this bacterium is extremely oxygen sensitive making it impossible to be grown commercially, Koga et al. administered kestose to children with AD with the intention of expanding the *F. prausnitzii* population and observed an improvement in AD symptoms in older children (2–5 years), which correlated with an increase in their fecal *F. prausnitzii* numbers.⁵⁷

It can be said that probiotics and their potential are still being discovered. The recent GLAD-P: Prebiotics position article suggests the use of prebiotic supplementation in infants who are

not exclusively breastfed and not using prebiotic supplementation in exclusively breastfed infants, although both recommendations are conditional and based on very low certainty of evidence. No recommendations have been made about prebiotic supplementation in pregnancy or during breastfeeding, as there are no observational or experimental studies to support this.⁵⁸ With more studies focused on identifying the mechanisms of action of prebiotics, it may be possible to use them to complement the function of probiotics.

Synbiotics and AD

Mixtures of probiotic bacteria and prebiotics, known as synbiotics, have also been used for the prevention and treatment of allergic diseases, including AD. As probiotic bacteria feed on prebiotics, they may provide a favorable environment for the growth of some probiotic bacteria, giving them a selective advantage over other species. With ideal pairing of probiotic and prebiotic, it can be anticipated that the gut will be colonized with the most beneficial microbial species.

Although not many studies are available on synbiotics and AD, a meta-analysis found synbiotics to be beneficial in the treatment, but not in the prevention of AD.⁵⁹ This beneficial effect was particularly seen when using multiple probiotic strains and in children who were 1 year or older. They also found an improvement of the SCORAD score for children 1 year or older with the effect being lost on infants.⁵⁹ A study evaluating the benefits of synbiotics over prebiotics alone, found that *Lactobacillus salivarius* and FOS together helped improve moderate to severe childhood AD.⁶⁰ However, as only a few studies are available, conclusions cannot be made as to the real efficacy of synbiotics in the prevention nor in the treatment of AD. Therefore, there is a need for more studies on their efficacy and their mechanisms of action before recommendations can be made for their administration.

Factors Affecting the Efficacy of Probiotics and Prebiotics

As of now, the existing data seem to be insufficient to draw firm conclusions about the effect of probiotics and

prebiotics on AD because of the heterogeneity in the reported results. These discrepancies in results may arise from the differences in environmental factors, probiotic/prebiotic factors, and host factors (Fig. 2).

Environmental factors include maternal flora, mode of delivery, use of antibiotics, environmental microbial burden, and food habits. Studies have linked the gut microbial dysbiosis resulting from cesarean deliveries to the development of AD,⁶¹ although recent meta-analyses suggest that the mode of delivery may not affect the development of AD directly.⁵² Epidemiological studies have shown a decrease in the incidence of allergic diseases among children of farmers especially when the exposure is while *in utero*,^{16,62,63} with higher loads of bacterial endotoxin, a lipopolysaccharide, in the farming environment being shown to be a protective factor.^{64,65}

The probiotic/prebiotic factors include the dose of the probiotic/prebiotic, the number of strains used, timing of the supplementation (eg, prenatal and/or postnatal), the use of synbiotics, and potentially even the growth stage of the bacteria in a preparation. For example, Winkler et al. described how lactic acid bacteria alone have shown various strain-specific immunomodulatory effects³¹ and this highlights the importance of considering these factors when interpreting results.

Host factors include the basal intestinal gut microbial composition, genetic and epigenetic traits, and the inherent immune competency of the host.^{66–71} The effect of probiotics has been shown to be modified by the genetic susceptibility to AD: pre- and postnatal *L. rhamnosus* HN001 or *Bifidobacterium animalis* subsp. *lactis* strain HN019 supplementation of children with toll-like receptor (TLR)2 and TLR9 SNPs resulted in a decrease in the occurrence of AD.^{72,73} This is supported by the observation that *L. rhamnosus* GG promotes anti-inflammatory effects of the TLR/IL-1R signaling pathway in human fetal intestinal epithelial cells as early as in 14–21 weeks of gestation.⁷⁴

Several studies using *L. rhamnosus* GG to alleviate AD in children, reported a consistent effect of this probiotic strain on the IgE-sensitized group of children with AD.^{75–79} It has also been shown that a reduced Treg cell response to

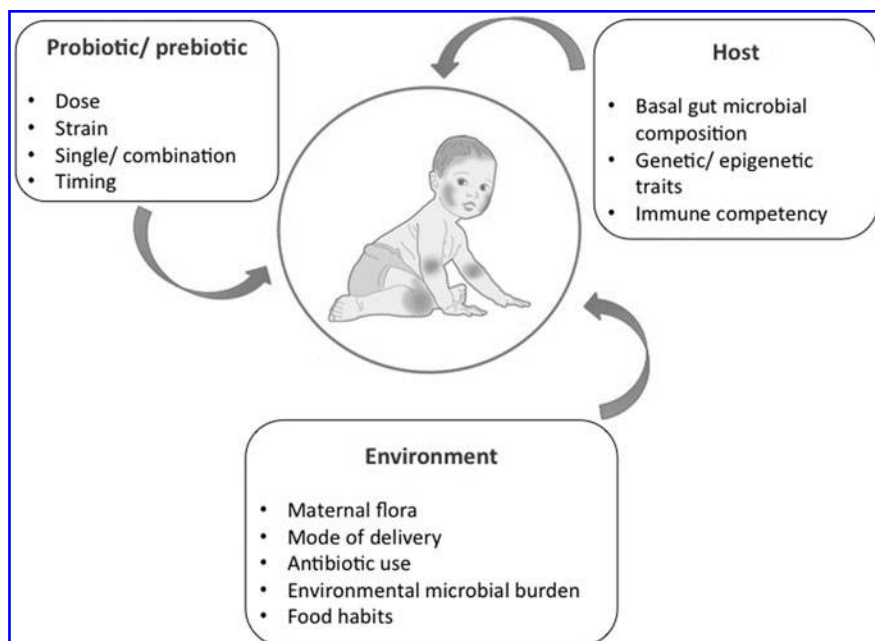


FIG. 2. Factors affecting the efficacy of probiotics and prebiotics.

microbial stimuli at birth is associated with the development of AD in high-risk infants.⁷⁰ These findings strongly indicate that the host's background and subject stratification are important when interpreting results.

As can be seen, many factors influence the efficacy of probiotics and prebiotics. The interplay of the probiotic/prebiotic factors, host factors, and environmental factors will determine the fate of the supplement as well as the outcome of the disease.

Conclusions

In this review, we have briefly discussed the current knowledge on the role of probiotics and prebiotics in AD. As can be seen, there is a need for more knowledge on the specific effects of probiotics/prebiotics and the factors determining their efficacy.

In our opinion, synbiotics may have greater potential than that already explored. As some studies have demonstrated, probiotics may be transient colonizers, which makes it even more important to identify the ideal compositions and conditions for their administration.^{71,80} To this effect, the strain-specific effect of the probiotic bacteria could be enhanced by facilitating colonization using "strain-specific" prebiotics,⁵⁷ thus making their combination an ideal symbiotic. However, more studies are necessary to understand the molecular mechanisms of action of these substances.

From a clinical perspective, identifying the ideal candidates for probiotic/prebiotic therapy is of utmost importance. Therefore, it is necessary to gain insight into the disease mechanisms and host factors that influence the efficacy of prebiotics/probiotics, including the individual responses to pro-/prebiotic interventions. As Isolauri and Salminen suggest, there is also a need to characterize probiotics to strain level and to select strains with documented properties to ensure maximal benefit to patients.⁸¹ By doing so, it may be possible to match the clinical needs with the suitable probiotic and/or prebiotic treatment option. This may be a step further in the direction of personalized medicine.

Author Disclosure Statement

No competing financial interests exist.

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