

Any benefits of probiotics in allergic disorders?

Öner Özdemir, M.D.

ABSTRACT

Development of the child's immune system tends to be directed toward a T-helper 2 (Th2) phenotype in infants. To prevent development of childhood allergic/atopic diseases, immature Th2-dominant neonatal responses must undergo environment-driven maturation via microbial contact in the early postnatal period. Lactic acid bacteria and bifidobacteria are found more commonly in the composition of the intestinal flora of nonallergic children. Epidemiological data also showed that atopic children have a different intestinal flora from healthy children. Probiotics are ingested live health-promoting microbes that can modify intestinal microbial populations in a way that benefits the host; and enhanced presence of probiotic bacteria in the intestinal microbiota is found to correlate with protection against atopy. There is insufficient but very promising evidence to recommend the addition of probiotics to foods for prevention and treatment of allergic diseases, especially atopic dermatitis. Clinical improvement especially in allergic rhinitis and IgE-sensitized (atopic) eczema has been reported too. Literature data for food allergy/hypersensitivity and asthma are not adequate for this guaranteed conclusion; however, clinical benefit of probiotic therapy depends on numerous factors, such as type of bacterium, dosing regimen, delivery method, and other underlying host factors, e.g., the age and diet of the host. The selection of the most beneficial probiotic strain, the dose, and the timing of supplementation still need to be determined. Accordingly, probiotics can not be recommended generally for primary prevention of atopic disease; and if probiotics are used in atopic infants/children for any reason, such as therapy or prevention, cautionary approach ought to be taken.

(Allergy Asthma Proc 31:103–111, 2010; doi: 10.2500/aap.2010.31.3313)

Key words: Allergic disease, allergic rhinitis, allergy, asthma, atopic dermatitis, atopic disease, atopy, food allergy, food hypersensitivity, probiotics

Development of the child's immune system tends to be directed toward a T-helper 2 (Th2) phenotype in infants, whereas postnatal maturation is associated with gradual inhibition of Th2 and increasing Th1 affinity.¹ Thus, immature Th2-dominant neonatal responses must undergo environment-driven maturation *via* microbial contact in the early postnatal period to prevent development of childhood allergic diseases. Otherwise, at an early age, the infant's immune system results in subsequent polarization toward a Th2 phenotype during postnatal maturation. Today, the increased use of antimicrobial medication, the consumption of sterile food, and reduced family size that result in lower rates of infection during childhood also reduce early contact to microbes. Consequentially, the present increase in allergic diseases seen in the industrialized countries has been attributed, among several other phenomena, to a relative lack of microbial stimulation of the infantile gut immune system and the exaggerated hygiene of the typical western lifestyle

during early childhood. This is known as the hygiene hypothesis.²

The newborn is first colonized by microbes at birth. The colonization of the gut that begins promptly after birth is affected by mode of delivery, early feeding strategies, and the hygienic conditions around the child (the early environment). The colonizing bacteria originate mainly from the mother's gut and vaginal tract.³ For instance, children born by cesarean section are colonized with bifidobacteria (Bfdb) and lactobacilli (Lctb) later than vaginally delivered children, and are shown to have more frequent respiratory allergies.⁴ After delivery, breastfeeding continues to enhance the original inoculum by the introduction of specific lactic acid bacteria (LAB), Bfdb, and bacteria from the mother's skin, all of which enable the infant gut microbiota that is dominated by Bfdb. Breast milk also contains plentiful indigestible oligosaccharides, which pass through the whole intestine and promote the growth and activity of commensal bacteria, composed mainly of Bfdb.⁵ These bacteria set the basis for gut microbiota development and modulation, along with environmental exposures such as antibiotic administration.

The greatest differences between breastfed and formula-fed infants appear to be in LAB and Bfdb colonization. Usually, Bfdb appear after birth and, within a week, are reported as the dominant bacterial group, with *Bifidobacterium infantis/longum/breve* being the

From the Division of Allergy/Immunology, Department of Pediatrics, Private SEMA Research and Training Hospital, Istanbul, Turkey

Address correspondence and reprint requests to Öner Özdemir, M.D., Orhantepi Mahallesi, Defne sokak Özer Apt. #86/5, Dragos-Kartal, 89530 Istanbul, Turkey
E-mail: ozdemir_oner@hotmail.com, oner.ozdemir.md@gmail.com

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most common species in breastfed infants.⁶ In addition, *Lactobacillus acidophilus* is the most common Lctb in the feces of breastfed infants. Formula-fed infants, on the other hand, tend to have a flora that is more complex, consisting mostly of coliforms and *Bacteroides*, which significantly lower the prevalence of Bfdb. After weaning, the microflora of children begins to resemble that of adults, with increased *Bacteroides*, *Veillonella*, and *Fusobacterium*.⁸

Epidemiologic data showed that atopic children have a different intestinal flora from that of healthy ones, with higher levels of Clostridia and lower levels of Bfdb. Furthermore, other studies have also shown that early colonization with potentially more pathogenic bacteria such as *Clostridium difficile* and *Staphylococcus aureus* is more likely to occur in children who go on to develop allergy. In contrast, LAB and Bfdb are found more commonly in the composition of the intestinal flora of nonallergic children. The enhanced presence of these probiotic bacteria in the intestinal microbiota seems to correlate with protection against atopy.⁹ Based on these data, "harmless" microbial agents that are probiotics have been presently tested for their efficacy in the prevention and therapy of allergy in infants. Aims of this review are to comprehensively define probiotic properties and to characterize current knowledge of probiotics, including the key mechanisms of probiotic effects and their preventive/therapeutic role in various allergic diseases.

WHAT ARE PROBIOTICS?

The year 2009 marks the 102nd year since Eli Metchnikoff suggested that the consumption of LAB may benefit the human host's immune system.¹⁰ However, not until the mid-1960s did the term probiotic become a trend.¹¹ Probiotics means "for life" and is defined by the World Health Organization and the Food and Agriculture Organization of the United Nations as "live microorganisms which, when administered in adequate amounts as part of food, confer a beneficial health effect by producing gut microflora on the host." These probiotics are mainly represented by LAB.¹² Simply, probiotics are ingested live health-promoting microbes that can modify intestinal microbial populations in a way that benefits the host.

Characteristics of Probiotics

There are several generally accepted characteristics that define probiotic bacteria.

Probiotics:

- Are microbial organisms.
- Remain viable and stable after culture, manipulation, and storage before use.
- Survive gastric, biliary, and pancreatic digestion.

- Are able to induce a host response once they enter the intestinal microbial ecosystem.
- Yield a functional or clinical benefit to the host when consumed.¹⁰⁻¹²

WHAT IS YOGURT (YOĞURT)?

Fermented foods, particularly dairy products such as yogurt, have been consumed for centuries, and accepted as a part of culture in some countries, for instance Turkey. Particularly, LAB members of the genus *Lactobillus*, *Bifidobacterium*, and *Streptococcus*, are the most widely used in the food supply. Yogurt contains viable bacteria culture including *Streptococcus thermophilus* and *Lactobacillus delbrueckii* sp. *bulgaricus*. Although these cultures clearly fulfill the current concept of probiotics, only a small number of these bacteria have been studied. However, some specifically have been shown to have a probiotic effect.¹³

PROBIOTICS AND THEIR ROLE IN ALLERGIC DISEASES/DISORDERS

Current laboratory and clinical data regarding the possibility of probiotics' role on preventing the development of allergic diseases, sensitization, or both are still contradictory and somewhat insufficient to strongly recommend the use of probiotics. To improve on the knowledge of probiotic bacteria, this review first discusses supposed mechanisms of probiotic effects and then their role in various allergic diseases under the light of recent literature searched from Pubmed/Medline.

SUPPOSED MECHANISMS OF PROBIOTICS' EFFECTS

Mechanisms of probiotics' action are multifaceted, and each probiotic may have specific functions affecting the host.^{14,15} Hypothesized mechanisms that reduce the risk of allergic diseases and help in therapy are discussed in detail in the following sections.

Maturing Gut Barrier

Recent data indicate that commensal intestinal microbiota represents a major modulator of intestinal homeostasis. Dysregulation of the symbiotic interaction between intestinal microbiota and the mucosa may result in a pathological condition with potential clinical repercussions. For instance, it is shown that mice reared in germ-free conditions have underdeveloped immune systems and have no oral tolerance. In contrast, pathogen-free mice are capable of reconstituting the bacterial flora with Bfdb and tolerance development.¹⁶

In addition to providing maturational signals for the gut-associated lymphoid tissue, probiotics balance the generation of pro- and anti-inflammatory cytokines in

the gut. After probiotic consumption, decrease in fecal α -1 antitrypsin, serum TNF- α , and changes in transforming growth factor (TGF)- β and other cytokines point to down-regulation of inflammatory mediators.¹⁷ For instance, after a challenge study in infants allergic to cow's milk, fecal IgA levels were detected to be higher and TNF- α levels were lower in the *Lactobacillus rhamnosus* GG (LGG) applied group compared with the placebo.¹⁸ Additionally, probiotic bacteria may counteract the inflammatory process by stabilizing the gut microbial environment and the permeability barrier of the intestine and by enhancing the degradation of enteric antigens and altering their immunogenicity.¹⁹ This gut-stabilizing effect of probiotics could be explained by the improvement by probiotics of the immunologic barrier of the intestine through intestinal IgA responses, specifically.^{20,21} Consistent with these explanations, in children with food allergies, probiotics are shown to reverse increased intestinal permeability and to enhance frequently defective IgA responses.²²

Immunomodulation: Cytokines, Th1/Th2 Balance, IgE Production, and Serum Inflammatory Parameters

In addition to maturing gut barrier, certain strains of *Lctb* and *Bfdb* modulate the production of cytokines by monocytes and lymphocytes, and may divert the immune system in a regulatory or tolerant mode.²³ Nonetheless, there are still some studies showing no significant effects of probiotics on either Th1 or Th2 cell responses to allergens. Although the cytokine stimulation profiles of different probiotic strains vary, the strains isolated from healthy infants mainly stimulate noninflammatory cytokines.²⁴ Therefore, it seems that changes in cytokine profile induced by probiotics may be probiotic strain- or site-specific and dependent on the experimental system used.

Several studies have shown the immunomodulatory effects of probiotic bacteria. In one study, *Bifidobacterium bifidum/infantis* and *Lactobacillus lactis* reduced Th2 cytokines and acted as potent inducers of IL-10 production in different peripheral blood mononuclear cell cultures.²⁵ In another study, eight common *Lactobacillus* strains were studied with respect to induction of cytokines by the murine gut mucosa in response to a parenterally administered antigen. *Lactobacillus reuteri* induced proinflammatory and Th1 cytokines; however, *Lactobacillus casei* tended to induce IL-10/IL-4.²⁶ In a mouse model, effect of oral probiotics administration, including *Bifidobacterium lactis/bifidum* and *L. acidophilus*, on mice with ovalbumin (OVA)-induced food allergy was studied. The mice treated with probiotics suppressed production of the OVA-specific IgE, IgG₁, and IgA. Additionally, the level of IL-4 was significantly lower, and the levels of interferon γ and IL-10 were significantly higher in the mice

treated with probiotics than that in the nontreated mice.²⁷ Another murine model showed that oral administration of an immunostimulatory DNA sequence from *B. longum* suppressed Th2 immune responses in mice and inhibited IgE production *in vitro*.²⁸ A final study showed that the administration of either *B. lactis* Bb-12 or LGG suppressed antigen-specific IgE production too.^{29,30}

Oral administration of LGG resulted in elevated IL-10 concentrations in atopic children, indicating that specific probiotics may have anti-inflammatory effects *in vivo* and possible enhancing regulatory or tolerance-inducing mechanisms as well. Probiotics also increased Th1 cytokines and inhibited allergen-induced IgE and Th2 cytokines in some atopic children.^{31,32} However, on the contrary, in some children receiving probiotics, reduced IL-10 responsiveness to house-dust mite allergens was observed.³³

Development of Tolerogenic Dendritic Cells (DCs)

Selected species of the *Bifidobacterium* genus were shown to prime *in vitro*-cultured neonatal DCs to polarize T-cell responses and may therefore be used as candidates in primary prevention of allergic diseases.³⁴ *B. bifidum* was found to be most potent polarizer *in vitro*-cultured DCs to drive Th1-cell responses involving increased interferon γ -producing T cells concomitant with reduction of IL-4-producing T cells.³⁵ In addition, T-cells stimulated by *B. bifidum* matured DCs as producers of more IL-10.³⁶ Moreover, *L. rhamnosus*, a member of another genus of probiotic bacteria, modulates DC function to induce a novel form of T-cell hyporesponsiveness.³⁷ *L. reuteri/casei* have been also shown to prime monocyte-derived DCs through the C-type lectin DC-specific intercellular adhesion molecule 3-grabbing nonintegrin (DC-SIGN) to drive the development of T-regulatory (T-reg) cells.³⁸ These T-reg cells produce increased levels of IL-10 and are capable of inhibiting the proliferation of bystander T cells. This study suggests that the targeting of DC-SIGN by certain probiotic bacteria might explain their beneficial effect in the treatment of a number of inflammatory diseases, including atopic dermatitis (AD).

Toll-Like Receptor (TLR) Stimulation

Some researchers supposed that the protection offered by probiotics against allergic diseases is based on stimulation of TLRs, which produce mediators such as IL-6; these further induce IgA differentiation from naive B cells. Consistently, LAB species such as *B. bifidum/infantis* and *Lactobacillus salivarius* were shown to be capable of activating TLR-2.³⁹ Oral administration of *L. reuteri* attenuated major characteristics of an asthmatic response, including airway eosinophilia, local cytokine responses, and hyperresponsiveness to methacholine. This effect of *L. reuteri* on the allergic

airway response was found to be dependent on TLR-9.⁴⁰ Furthermore, TLR stimulation was also thought to happen after probiotic administration in infants with eczema who showed increased levels of serum c-reactive protein, IL-10, and IgE.⁴¹

T-reg Cell Production

In a food allergy mouse model, oral administration of *B. bifidum* and *L. acidophilus* suppressed OVA-specific IgE production, which was caused by inducing T-reg-associated TGF- β production.⁴² Another study indicated that neonatal application of probiotic bacteria inhibits subsequent allergic sensitization and airway disease in a murine model of asthma by induction of T-reg cells and TGF- β production.⁴³ As mentioned earlier, *L. reuteri/casei* have been also shown to prime monocyte-derived DCs through the DC-SIGN to drive the development of T-reg cells.³⁸ Interestingly, the probiotic combinations are alleged to cause a paradoxical Th2 stimulation, practically the same as in chronic and balanced helminth infection, which is associated with activation of T-reg cells suppressing allergic inflammation. Because the colonization is still transient, the induction of T-reg cells is not permanent. Thus, when these immunologic effects no longer operate, the clinical effect is simultaneously lost. For instance, when helminth infections are treated, the prevalence of allergic sensitization increases rapidly. This is a plausible explanation for the fading probiotic effect as well.⁴⁴

In summary, local influences of probiotics potentially include reduction of permeability and systemic penetration of antigens, increased local IgA production, and alteration of local inflammation or tolerance induction. Some possible systemic effects consist of anti-inflammatory effects mediated by TLRs, Th1 skewing of responses to allergens, and activation of tolerogenic DCs, in addition to T-reg cell production.

ATOPIC/ALLERGIC DISORDERS

Today, the increased prevalence of atopic diseases is defined as an epidemic. AD, known as the earliest of these conditions, might act as an indicator for the development of IgE-mediated atopic manifestations. Thus, being aware of possible measures, such as probiotic use, to prevent and/or heal atopic disease is essential for the practicing allergist.

AD (Eczema)

Previously, there have been several published double-blind, randomized, placebo-controlled trials that showed a preventive effect of LGG on atopic disease in a population at high risk. A Finnish study was the first report to describe that the frequency of AD in the probiotic group was half that of the placebo.⁴⁵ Nevertheless, these results have recently been questioned by

a trial conducted by an Australian group, who reported no difference in the development of AD, but observed increased sensitization to allergens in neonates supplemented with a different *Lactobacillus* strain.⁴⁶ Taken together, these studies suggested that probiotics may not be effective for prevention or therapy of all atopic children, but might offer benefit in a subset of IgE-sensitized children.

IgE-Sensitized (Atopic) versus Non-IgE-Sensitized (Nonatopic) Eczema Prevention

In support of the efficacy of probiotics in IgE-sensitized children, some other studies also showed comparable results as well. Treatment with *L. rhamnosus* for the first 2 years of life was associated with a significant reduction in the prevalence of any IgE-associated eczema by about one-half.⁴⁷ In cesarean-delivered children, probiotic use has been shown to prevent IgE-associated allergy until the age of 5 years.⁴⁸

Additionally, a review evaluating 13 randomized controlled trials (RCTs) about routine probiotic use in the treatment or prevention of AD proved effective. This study, in which 10 of the 13 RCTs evaluated probiotics as treatment and 3 for prevention, concluded that regardless of IgE-sensitization probiotics, especially LGG, were effective in the prevention of AD.⁴⁹ A meta-analysis assessing six studies reported significant benefits in enrolled infants at high risk of allergy who were put on probiotic supplements containing *L. rhamnosus*.⁵⁰ Another meta-analysis of 11 studies that focused on pediatric AD showed that probiotics are effective in the prevention of AD.⁵¹

However, some other studies failed to show that the severity and frequency of allergic diseases were decreased with the supplementation of probiotics, regardless of their IgE sensitization status. For instance, Brouwer *et al.* and others did not show any effect for LGG in infants with AD.⁵² A meta-analysis also could not confirm that IgE sensitization was indeed a factor in determining the efficacy of probiotics in atopic children.⁵³

IgE-Sensitized (Atopic) versus Non-IgE-Sensitized (Nonatopic) Eczema Therapy

Another study indicated that LGG alleviated atopic eczema/dermatitis syndrome symptoms in IgE-sensitized infants.⁵⁴ In food-sensitized atopic children, the efficacy of the probiotics such as *L. rhamnosus* and *B. lactis* was established too.³¹ The beneficial effect of two *Lactobacillus* strains (*rhamnosus* and *reuteri*) in children with AD was also shown. This effect was more pronounced in patients with a positive skin-prick test and increased IgE levels.⁵⁵

Food Allergy and Anaphylaxis

Because food allergies are thought to be central in the pathogenesis of AD, targeting the enteric mucosa, the

primary route of food antigen contact, and sensitization with probiotics might influence crucial mechanisms. In addition, there have been several published studies showing that oral administration of *Bifidobacterium* or *Lactobacillus* strains could alleviate the food allergy.⁵⁶ In another study, *L. acidophilus* and *B. lactis* treatments prevented OVA-induced allergic symptoms on the skin and gastrointestinal tract, e.g., eosinophilic infiltration.²⁷ Previous studies showed that administration of the probiotic LGG to highly selected food allergic patients (age, <2 years, challenge-proven, and mild-to-moderate eczema) significantly improved the eczema score.⁵⁷ Studies in infants with eczema who received formulas supplemented with LGG have shown benefit in decreasing gastrointestinal symptoms too.⁵⁸ Oral therapy with the probiotic mixture VSL#3 and *L. casei* strain *shirota*, in addition, were able to reduce anaphylactic symptoms in a food allergy model.^{59,60}

In contrast, supplementation of *L. casei* and *Bifidobacterium* Bb-12 to extensively hydrolyzed formula did not accelerate cow's milk tolerance in infants with cow's milk allergy.⁶¹ Moreover, a few RCTs also showed no effects of probiotics, specifically LGG or *L. acidophilus*, in protection against cow's milk allergy in infancy.^{52,62,63} Osborn *et al.* reviewed 6 studies enrolling 1549 infants and reported no other benefits of probiotics for food hypersensitivity as well.⁵⁰

Allergic Rhinitis (AR)

Probiotic treatment in patients with seasonal and perennial AR showed clinical improvement in most of the published studies.^{51,64} The majority of the RCTs showed a reduction in symptom severity and decreased use of relief medications.^{65,66} Moreover, the immunomodulatory activity of the probiotic mixture VSL#3, studied in the mouse models of allergic sensitization with inhalants, prevented the development of *Parietaria* major allergen-specific local and systemic response when delivered intranasally.⁵⁹ Twelve-month consumption of fermented milk containing *L. casei* improved the health status of children with AR.⁶⁷ Furthermore, the fermented milk prepared with LGG and *Lactobacillus gasseri* were found to be beneficial in a seasonal AR such as in Japanese cedar pollinosis (JCP) because of its effect on nasal blockage.^{68,69} Intake of *B. longum*-supplemented yogurt also relieved JCP symptoms.^{70,71} A meta-analysis by Vliagoftis concluded that all of the trials studied in children showed improvement in clinical outcomes.⁵¹

Nonetheless, one study suggested that fermented milk containing *L. casei* strain *shirota* does not prevent allergic symptoms in patients sensitive to JCP, although the addition of the strain may delay the occurrence of allergic symptoms in patients with moderate-to-severe nasal symptom.⁷² A meta-analysis evaluating

six relevant studies also reported no other benefits of probiotic use for any allergic disease.⁵⁰

Asthma

Some researchers showed that LGG may exert beneficial effects on the development of experimental allergic asthma, when applied in a very early phase of life. For example, in one study, perinatal maternal application of LGG suppressed allergic airway inflammation in mouse offspring.⁷³ Additionally, in these offspring that were supplemented with maternal LGG, the allergic airway and peribronchial inflammation, as well as goblet cell hyperplasia, were significantly reduced.⁷³ In another mouse model, the administration of either *Bifidobacterium*-12 or LGG suppressed all aspects of the asthmatic phenotype, including airway reactivity, antigen-specific IgE production, and pulmonary eosinophilia.⁴³ A few other studies showed the following: intranasal administration of *Lactobacillus plantarum* suppressed antigen-induced Th1 and Th2 immune responses in Der p1-sensitized animals.³³ Co-application of *Lactococcus lactis* and *L. plantarum* with the major birch pollen allergen (Bet v1) caused suppression of allergen-induced basophil degranulation.⁷⁴ Finally, oral administration of live *L. reuteri* attenuated major characteristics of an asthmatic response, including airway eosinophilia, local cytokine responses, and hyperresponsiveness to methacholine in a mouse model concerning allergic airway inflammation.^{40,75}

A recent study showed that the interactive treatment by acupuncture and probiotics has a beneficial clinical effect on bronchial hyperreactivity in children with asthma and might be helpful in the prevention of acute respiratory exacerbations.⁷⁶ However, adolescents suffering from pollen allergy did not benefit from LGG administration.^{77,78} Furthermore, Osborn *et al.* reviewed six studies and reported no other benefits for any other allergic disease.⁵⁰ A review concluded that trials of the effects of probiotics on asthma are few and show inconsistent results, and thus a decision on the benefits of probiotics can not be reached, although some positive experimental evidence from animal studies suggests the need for further investigation.⁵¹

WHY INCONSISTENT RESULTS IN SOME STUDIES?

As discussed previously in detail, the value of probiotics for primary prevention is controversial. Published trials vary considerably in study design, including applied probiotics type (e.g., killed/live or species such as *Lactobacillus* or *Bifidobacterium*) or time (postnatal/prenatal) and period of probiotics' supplementation, thereby limiting comparison of the results. Mixing probiotics with prebiotics or a hydrolyzed whey formula or using probiotic combinations also might play a role in confusing

Table 1 Effects of the different probiotic strains in allergic diseases are shown from various studies referred in the text

Source	Type of Allergic Disease	Probiotic Strain	Outcome
Atopic dermatitis (Eczema)			
Sistek <i>et al.</i> ³¹	Food-sensitized atopic children	<i>Lactobacillus rhamnosus</i> + <i>Bifidobacterium lactis</i>	↓
Kalliomäki <i>et al.</i> ⁴⁵	Atopic dermatitis	<i>Lactobacillus</i> GG	↓
Kopp <i>et al.</i> ⁴⁶	Atopic dermatitis	<i>Lactobacillus</i> GG	↔, ↑
Wickens <i>et al.</i> ⁴⁷	IgE-associated eczema	<i>L. rhamnosus</i>	↓
Kuitunen <i>et al.</i> ⁴⁸	IgE-associated allergy	<i>Lactobacillus</i> + <i>Bifidobacterium</i> + <i>Propionibacteria</i>	↓
Brouwer <i>et al.</i> ⁵²	Atopic dermatitis	LGG	↔
Viljanen <i>et al.</i> ⁵⁴	Atopic eczema/dermatitis syndrome	LGG	↓
Rosenfeldt <i>et al.</i> ⁵⁵	Atopic dermatitis	<i>L. rhamnosus</i> + <i>Lactobacillus reuteri</i>	↓
Soh <i>et al.</i> ⁶³	Eczema and atopic sensitization	<i>Bifidobacterium longum</i> + <i>L. rhamnosus</i>	↔
Food allergy and anaphylaxis			
Kim <i>et al.</i> ²⁷	OVA-induced allergic symptoms	<i>Lactobacillus acidophilus</i> + <i>B. lactis</i>	↓
Isolauri <i>et al.</i> ⁵⁶	Food allergy	<i>Bifidobacterium</i> or <i>Lactobacillus</i>	↓
Majamaa <i>et al.</i> ⁵⁷	Food-sensitized eczema	LGG	↓
Shida <i>et al.</i> ⁶⁰	Anaphylaxis with food allergy	VSL#3 + <i>Lactobacillus casei</i> strain shirota	↓
Hol <i>et al.</i> ⁶¹	Cow's milk allergy	<i>L. casei</i> + <i>Bifidobacterium</i> Bb-12	↔
Taylor <i>et al.</i> ⁶²	Cow's milk allergy	LGG or <i>Lctbs acidophilus</i>	↔, ↑
Allergic rhinitis			
Di Felice <i>et al.</i> ⁵⁹	Allergic rhinitis	VSL#3	↓
Giovannini <i>et al.</i> ⁶⁷	Allergic rhinitis	<i>L. casei</i>	↓
Morita <i>et al.</i> ⁶⁹	Allergic rhinitis	LGG + <i>Lactobacillus gasseri</i>	↓
Xiao <i>et al.</i> ⁷¹	Allergic rhinitis; JCP	<i>B. longum</i>	↓
Tamura <i>et al.</i> ⁷²	Allergic rhinitis; JCP	<i>L. casei</i> strain shirota	↔
Asthma			
Kruisselbrink <i>et al.</i> ³³	Dermatophagoides (Der p1) sensitization	<i>Lactobacillus plantarum</i>	↓
Feleszko <i>et al.</i> ⁴³	Airway reactivity	<i>Bifidobacterium</i> 12	↓
Blümer <i>et al.</i> ⁷³	Allergic asthma	LGG	↓
Repa <i>et al.</i> ⁷⁴	Birch pollen allergen (Bet v1) sensitization	<i>L. lactis</i> + <i>L. plantarum</i>	↓
Karimi <i>et al.</i> ⁷⁵	Allergic airway inflammation	<i>L. reuteri</i>	↓
Helin <i>et al.</i> ⁷⁸	Pollen allergy	LGG	↔

OVA = ovalbumin; LGG = *Lactobacillus rhamnosus* GG; VSL#3 = probiotic mixture; JCP = Japanese cedar pollinosis; ↑ = increase in symptoms or negative effect; ↓ = decrease in symptoms or positive effect; ↔ = No change in symptoms or no effect

results of different studies. No two probiotics are exactly alike, and therefore researchers should not expect reproducible results from studies that use different species or strains, variable formulations, and diverse dosing schedules (Table 1). Additionally, host factors (including genetic differences in microbial responses and allergic predisposition) and other environmental factors such as general microbial burden, individual microbiota, diet (in-

cluding consumption of prebiotic substances), and treatment with antibiotics are other major factors that can affect results.

PITFALLS (SIDE EFFECTS) OF PROBIOTIC USE

A joint Food and Agriculture Organization/World Health Organization report on the evaluation of probiot-

ics in food stated that “documented correlations between systemic infections and probiotic consumption are few, and all occurred in patients with underlying medical conditions.” Safety of *B. lactis* is documented in infants from birth and in vulnerable populations such as preterm infants, malnourished infants, and infants born to mothers with human immunodeficiency virus disease. Additionally, *B. lactis* is the only probiotic bacterium that has undergone Food and Drug Administration evaluation for use in infant formulas from birth and that can be commercialized for this application.⁷⁹ LGG also seems generally safe and to be a probiotic appropriate for older infants/children:

- Clinical benefit of probiotic therapy depends on numerous factors, such as type of bacterium (strain) as shown in Table 1, dosing regimen, delivery method, and other underlying host factors *e.g.*, the age and diet of the host.
- Probiotics might cause sepsis in immunocompromised populations. *Lactobacillus septicemia* has been reported in two children with short bowel syndrome receiving LGG supplementation.⁸⁰ Children with abnormal immune function, premature infants, immunocompromised hosts, and those with indwelling central lines and autoimmune disorders should use these products with caution.⁸¹
- An increased rate of recurrent wheezing episodes.⁴⁶
- An augmented rate of atopic disorders.⁹
- Increased sensitization to allergens.^{45,46,62}
- Adverse gastrointestinal symptoms, *e.g.*, diarrhea, due to heat-inactivated LGG supplementation.

PEARLS OF PROBIOTIC USE

- There is very promising literature data to recommend the addition of probiotics to infant feeds for prevention of allergic disease or food hypersensitivity.
- Clinical improvement especially in AR and IgE-sensitized (atopic) eczema has been reported in most of the published studies.
- Enhanced response to some vaccines is shown in children taking LGG.^{82,83}
- Decrease in the number of respiratory infections is also shown in children receiving LGG.^{76,84}

CONCLUSION

There is a large amount of conflicting data on the preventive and therapeutic effects of probiotics in atopic diseases. Results from meta-analyses and systematic reviews that combine results of studies from different types of probiotics to examine the effects in any disease should be interpreted with caution (Table 1). Probiotics can not be recommended generally for primary prevention of atopic disease. Additionally, if probiotics are used in atopic infants/children for any reason—therapy or pre-

vention—cautionary approach ought to be taken. Following these guidelines, Bifidobacterium, particularly *B. lactis*, has a uniquely strong safety profile, making it a good probiotic candidate for newborns and young infants. No probiotics should be used in immunocompromised children, even if they have atopic diseases or are at risk. Finally, there is insufficient but very promising evidence to recommend the addition of probiotics to foods for prevention and treatment of allergic diseases.

FUTURE EXPECTATIONS

Better understanding of the effects of different probiotic strains and a deeper insight into the mechanisms of the heterogeneous manifestations of atopic disease are needed for the validation of specific strains carrying anti-allergic potential. Therefore, research activities are currently focusing on identification of specific probiotic strains with immunomodulatory potential and on how dietary content interacts with the most efficacious probiotic strains.⁸⁵ Moreover, the selection of the most beneficial probiotic strain, the dose, and the timing of supplementation still need to be determined. Additional studies should also clarify if any susceptible subgroups of atopic diseases exist and how these subgroups benefit from supplementation with certain probiotic strains.

ACKNOWLEDGMENTS

The author thanks to Liqiao Ma for editing English in this article.

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