Retraction Notice

"Preventative and Therapeutic Role of Probiotics in Various Allergic and Autoimmune Disorders: An Up-to-Date Literature Review of Essential Experimental and Clinical Data," by Öner Özdemir, *Journal of Evidence-Based Complementary & Alternative Medicine,* April 2013 (18:2), doi:10.1177/2156587212461279.

This article has been retracted due to unattributed overlap with material from other sources and due to duplicate publication.

The unattributed excerpts in the article were taken from the following sources:

1. Ouwehand AC. Antiallergic effects of probiotics. *J Nutr*. 2007;137(3 suppl 2):794S-797S.
2. Saavedra JM. Use of probiotics in pediatrics: rationale, mechanisms of action, and practical aspects. *Nutr Clin Pract*. 2007;22:351-365. doi: 10.1177/0115426507022003351.
3. Rook GA, Brunet LR. Microbes, immunoregulation, and the gut. *Gut*. 2005;54:317-320. doi:10.1136/gut.2004.053785.
4. Michail S. The role of probiotics in allergic diseases. *Allergy Asthma Clin Immunol*. 2009;5:5. doi:10.1186/1710-1492-5-5.

The author also published the following works that include significant unattributed excerpts from the article:

1. Özdemir Ö, Erol AY. Preventative and therapeutic probiotic use in allergic skin conditions: experimental and clinical findings. *BioMed Res Int*. 2013;2013:932391. doi:10.1155/2013/932391.
2. Özdemir Ö. The role of probiotics in atopic dermatitis prevention and therapy. In: Esparza-Gordillo J, Dekio I, eds. *Atopic Dermatitis: Disease Etiology and Clinical Management*. Rijeka, Croatia: InTech; 2012:353-386. doi:10.5772/25301.

Journal of Evidence-Based Complementary & Alternative Medicine
18(2) 121-151

DOI: 10.1177/2156587212461279
cam.sagepub.com
SAGE

Preventative and Therapeutic Role of Probiotics in Various Allergic and Autoimmune Disorders: An Up-to-Date Literature Review of Essential Experimental and Clinical Data

Öner Özdemir, MD[1]

Abstract

The increased prevalence of atopic/autoimmune diseases is nowadays defined as an endemic. Recent epidemiologic data showed that children with allergic/autoimmune disease have a different intestinal flora from healthy ones. Therefore, regulation of intestinal microflora composition by probiotics offers the possibility to influence the development of autoimmune/atopic diseases. And probiotics have been reported as capable preventive and therapeutic strategy in allergic/autoimmune diseases. The aim is to summarize/evaluate the available knowledge of probiotic use from randomized/nonrandomized controlled clinical trials, apart from reviews and meta-analyses. Those clinical trials involving studies of atopic/autoimmune disease indicated that not all patients receiving the probiotic agent benefited. But subsets of these patients, such as those with IgE-associated eczema and ulcerative colitis, seemed to have benefited the most. There is inadequate but quite promising evidence in the literature to recommend the addition of probiotics to foods. Nonetheless, probiotics still cannot be generally recommended for prevention/treatment of allergic/autoimmune diseases.

Keywords

probiotics, allergic disease, autoimmune disease, atopic dermatitis, asthma, IgE, ulcerative colitis, gastrointestinal microflora, Lactobacillus, Bifidobacteria

Received August 10, 2012. Accepted for publication August 17, 2012.

The gastrointestinal tract of the newborn baby is sterile. Soon after birth, however, it is colonized by many different microorganisms. 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.[1] Mode of delivery, either vaginal or through cesarean section, also has a major impact on early colonization patterns of the infant gut. For instance, children born by cesarean section are colonized with Bifidobacteria and Lactobacilli later than vaginally delivered children, and are shown to have more frequent respiratory allergies.[2] After delivery, breast-feeding continues to enhance the original inoculum by the introduction of specific lactic acid bacteria, Bifidobacteria and bacteria from the mother's skin, all of which enable the infant gut microbiota that is dominated by Bifidobacteria. 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 Bifidobacteria.[3] The greatest differences between breast-fed and formula-fed infants appear to be in lactic acid bacteria and Bifidobacteria colonization. Usually, Bifidobacteria appear after birth and, within a week, are reported as the dominant bacterial group, with *Bifidobacterium infantis*/*longum*/*breve* being the most common species in breast-fed infants.[4] In addition, *Lactobacillus acidophilus* is the most common Lactobacillus in the feces of breast-fed infants. Formula-fed infants, on the other hand, tend to have a flora that is more complex, consisting mostly of Coliforms and Bacteroides, with significantly lower the prevalence of Bifidobacteria.[5] After weaning, the microflora of children begins to resemble that of adults, with increased Bacteroides, Veillonella, and Fusobacterium.[6] These

[1] İstanbul Medeniyet University, Göztepe Research and Training Hospital, Istanbul, Turkey

Corresponding Author:
Öner Özdemir, MD, Department of Pediatrics (3rd Clinic), Division of Allergy and Immunology, İstanbul Medeniyet University, Göztepe Research and Training Hospital, Göztepe, Kadıköy, 34726, İstanbul, Türkiye.
Email: ozdemir_oner@hotmail.com

bacteria set the basis for gut microbiota development and modulation, along with environmental exposures such as antibiotic administration.

Colonization is complete after approximately 1 week, but the numbers and species of intestinal bacteria fluctuate markedly during the first several months of life. The composition of the gut microbiota differs between healthy and allergic infants and even in countries with a high and low prevalence of allergies. In the case of allergy, the rationale for modulating the intestinal microbiota is supported by observations that allergic children have a different microbiota composition than healthy infants. The main changes associated with allergic trait are less frequent colonization with Lactobacilli and lower counts of Bifidobacteria.[7] 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 addition to these quantitative differences in the Bifidobacterium microbiota, qualitative differences have also been observed. Infants with atopic disease have been found to have a more adult type Bifidobacterium microbiota with high prevalence of *Bifidobacterium adolescentis*. Healthy infants, on the other hand, were found to be colonized mainly by *Bifidobacterium bifidum*, typical for breast-fed infants.[5,6] The Bifidobacteria from infants with atopic disease were found to induce a higher secretion of proinflammatory cytokines in vitro, whereas the Bifidobacteria from healthy infants induced the secretion of more anti-inflammatory cytokines. Also, Bifidobacteria of dairy origin stimulated more anti-inflammatory and less inflammatory cytokines than Bifidobacteria from allergic infants. In addition to differing in their induction of cytokines, Bifidobacteria from allergic and healthy infants also exhibited different in vitro adhesion to Caco-2 tissue culture cells and intestinal mucus. This difference in adhesion to the intestinal mucosa may result in a different or reduced stimulation of the immune system through the gut-associated lymphoid tissue.[8] Lower counts of Bifidobacteria have been reported in atopic versus nonatopic children preceding allergen sensitization. Bifidobacteria are hypothesized to more effectively promote tolerance to nonbacterial antigens, primarily by inhibiting the development of a Th2-type (proallergic) response. In a recent study, a positive change in stool colonization in atopic infants supplemented with *Bifidobacterium lactis* has been shown with a decrease of Bacteroides and *Escherichia coli* in the stool. Most interestingly, serum IgE correlated with *Escherichia coli* counts, and in highly sensitized infants, IgE correlated with Bacteroides counts.[9] Thus, certain probiotics seem to influence the gut's allergen-stimulated inflammatory response and provide a barrier effect against antigens that might otherwise ultimately lead to systemic allergic symptoms (such as eczema). The enhanced presence of these probiotic bacteria in the intestinal microbiota seems to correlate with protection against atopy.[7,10] 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.[11-13]

The new version of "hygiene hypothesis" proposes that reduced exposure to environmental and/or enteric stimuli, including microbes, underlies the rising incidence of childhood atopic as well as autoimmune diseases. This hypothesis is supported by data that highlight the importance of infant exposure to environmental microbes for appropriate development of the immune system.[14] This might explain the observation that administration of microbes or their components inhibits autoimmune diseases in animals such as insulin-dependent diabetes mellitus or autoimmune type 1 diabetes mellitus.[15,16] Recent studies, however, have revealed that exposure of genetically diabetes-susceptible animals to certain microbes or microbial agents at an early age prevent the induction and progression of disease. This suggests that microbes may act to modulate the immunological status or immune repertoire of an individual genetically programmed for type 1 diabetes mellitus away from an autoimmune response.[17] Immunization with microbial agents at an early age may offer an important new direction for the immunotherapy of type 1 diabetes.[17,18] The protective effect of a probiotic and a bacterial extract was reported on the onset of diabetes in nonobese diabetic mice.[19] These findings raise the possibility of using live, nonpathogenic microbes (eg, probiotics) or microbial components to modulate or "reeducate" the immune system.

Probiotic intestinal flora contributes to microbial antigen exposure in early life and is one of the most abundant sources of early immune stimulation. Because allergic and autoimmune responses manifest early in life, there has been obvious interest in the potential benefits of modifying the gastrointestinal flora by using probiotic supplementation. So far, there have been only several studies to address the role of probiotics in primary prevention/therapy, with a reported suspicious reduction in the incidence of atopic and autoimmune diseases. The role of probiotics in the prevention of allergy and autoimmunity development has still remained controversial,[13] and there has been an urgent call for similar studies to address this further. In this review article, we will try to highlight the issues with probiotics in the therapy/prevention of atopy /autoimmunity and future of this therapy. First, the ethiopathogenesis of allergic/autoimmune disease and then its relation to gut and environmental microbiota (hygiene) are considered before discussing the mechanisms of probiotic effect and the beneficial effects that they may confer to individuals with allergic/autoimmune disease. Lastly, under the light of recent literature probiotic use in the therapy and prevention of atopic as well as autoimmune diseases is being discussed in detail.

Ethiopathogenesis of Allergic and Autoimmune Disease

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.[20] 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 and/or autoimmune

diseases. Nevertheless, nowadays 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. Among several other phenomena, the present increase in allergic or autoimmune diseases seen in the industrialized countries has been attributed, 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. And this is known as the "hygiene hypothesis."[14]

The other hypotheses in the allergic and autoimmune disease pathogenesis besides "hygiene–old friends–hypothesis," such as bystander immunoregulation and regulatory T cell (Treg) defects are briefly discussed below as well.[21] Because of our long association with environmental organisms (old friends), they are recognized by the innate immune system as harmless or, in the case of some helminths, treated as "friends" because a response would merely lead to immunopathology.[14] Therefore, rather than priming aggressive immune responses, these organisms prime immunoregulation. They do it by inducing an unusual pattern of maturation of dendritic cells such that these retain the ability to drive Treg. Toll-like receptor (TLR)-2 may be involved for helminths and TLR-9 for lactobacilli. It is interesting that polymorphisms of NOD2 (an intracellular receptor for bacterial peptidoglycan) are linked to increased susceptibility to both Crohn's disease and asthma.[22] Thus, an extension of the "hygiene hypothesis" mechanism suggests that in an environment that less actively primes Treg activity, immunoregulatory disorders will occur first in those individuals whose innate immune systems are least efficient at driving Treg.

The increased regulatory dendritic cells and Treg induced by "old friends" then lead to 2 immunoregulatory mechanisms mediated in part by release of interleukin-10 (IL-10) and transforming growth factor-β (TGF-β). First, continuing exposure to "old friends" will cause continuous background activation of Treg specific for the "old friends" themselves, resulting in a constant background of "bystander suppression."[23] This mechanism has been demonstrated in a model of colitis. Second, regulatory dendritic cells inevitably sample self and gut contents and so induce Treg specific for the target antigens of the groups of chronic inflammatory disorder. These mechanisms may be aborted when there are legitimate "danger signals." For example, Treg function can be turned off by appropriate "danger signals" in vitro.[24]

The unifying hypothesis explaining the simultaneous increase in Th2-mediated allergies and Th1-mediated autoimmunity is that modern living conditions can lead to defective maturation of Treg and regulatory antigen presenting cell or regulatory dendritic cells.[25] Therefore, rather than Th1/Th2 balance, the crucial factor is likely to be the effector T cells/Treg balance. Thus diminished immunoregulation can lead to inappropriate immune responses to allergens, gut contents, or self. In the absence of optimal levels of immunoregulation, the individual may develop a Th1-/Th2-mediated inflammatory disorder, depending on his or her own particular Th1/Th2 bias, immunological history, and genetic background. Evidence to confirm this hypothesis has come from studies of allergic disorders, multiple sclerosis, and autoimmune polyglandular syndromes.[21]

Any Role for Hygiene (Environmental/Intestinal Microbiota) in Allergic and Autoimmune Disease Development?

According to the "hygiene–old friends hypothesis," the decreasing incidence of infections in developed and developing countries is at the origin of the increasing incidence of allergic diseases.[14] New practices, introduced as a result of industrialization, such as childbirth by surgical delivery, ingestion of pasteurized food, cleaner homes, indiscriminate use of antibiotics, and so on, have led in recent years to the replacement of probiotics by other microorganisms that are not as well adapted to the microenvironments of the human body. The hygiene hypothesis is based on epidemiological data, particularly migration studies, showing that subjects migrating from a low incidence of infections to a high-incidence country acquire the allergic/autoimmune disorders with a high incidence at the first generation as well. Therefore, it was possible to extend the old hypothesis from the field of allergy, where it was formulated, to those of autoimmune diseases such as type 1 diabetes or multiple sclerosis.[25] However, some data and others showing a correlation between high autoimmune disease incidence and high socioeconomic level do not prove a causal link between infections and immune disorders. Part of the increased incidence of these diseases may be somewhat attributed to better diagnosis or improved access to medical facilities in economically developed countries. However, this cannot explain the marked increase in immunological disorder prevalence that has occurred over such a short period of time in those countries, particularly for diseases which can be diagnosed easily, such as type 1 diabetes mellitus or multiple sclerosis. Based on hygiene hypothesis, the sudden change in human intestinal microflora may importantly contribute to the rise in the incidence of autoimmune and allergic diseases, observed in the last half of 20th century. More than 17 bacterial families encompassing 500 different microbial species can be found in human adults. These commensal bacteria regulate a myriad of host processes and provide several nutrients to their host and their symbionts within the microbial community. In healthy individuals these relationships are thought to occur in equilibrium. However, disruption of this equilibrium may contribute to a variety of conditions including autoimmune, inflammatory bowel, and atopic disease.[26,27] This connection is gaining credibility as associations between gut microbiota and either the risk for or presence of a variety of specific human diseases is demonstrated.

The diversity of intestinal bifidobacteria could be a prospective target for using probiotics in the results management of immunoglobulin E (IgE)-mediated allergic disorders, including Japanese cedar pollinosis. Correspondingly; a study by Kubota

et al[28] suggests that lower diversity of intestinal Bifidobacterium species might be a pathological aspect of Japanese cedar pollinosis. The serum IgE concentration of Japanese cedar pollinosis patients with more than 3 detectable Bifidobacterium species was significantly lower than that of patients with less than 2 detected species. Another randomized double-blind, placebo-controlled trial by the same team was conducted to ascertain the intestinal microbiota-altering properties of *Lactobacillus rhamnosus* GG (LGG) and *Lactobacillus gasseri* in patients with Japanese cedar pollinosis. Stabilization of intestinal microbiota by selected probiotic strains such as LGG and *Lactobacillus gasseri* could be beneficial to homeostasis of the intestinal microbiota and useful in the management of Japanese cedar pollinosis.[28]

Accordingly, the pathogenesis of autoimmune diseases has been recently thought to involve an interaction between genetically determined host susceptibility, the enteric microbiota and dysregulated immune response. Interactions between the intestinal environment, barrier function, and immune system have been shown to have a major impact in the rate of autoimmunity development. Disruption of intestinal barrier function and aberrant mucosal immune activation has been implicated in a variety of diseases within and outside of the gastrointestinal tract.[26-29] The penetration of gut bacterial antigens into lymphoid tissues is one of the suggested initial factors leading to a loss of tolerance towards self components in genetically predisposed individuals. With this model in mind, recent studies have shown a link between diet, composition of intestinal microbiota, and pathogenesis of autoimmune diseases. Furthermore, this new paradigm subverts traditional theories underlying autoimmunity development, which are mainly based on molecular mimicry, and suggests that the autoimmune process can be arrested if the interplay between genes and environmental triggers is prevented by reestablishing intestinal barrier function.[15]

A hypothesis previously has been proposed involving a trio of interacting factors that may create a "perfect intestinal/environmental storm" for autoimmune diseases such as type 1 diabetes development. These factors include (*a*) an aberrant intestinal microbiota, (*b*) a "leaky" intestinal mucosal barrier, and (*c*) an altered intestinal immune responsiveness.[16] In support of this model, modulation of type 1 diabetes pathogenesis in animal models has proved successful through early intervention with a variety of dietary alterations. Indeed, the administration of a hydrolyzed casein diet or the administration of antibiotics has strengthened the hypothesis that an aberrant microbiota could accelerate disease development. More important, this is not a phenomenon that occurs only in rodent models of diabetes, as very recent studies have noted that humans with a propensity to develop type 1 diabetes as well as other autoimmune diseases possess an abnormal intestinal barrier; the so called "leaky gut."[15,30] Together with the gut-associated lymphoid tissue and the neuroendocrine network, the intestinal epithelial barrier, with its intercellular tight junctions, controls the equilibrium between tolerance and immunity to nonself-antigens. Other modulators of tight junction proteins such as certain probiotics may also play a role in modulation of "intestinal leakiness."[27,28,31]

What Are Probiotics?

Probiotic is derived from the Greek word meaning "supporting/favoring life or for life." The works of Metchnikoff and Tissier were the first to make scientific suggestions about the probiotic use of bacteria, even if the word "probiotic" was not coined until 1960, to name substances produced by microorganisms that promoted the growth of other microorganisms.[12] The year 2012 marks the 105th year since Eli Metchnikoff[11] suggested that the consumption of lactic acid bacteria may benefit the human host's immune system. Although probiotics are mainly thought to be represented by lactic acid bacteria, probiotic activity has been found to be associated with Lactobacilli (LGG, gasseri, salivarius), Lactococci, Bifidobacteria (bifidum, longum, infantis), Streptococcus (thermophilus, cremoris, faecium, infantis), Enterococcus (faecium), nonpathogenic *Escherichia coli* (Nissle 1917), *Bacillus coagulans*, and Saccharomyces strains (boulardii and cerevisiae).[11,12] The most popular lactic acid bacteria are members of the genera Lactobacilli and Lactococci, which have a long history of safe use. *Lactobacillus acidophilus* is the most well-known and one of the most important probiotics for the health of the small intestine.

Probiotics are usually isolated from the commensal microflora that inhabits the skin and mucosas. And they represent the species of viable microorganisms (bacteria or yeasts) that have a clear beneficial effect on the health of the host thru establishing a true symbiotic relationship with humans for the longest time. Probiotics are first described as selective nonpathogenic living microorganisms or components of bacteria in food supplements, including some commensal bacterial flora, which have beneficial effects on host health and disease prevention and/or treatment.[27,28] However, experts have debated how to define probiotics. One widely used definition, developed by the World Health Organization (WHO) and the Food and Agriculture Organization of the United Nations, is that probiotics are "live microorganisms, which, when administered in adequate amounts, confer a health benefit by producing gut microflora on the host." Probiotics are also defined as "mono- or mixed cultures of live microorganisms which, when applied to animal or man, beneficially affect the host by improving the properties of the indigenous microflora."[12] Simply put, probiotics are ingested live microbes that can modify intestinal microbial populations in a way that benefits the host.

There are several generally accepted characteristics that identify probiotic bacteria. Probiotics are microbial organisms of human origin and having generally regarded as safe status; remain viable and stable after culture, manipulation, and storage before utilization; survive gastric, biliary, and pancreatic digestion (acid and bile stability); are able to induce a host response once they enter the intestinal microbial ecosystem (adherence to intestinal cells); and yield a functional or clinical benefit (ability to produce antimicrobial substances and

antagonize against pathogenic bacteria and/or ability to modulate the immune response) to the host when consumed.[11-13,27,28]

The number of commercially available products that are supplemented with probiotics is rising. Dairy products that contain probiotics are sold in every supermarket and probiotic food supplements (eg, capsules, tablets, and powders) can be purchased in pharmacies or via the internet. For infants, infant formulas containing probiotics are also currently available. Live probiotic cultures are available in fermented dairy products and probiotic fortified foods. Examples of foods containing live probiotics are yogurt, fermented and unfermented milk, miso, tempeh, and some juices and soy beverages. However, tablets, capsules, powders, and sachets containing the bacteria in freeze-dried form are also available.

Can Probiotics Really Prevent and/or Treat Any Type of Allergic or Autoimmune Disease?

The interest in probiotic therapeutic potential in allergic disorders stemmed from the fact that they have been shown to improve intestinal permeability and reduce inflammatory cytokines. Such effects would be desirable in treating allergic and autoimmune disorders.[10,32] Therefore, several studies have been designed to examine the efficacy of probiotics in many allergic and autoimmune diseases. Experimental and clinical trials of probiotic use as capable preventive and therapeutic strategy in different diseases varying from allergic to autoimmune disease have recently reported. More than 50 randomized, double-blind, placebo-controlled human clinical trials have been conducted so far to study the effects of various probiotics on treatment and prevention of allergic/autoimmune diseases. In the first-time study done by Majamaa and Isolauri[33] in 1997, the administration of LGG to highly selected patients (age <2 years, challenge-proven cow's milk allergy, and mild-to-moderate eczema) significantly improved the total SCORAD score. Later the Finnish study of Kalliomaki was the first report to describe that the frequency of eczema in neonates treated with LGG was half that of the placebo.[34] However, these results recently have been questioned by some other trials, which reported no difference in the development and therapy of allergy in neonates supplemented with LGG or other probiotics.

Proof of principle of the hygiene hypothesis is supported by animal models and to a lesser degree by intervention trials in humans. The incidence of spontaneous type 1 diabetes is directly correlated with the sanitary conditions of the animal facilities, for both the nonobese diabetes mouse and the bio-breeding diabetes-prone rat: the lower the infectious burden, the higher the disease incidence.[15-19,25] Diabetes has a very low incidence and may even be absent in nonobese diabetes mice bred in ''conventional'' facilities, whereas the incidence is close to 100% in female mice bred in specific pathogen-free conditions.[35] Furthermore, bio-breeding diabetes-prone rats subject to cesarean derivation have been noted to develop accelerated disease due to lack of contamination with microbiota in birth canal.[36] Taken together, these data from animal models open new therapeutic perspectives in the prevention of allergic and autoimmune diseases by using probiotics. Consequently, dietary manipulation for β-cell autoimmunity in infants at increased risk of type 1 diabetes was performed in a pilot study. This pilot study, called as PRODIA (probiotics for the prevention of β-cell autoimmunity in children at genetic risk of type 1 diabetes), included 200 children with genetic risk for type 1 diabetes. However, the prevalence of type 1 diabetes–associated autoantibodies among the study subjects at 6, 12, and 24 months of age was at levels close to the expected.[15]

As seen above, preventive or therapeutic effect of probiotics in allergy and autoimmune disease could not be consistently established for now. One of the aims of this review is to delineate current knowledge of probiotics, including the key mechanisms of probiotic effects and their real preventative/therapeutic role in both diseases.

Experimental and Clinical Studies Showing Mechanisms of Probiotics' Effects in Allergic and Autoimmune Diseases

Although the beneficial effects of probiotics on wide variety of atopic diseases have been suggested, little is known about how probiotics modulate the immune system, atopic disease, and autoimmunity development. Currently, only limited publications are available defining the effects of probiotics in murine or human models of atopy and autoimmunity. Therefore, it is important to explore the effect of probiotics in various experimental and clinical atopic and autoimmune disease models. Here, some experimental (animal) and clinical studies of probiotics under the recent literature gathered from Medline and PubMed showing supposed mechanisms of probiotics' effects in atopic and autoimmune disease are being described below (as summarized in Table 1 and Figure 1).

Maturing gut barrier: Probiotic regulation in intestinal epithelium and upregulation of host immune responses. 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 an underdeveloped immune system and have no oral tolerance. In contrast, pathogen-free mice are capable of reconstituting the bacterial flora with Bifidobacteria and tolerance development.[37] Likewise; based on the hygiene hypothesis, it has been theorized that changes in human intestinal microflora in developed societies cause an increase in the prevalence of autoimmune disease besides allergies. Regulation of intestinal microflora composition by probiotics may offer the possibility to influence the development of mucosal/systemic immunity as well as allergy and autoimmune disease development. Probiotics are used in allergic diseases, which

Table 1. Various Mechanisms for Effects of Probiotic Strains in Atopic and Autoimmune Disorders (From Experimental [Animal] and Clinical [Human] Studies Referred in This Review Text).

References	Probiotic Strain	Effect of probiotic	Outcome
		Maturing gut barrier	
Sudo et al[37]	Bfdbm	Oral tolerance	↑
Dotan et al[39]	VSL#3	Local anti-inflammatory effect	↑
Cebra et al[41]	various	Decreased fecal α-1 antitrypsin (local anti-inflammatory)	↑
Sistek et al[42]	LGG	Increased fecal IgA	↑
Kaila et al[44]	Lctbs	Intestinal permeability	↓
Isolauri et al[45,123]	LGG	Gut-stabilizing effect	↑
		Th1/Th2 balance	
Kim et al[30,55,112]	Bfdbm lactis/bifidum; Lctbs acidophilus	IL-10, IFN-γ/IL-4, IgE	↑ / ↓
Sistek et al[42]	LGG	IL-10 production	↑
Takahashi et al[48]	Bfdbm longum	Th2 cytokines and IgE production	↓
Maassen et al[50]	Lctbs casei	IL-10 and Th1 cytokines production	↑
Niers et al[52,78,111]	Bfdbm bifidum/infantis; LL	Th2 cytokines/IL-10 production	↓ / ↑
Kruisselbrink et al[53]	Lctbs plantarum	IL-10 production	↓
West et al[54]	Lctbs F19	Th1/Th2	↑
Shida et al[57]	Bfdbm lactis Bb-12 or LGG	Antigen-specific IgE production	↓
Watanabe et al[58]	Lctbs delbrueckii subsp lactis	Potent Th1 inducer	↑
Hayashi et al[59]	Enterococcus faecium	IgE production	↓
Won et al[60]	Lctbs plantarum	Th1/Th2 cytokines, IL-10 production	↑
Ogawa et al[61]	Lctbs casei subsp Casei	IgE production	↓
Segawa et al[63]	Lctbs brevis	IgE production	↓
Rosenfeldt et al[68]; Brouwer et al[69]	Various	Th1/Th2 cytokines	↔
Hart et al[79]	Bfdbm bifidum	IL-10 production	↑
Zuercher et al[129]	LL	Th2 cytokines	↓
Rupa et al[130]	LL	Th1–Th2 balance	↑
		Serum inflammatory parameters	
Sistek et al[42]; Pessi et al[70]	LGG	Inflammatory parameters	↓
Maassen et al[50]	Lctbs reuteri	Immunomodulation	↑
Brouwer et al[69]	various	Serum inflammatory parameters	↔
Betsi et al[71]	various	Serum inflammatory parameters	↓
Woo et al[72]	Lctbs sakei	CCL17 and CCL27	↓
Marschan et al[74]	various	CRP	↑
Inoue et al[73]	Lctbs johnsonii	Pro-inflammatory cytokines	↓
So et al[76]	Lctbs casei	Effect on Th17 cells	↓
Lavasani et al[77]	probiotics mixture	Th17 cytokines	↓
Jan et al[157]	Lctbs gasseri	Airway inflammation/Th17-cell	↓
Zhang et al[158]	Enterococcus faecalis FK-23	Asthmatic response / Th17-cell	↓
		Development of tolerogenic dendritic cells	
Niers et al[52,78,111]	Bfdbm bifidum	Prime neonatal dendritic cell (most potent polarizer)	↑
Braat et al[49]	Lctbs rhamnosus	Modulates dendritic cell function (function modulator)	↑
Hart et al[79]	Bfdbm bifidum	Matures dendritic cells (phenotype modulator)	↑
Smits et al[80]	Lctbs reuteri/casei	Prime monocyte-derived dendritic cell	↑
		Immunoregulation (Treg production)	
Kim et al[31,55,112]	Bfdbm bifidum; Lctbs acidophilus	Treg-associated TGF-β production	↑
Schwartz et al[21]; Issazadeh-Navikas et al[81]	Various	IL-10-dependent, TGF-β-bearing Tregs	↑
Smits et al[80]	Lctbs reuteri/casei	Prime monocyte-derived dendritic cell	↑
Feleszko et al[82]	LGG, Bfdbm lactis (Bb-12)	TGF-β production	↑
Di Giacinto et al[83]	VSL#3	IL-10-dependent, TGF-β-bearing Tregs	↑
Hacini-Rachinel et al[84]	Lctbs casei	CD4+/CD25+ Tregs	↑
Kwon et al[86]	Probiotic mixture	Foxp3+ Tregs	↑
Weise et al[88]	Escherichia coli Nissle	Foxp3+ Tregs	↑
Karimi et al[159]	Lctbs reuteri	Tregs	↑

(continued)

Table 1. (continued)

References	Probiotic Strain	Effect of probiotic	Outcome
		T-cell hyporesponsiveness	
Braat et al[49]	Lctbs rhamnosus	Peripheral hyporesponsiveness in CD4+ T cells	↑
Kruisselbrink et al[53]	Lctbs plantarum	Inhibits specific T-cell responses	↑
		Lymphocyte subpopulation changes	
Hacini-Rachinel et al[84]	Lctbs casei	CD8+ T cell	↓
Gerasimov et al[89]	Lctbs acidophilus, Bfdbm lactis	CD8+ T cell	↑
Chapat et al[90]	Lctbs casei	Hapten-specific IFN-γ-producing CD8+ T cell	↓
Roessler et al[91]	Probiotic mixture	CD57+ T cells	↑
		Toll-like receptor stimulation	
Hoarau et al[94]	Bfdbm bifidum/infantis; Lctbs salivarius	Activate TLR-2	↑
Forsythe et al[95]	Lctbs reuteri	Activate TLR-9	↑
Aumeunier et al[96]	various	TLR-3 and TLR-4	↑

Abbreviations: Lctbs, Lactobacillus; Bfdbm, bifidobacterium; LGG, *Lactobacillus rhamnosus* GG; LL, *Lactococcus lactis*; IFN-γ, interferon-γ; TGF-β, transforming growth factor-β; TLR, Toll-like receptor; ↑, increase in symptoms or negative effect; ↓, decrease in symptoms or positive effect; ↔, no change in symptoms or no effect.

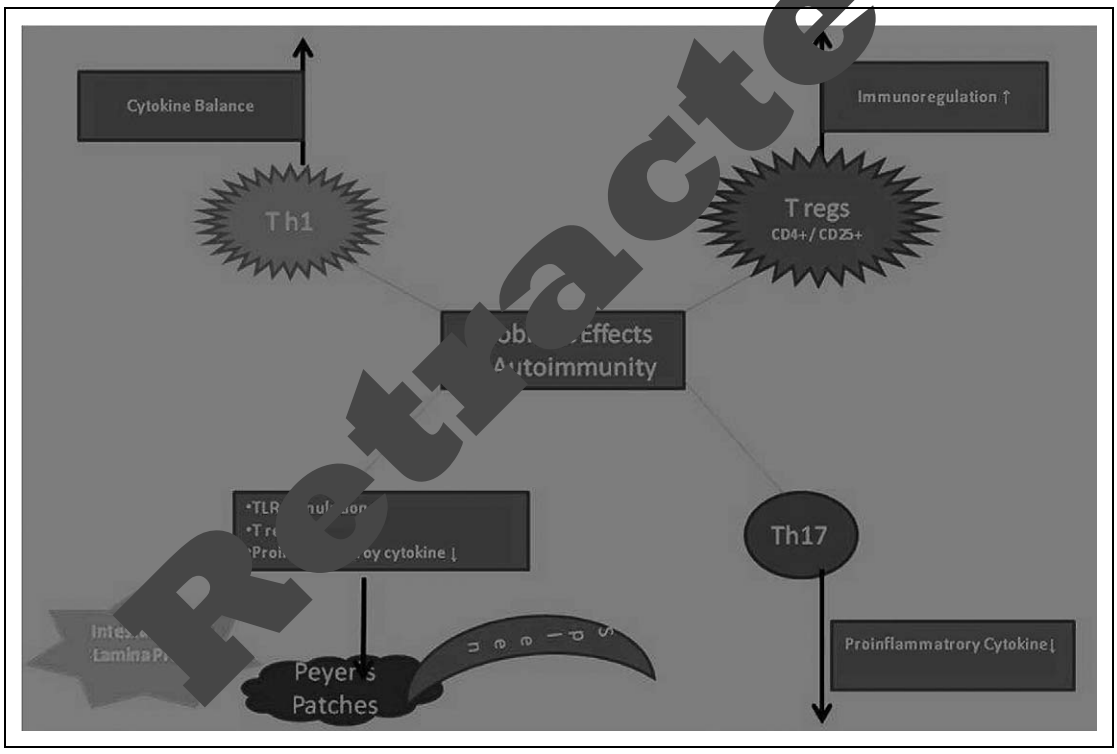

Figure 1. Illustration of some supposed mechanisms of probiotic effects on the development of autoimmunity and autoimmune diseases. Probiotics seem to have a regulatory effect on Treg (regulatory T cell), Th1 (T-helper 1), Th17 (T-helper 17), intestinal cells, and splenocytes.

have shown to be beneficial in some patients with atopic dermatitis and allergic rhinitis.[13,32] Similarly, there is an increasing amount of data showing that intestinal microbiota changes could contribute to the modulation of immune-mediated disorders but evidence is still slim, except in inflammatory bowel disease. The case of probiotics in inflammatory bowel disease is more complex because of the possible local anti-inflammatory effect, which could explain the relief of symptoms without changes in disease progression. Following a number of uncontrolled studies in a small cohort of 14 pediatric patients with newly diagnosed ulcerative colitis, probiotic treatment induced a significant rate of remission and a lower relapse rate.[38,39]

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. Some components of heat-treated LGG may have an ability to delay the onset and suppress the development of atopic dermatitis, probably through a strong induction of IL-10 in intestinal lymphoid organs and systemic levels.[40] After probiotic consumption,

decrease in fecal α-1 antitrypsin, serum tumor necrosis factor-α (TNF-α), and changes in TGF-β and other cytokines point to downregulation of inflammatory mediators.[41] For instance, after a challenge study in infants allergic to cow's milk, fecal IgA levels were detected to be higher and serum TNF-α level were lower in the LGG-applied group compared with the placebo.[42] Similarly, another study by Kirjavainen et al[8] suggested that *Bifidobacterium lactis* might modify gut microflora to alleviate early onset atopic eczema. And this modification was found to be compatible with reductions of serum TNF-α and fecal α-1-antitrypsin levels as well as an increase in fecal IgA level.[8]

Moreover, 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 enteral antigens and altering their immunogenicity.[43] This gut-stabilizing effect of probiotics could be explained by the improvement by probiotics of the immunological barrier of the intestine through intestinal IgA responses, specifically.[44,45] Oral treatment with probiotic *Lactobacillus johnsonii* for a specific part of the weaning period was also shown to prevent the development of atopic dermatitis in model mice, NC/Nga, by modulating or accelerating the gut immune response with increased intestinal secretory IgA.[46] Consistent with these explanations, in children with food allergies, probiotics are shown to reverse increased intestinal permeability and to enhance frequently defective IgA responses.[42,47]

Immunomodulation: Th1/Th2 balance, serum cytokines and IgE production. In addition to maturing gut barrier, certain strains of Lactobacilli and Bifidobacteria modulate the production of cytokines by monocytes and lymphocytes, and may divert the immune system in a regulatory or tolerant mode.[48,49] Although the cytokine stimulation profiles of different probiotic strains vary, the strains isolated from healthy infants mainly stimulate non-inflammatory cytokines.[50] For instance, *Lactobacillus reuteri* induced proinflammatory and Th1 cytokines; and *Bifidobacterium bifidum*/*infantis* and *Lactobacillus lactis* reduced Th2 cytokines.[51] Nonetheless, there are still some studies showing no significant effects of probiotics on either Th1/Th2 cell responses to allergens.

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.[52] In another study, 8 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 pro-inflammatory and Th1 cytokines; however, *Lactobacillus casei* tended to induce IL-10/IL-4.[50] Yet on the contrary, in some children receiving probiotics, reduced IL-10 responsiveness to house dust mites allergens was observed.[53] In a study, the effects of feeding Lactobacillus F19 were evaluated during weaning on the incidence of eczema and Th1/Th2 balance. At 13 months of age, the higher Th1/Th2 ratio and reduced eczema incidence in the probiotic compared with the placebo group suggests enhancing effects of Lactobacillus F19 on the T cell–mediated immune response.[54]

In a mouse model, effect of oral probiotics administration, including *Bifidobacterium lactis*/*bifidum* and *Lactobacillus 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 (IFN-γ) and IL-10 were significantly higher in the mice treated with probiotics than that in the non-treated mice.[55] Another murine model showed that oral administration of an immunostimulatory DNA sequence from *Bifidobacterium longum* suppressed Th2 immune responses in mice and inhibited IgE production in vitro.[48] Similarly, *Lactobacillus acidophilus* suppressed the development of atopic dermatitis–like skin lesions in sensitized NC/Nga mice via decreasing serum total IgE level.[56] A final study showed that the administration of either *Bifidobacterium lactis* or LGG suppressed antigen-specific IgE production too.[57]

Atopic dermatitis–like skin lesions were induced by repeated challenges with mostly picrylchloride in the Th2-skewed NC/Nga mouse strain. Oral administration of lactic acid bacteria (*Lactobacillus delbrueckii* subsp *lactis* R-037) isolated from traditional South Asian fermented milk "dahi" inhibits the development of atopic dermatitis thru exhibiting IL-12 as a potent Th1 inducer.[58] Also, the antiallergic effects of one strain (T120) of lactic acid bacteria isolated from Mongolian fermented milk using AD model mice (NC/Nga mice) were investigated. Strain T120 has already been identified as Enterococcus faecium and suppressed total IgE production and induced IL-12 and IFN-γ production by splenocytes of NC/Nga mice. Furthermore, this strain enhanced the production of IL-10 by splenocytes and activation of Tregs by strain T120 may inhibit atopic disease.[59] In another study, *Lactobacillus plantarum* strains from Kimchi were demonstrated to inhibit atopic dermatitis (house dust mite–induced dermatitis) in NC/Nga mouse. Lactobacilli isolated from Kimchi inhibit atopic dermatitis, probably by altering the balance of Th1/Th2 ratio or inducing IL–10 production.[60] A new synbiotic, *Lactobacillus casei* subsp *casei* together with dextran, reduces the development of atopic dermatitis–like skin lesions in NC/Nga mice. This synbiotic combination significantly decreased clinical skin severity scores induced by picryl chloride and total IgE levels in sera of NC/Nga mice.[61] Also, supplementation with KW3110 strain of lactic acid bacteria significantly attenuated the onset and exacerbation of atopic dermatitis–like skin lesions, accompanied by lower plasma IgE levels through its effects on IL-12 and IL-4 production in vitro.[62] Oral administration of *Lactobacillus brevis* significantly inhibited IgE production and ear swelling, and suppressed the development of dermatitis in a dose-dependent manner in atopic dermatitis model of NC/Nga mice. Cytokines, for example, IL-10 and TGF-β production from Peyer's patch cells significantly increased in the treatment group.[63] Consistently, oral

supplementation with *Lactobacillus rhamnosus* in a study by Tanaka et al[64] has been demonstrated to prevent development of atopic dermatitis in NC/NgaTnd mice, possibly by modulating local production of IFN-γ and plasma total IgE in skin biopsies.[64]

Probiotic supplementation decreased the severity of allergic skin responses in allergen-sensitized pigs with a corresponding increase in IFN-γ expression.[65] Consistently, Pohjavuori et al[66] were able to demonstrate an increase of IFN-γ production in peripheral blood mononuclear cells in infants with atopic dermatitis treated with LGG. Additionally, the improvement in atopic dermatitis severity of very young children with probiotic treatment was detected to be associated with increases in IFN-γ responses.[67] However, Rosenfeldt et al[68] demonstrated no significant changes in serum cytokines during 6 weeks of probiotic treatment. Brouwer et al[69] also showed no statistically significant effects of probiotic supplementation on cytokine production. As a result, it seems that changes in cytokine profile induced by probiotics could be probiotic strain- or site-specific and dependent on the experimental system used.

Systemic anti-inflammatory effects. The anti-inflammatory effect of probiotics has been attributed to increased production of IL-10 by immune cells in the lamina propria, Peyer's patches, and the spleen of treated animals. Moreover, a decrease in the secretion of pro-inflammatory cytokines, IFN-γ, TNF-α, and IL-12 has been demonstrated.[39,47,50,52] 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.[70] A review of the evidence from randomized controlled trials by Betsi et al[71] about probiotics for the treatment or prevention of atopic dermatitis: The results of 13 relevant randomized controlled trials were reviewed, 10 of which evaluated probiotics as treatment and 3 for prevention of atopic dermatitis. In 4 of these 6 randomized controlled trials, clinical improvement was associated with a change in some inflammatory markers.[71]

A study by Woo et al[72] evaluated the effect of *Lactobacillus sakei* supplementation in children with atopic eczema–dermatitis syndrome. In this study, compared with placebo, probiotic administration was associated with lower pretreatment-adjusted serum levels of chemokines such as CCL17 and CCL27, which were significantly correlated with SCORAD total score.[72] Primary administration of *Lactobacillus johnsonii* in the weaning period suppressed the elevation of proinflammatory cytokines and CD86 gene expressions in skin lesions of NC/Nga model mice. The suppression of proinflammatory cytokines, for example, IL-8, IL-12, and IL-23, and CD86 expression by *Lactobacillus johnsonii* may significantly contribute to the inhibitory effect on the skin lesion like atopic dermatitis.[73]

Nevertheless, another randomized, double-blind, placebo-controlled study conducted by Brouwer et al[69] showed no statistically significant effects of probiotic supplementation on inflammatory parameters. Interestingly; probiotic-induced chronic low-grade inflammation characterized by elevation of C-reactive protein (CRP), IgE, IgA, and IL-10 was shown in some studies, the changes typically observed in helminth infection-associated induction of regulatory mechanisms. The association of increased CRP with a decreased risk of eczema at 2 years of age in allergy-prone children supports the view that chronic, low-grade inflammation protects from eczema. The findings emphasize the role of chronic microbial exposure as an immunomodulator protecting from allergy.[74]

Suppression of Th17 cells (reducing pro-inflammatory cytokines through Th17 cells). T-helper 17 (Th17) cells, a subset of CD4+ T cells have been implicated as having an important role in the development of several allergic disorders, but the relationship between oral administration of probiotics and Th17 development has not been well studied. Th17 cells have been also shown as pathogenic cells in some autoimmune diseases such as experimental autoimmune encephalomyelitis and arthritis.[75] Some probiotics have been reported to reduce proinflammatory cytokines through Th17 cells. Suppression of this newly discovered subset of T cells by probiotics might explain effects observed in different experimental models that all involve inflammatory responses, that is, colitis. For instance, *Lactobacillus casei* suppressed inflammation in experimental arthritis reducing pro-inflammatory cytokines released from Th17 cells.[76] Also, in a study administration of a probiotics mixture (*Lactobacillus acidophilus*, *Lactobacillus casei*, *Lactobacillus reuteri*, *Bifidobacterium bifidium*, and *Streptococcus thermophilus*) induced both T-cell and B-cell hyporesponsiveness and downregulated Th1, Th2, and Th17 cytokines.[77]

Development of tolerogenic dendritic cells. Selected species of the Bifidobacterium genus were demonstrated to prime in vitro cultured neonatal dendritic cells to polarize T-cell responses and may therefore be used as candidates in primary prevention of allergic diseases. *Bifidobacterium bifidum* was found to be most potent polarizer in vitro–cultured dendritic cells to drive Th1-cell responses involving increased IFN-γ producing T cells concomitant with reduction of IL-4-producing T-cells.[78] In addition, T-cells stimulated by *Bifidobacterium bifidum* matured dendritic cells as producers of more IL-10.[79] Moreover, *Lactobacillus rhamnosus*, member of another genus of probiotic bacteria, modulates dendritic cell function to induce a novel form of T-cell hyporesponsiveness.[49] *Lactobacillus reuteri*/*casei* have been also shown to prime monocyte-derived dendritic cells through the C-type lectin dendritic cell-specific intercellular adhesion molecule 3-grabbing non-integrin (dendritic cell-SIGN) to drive the development of Tregs.[80] These Treg 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 dendritic cell-SIGN by certain probiotic bacteria might explain their beneficial effect in the treatment of a number of inflammatory diseases, including atopic and autoimmune diseases.

Immunoregulation by T regulatory (Treg) cells. As mentioned earlier, *Lactobacillus reuteri*/*casei* have been also shown to

prime monocyte-derived dendritic cells through the dendritic cell-SIGN to drive the development of Tregs.[80] And the probiotic combinations are alleged to cause a paradoxic Th2 stimulation and to induce chronic low-grade inflammation, practically the same as in chronic and balanced helminth infection, which is associated with activation of Treg cells suppressing allergic inflammation.[74] CD4+/CD25+ Tregs have shown to be pivotal players in the maintenance of immune tolerance. Their role in the prevention of autoimmunity in animal models and evidence for disturbed or dysfunction of Tregs have also been observed in patients with different autoimmune diseases, including multiple sclerosis.[21]

Recent studies provided evidence that one effect of probiotics may involve induction of differentiation of IL-10-dependent, TGF-β-bearing Tregs.[21,81] They also can suppress immune responses distinct from responses against the antigen in question, here antigens expressed by infectious agents (a phenomenon called bystander suppression). In a food allergy mouse model, oral administration of *Bifidobacterium bifidum* and *Lactobacillus acidophilus* suppressed OVA-specific IgE production, which was caused by inducing Treg-associated TGF-β production.[55] Another study demonstrated that neonatal application of probiotic bacteria inhibits subsequent allergic sensitization and airway disease in a murine model of asthma by induction of Treg cells and TGF-β production.[82] In another study, the regulatory cytokine and cell response to probiotic (VSL#3) administration in the context of the Th1-mediated colitis of SJL/J mice was analyzed. Probiotic VSL#3 administration during a remission period ameliorated the severity of recurrent colitis by inducing an immunoregulatory response involving an early increase in the production of IL-10 and TGF-β-bearing T-regs.[83]

Generation of CD4+/Foxp3+ Treg cells by probiotics administration suppresses autoimmune and allergic disorders. Recently, 2 studies reported that oral administration of a certain probiotic strain, for example, *Lactobacillus casei* could increase Foxp3+ Tregs.[84,85] It is known that the lower percentage of epidermal or dermal Foxp3+ cells in eczematous dermatitis can contribute to their pathogenesis.[85] The strain T120 of lactic acid bacteria was shown to be able to inhibit atopic disease in NC/Nga mice through enhanced production of IL–10 by splenocytes and activation of Teg cells.[84] In a recent study, a mixture of probiotics (*Lactobacillus acidophilus*, *Lactobacillus casei*, *Lactobacillus reuteri*, *Bifidobacterium bifidium*, and *Streptococcus thermophilus*) was identified that upregulates CD4+/Foxp3+ Treg cells. Administration of the probiotics mixture induced both T-cell and B-cell hyporesponsiveness and downregulated Th1, Th2, and Th17 cytokines. It also induced generation of CD4+/Foxp3+ Tregs from the CD4+/CD25− population and increased the suppressor activity of naturally occurring CD4+/CD25+ Tregs. Conversion of T cells into Foxp3+ Tregs is directly mediated by regulatory dendritic cells that express high levels of IL-10 and TGF-β.[86] However, another study showed that Foxp3 mRNA expression at 6 months of age is higher in infants having atopic dermatitis, but it is not affected by giving probiotics from birth.[87] In sensitized BALB/c mice, skin inflammation was induced by topical allergen application. *Escherichia coli* Nissle 1917 was administered orally in a preventive manner and it improved allergen-induced dermatitis dose dependently. *Escherichia coli* Nissle altered the local allergen-induced immune response by Foxp3+ cell increase and by favoring immunoregulatory cytokine patterns.[88]

Changes in lymphocyte subpopulations. Several studies reveal that the probiotics differently modulate peripheral blood immune parameters in healthy subjects and patients with atopic diseases. Gerasimov et al[89] conducted a study to assess the clinical efficacy and impact of *Lactobacillus acidophilus* plus *Bifidobacterium lactis* with fructo-oligosaccharide on peripheral blood lymphocyte subsets in preschool children with moderate-to-severe atopic dermatitis. The percentage of CD4, and the percentage/absolute count of CD25 decreased, and the percentage/absolute count of CD8 increased in the probiotic group at week 8, compared with placebo. They found a significant correlation between CD4 percentage, CD25 percentage, CD25 absolute count, and SCORAD values in the probiotic group at week 8. The administration of a probiotic mixture and fructo-oligosaccharide was correlated with significant clinical improvement in children with atopic dermatitis, with corresponding lymphocyte subpopulation changes in peripheral blood.[89]

Also in other mice studies, contact hypersensitivity to the hapten 2,4-dinitrofluorobenzene, a model of allergic contact dermatitis mediated by CD8+ cytotoxic T lymphocytes and controlled by CD4+ Treg cells was studied. Daily oral administration of fermented milk containing *Lactobacillus casei* or *Lactobacillus casei* alone decreased skin inflammation by inhibiting the priming/expansion of hapten-specific IFN-γ-producing CD8+ effector T cells. This study provides the first evidence that oral administration of *Lactobacillus casei* can reduce antigen-specific skin inflammation by controlling the size of the CD8+ effector pool.[90]

However, in some studies major lymphocyte subsets were not affected by the probiotic intervention. The purpose of a study by Roessler et al[91] was to elucidate the influence of a probiotic drink containing a combination of the probiotics *Lactobacillus paracasei*, *Lactobacillus acidophilus*, and *Bifidobacterium animalis* in healthy volunteers and in patients with atopic dermatitis on clinical and immunological parameters and their detection in feces. This double-blind, randomized cross-over study was conducted in 15 healthy adults and 15 patients with atopic dermatitis. In atopic dermatitis patients, the SCORAD tended to decrease by 16%. The expression of CD4+/CD25+ T cells was similar in healthy subjects and atopic dermatitis patients, whereas CD4+/CD54+ cells decreased significantly in patients with atopic dermatitis and remained uninfluenced in healthy subjects. However, CD57+ T cells increased significantly in healthy subjects after probiotic intake and was not changed in patients.[91]

Systemic Toll-like receptor (TLR) stimulation via nonantigenic ligands. A number of experiments indicate that infectious agents

can promote protection from atopic and autoimmune diseases through mechanisms independent of their constitutive antigens, leading to stimulation of nonantigen-specific receptors such as TLRs. A family of pattern recognition receptors such as TLRs on gut lymphoid and epithelial cells mediates innate immune responses to bacterial molecular patterns and, thereby, orchestrates acquired immunity. The transient protection offered by probiotics against IgE-associated allergic diseases is based on stimulation of TLRs, which produce mediators such as IL-6; these further induce IgA differentiation from naive B cells. Both these events were shown to occur after probiotic administration to infants with eczema and also in infants who showed increased levels of serum CRP, IL-10, and IgE at the age of 6 months.[74] Similarly; an observation made for TLR-2/-3/-4/-7 and -9 that TLR stimulation could prevent the onset of type 1 diabetes in nonobese diabetes mice.[92,93]

As mentioned, TLR stimulation was also thought to occur after probiotic administration in infants with eczema who showed increased levels of serum CRP, IL-10, and IgE. This probiotic-induced low-grade inflammation was characterized by elevation of CRP, IgE, IgA, and IL-10, the changes typically observed in helminth infection–associated induction of regulatory mechanisms. Moreover, the association of increased CRP with a decreased risk of eczema at 2 years of age in allergy-prone children supports the view that chronic, low-grade inflammation protects from eczema. The findings emphasize the role of chronic microbial exposure as an immunomodulator protecting from allergy thru activation of Treg cells by TLR stimulation.[74] Consistently, lactic acid bacteria species such as *Bifidobacterium bifidum*/*infantis* and *Lactobacillus salivarius* were shown to be capable of activating TLR-2.[94] Oral administration of *Lactobacillus reuteri* attenuated major characteristics of an asthmatic response, including airway eosinophilia, local cytokine responses, and hyperresponsiveness to methacholine. This effect of *Lactobacillus reuteri* on the allergic airway response was found to depend on TLR-9.[95] A systematic study was performed by Aumeunier et al[96] on the disease-modifying effects of a set of natural or synthetic TLR agonists using 2 experimental nonobese diabetes mouse models, OVA-induced asthma and spontaneous autoimmune type 1 diabetes. In these models, probiotics that stimulate TLRs also were shown to protect from these 2 diseases. These results strongly indicate that the TLR-mediated effects involve immunoregulatory cytokines such as IL-10 and TGF-β and different subsets of Treg cells, notably CD4+/CD25+/FoxP3+ T cells for TLR-4 agonists and NKT cells for TLR-3 agonists.[96]

In summary, local influences of probiotics potentially include reduction of gut 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 Th17 cells and TLRs, Th1 skewing of responses to allergens, activation of tolerogenic dendritic cells, in addition to Treg cell production. The various effects of different probiotic strains in atopic and in autoimmune diseases are summarized in Table 1 and Figure 1.

The Role of Probiotics in the Prevention and Treatment of Allergic Diseases in Humans

The increased prevalence of atopic and autoimmune diseases is nowadays defined as an epidemic. Atopic dermatitis is 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. Here, their role in the prevention and therapy of atopic disease under the recent literature gathered from Medline and PubMed are discussed. First, clinical (human) studies showing probiotics' effects in various allergic diseases consisting of atopic dermatitis, food allergy, allergic rhinitis, asthma and then their role in autoimmune diseases will be mentioned. The various effects of different probiotic strains in allergic diseases from essential clinical studies referred in the text are shown in Table 2.

Clinical (Human) Studies Showing Probiotics' Effects in Atopic Dermatitis (Eczema)

Mostly reported clinical (human) studies showing effects of probiotcs in allergic disorders have been related to atopic dermatitis (eczema). Here, probiotics' effects in human atopic dermatitis are being discussed according to the IgE-sensitized (atopic) versus non-IgE-sensitized (nonatopic) eczema groups.

Any Difference for IgE-Sensitized (Atopic) Versus Non-IgE-Sensitized (Nonatopic) Eczema Groups?. A number of studies could only relate probiotic benefits to a certain subset of atopic dermatitis patients. In support of the efficacy of probiotics in IgE-sensitized children, some other studies also demonstrated comparable results as well. In brief, treatment with *Lactobacillus rhamnosus* for the first 2 years of life was associated with a significant reduction in the prevalence of any IgE-associated eczema by about a half.[34] Another study demonstrated that LGG alleviated atopic eczema–dermatitis syndrome symptoms in IgE-sensitized infants.[97] In food-sensitized atopic children, the efficacy of the probiotics such as *Lactobacillus rhamnosus* and *Bifidobacterium lactis* was demonstrated too. And this effect was more pronounced in patients with a positive skin prick test and increased IgE levels.[42,98]

Yet some other studies failed to demonstrate that the severity and frequency of atopic dermatitis were decreased with the supplementation of probiotics, regardless of their IgE sensitization status. For instance; Boyle et al[99] and others could not show any effect even for LGG in infants with atopic dermatitis. A few meta-analyses also could not confirm that IgE sensitization was indeed a factor in determining the efficacy of probiotics in atopic children. However, the heterogeneity between studies may be attributable to probiotic strain-specific effects and other factors as well, meaning that some probiotic strains may still have a therapeutic role in eczema.[13,32] Correspondingly; in a very recent meta-analysis of 7 studies, Doege et al[100] showed that the administration of Lactobacilli during

Table 2. The Various Effects of Different Probiotic Strains in Allergic Diseases (From Essential Clinical Studies Referred in the Text).

References	Probiotic Strain	Allergic Disease Type/Mechanisms	Outcome
		Atopic (IgE-associated) eczema	
Majamaa et al[33]	LGG	Food-sensitized eczema	↓
Kalliomäki et al[34]	LGG	Atopic dermatitis	↓
Sistek et al[42]	Lctbs rhamnosus + Bfdbm lactis	Eczema, food-sensitized atopy	↓
Isolauri et al[45,123]	Bfdbm or Lctbs	Food (cow's milk) allergy	↓
Rosenfeldt et al[68]	Lctbs rhamnosus + Lctbs reuteri	Atopic eczema	↓
Viljanen et al[97]	LGG	Atopic eczema/dermatitis syndrome	↓
Rautava et al[102]	LGG	IgE-associated eczema	↓
Kukkonen et al[103]	Probiotic mixture	Atopic eczema	↓
Kuitunen et al[104]	Lctbs + Bfdbm + Propionibacteria	IgE-associated allergy	↓
Abrahamsson et al[105]	Lctbs reuteri	Atopic eczema	↓
Kirjavainen et al[101]	LGG	IgE-associated eczema	↓
Wickens et al[110]	Lctbs rhamnosus	IgE-associated eczema	↓
		Nonatopic eczema	
West et al[54]	Lctbs casei F19	Atopic dermatitis	↓
Woo et al[72]	Lctbs sakei	Atopic dermatitis	↓
Marschan et al[74]	Probiotic mixture	Atopic dermatitis	↓
Gerasimov et al[89]	Lctbs acidophilus, Bfdbm lactis	Atopic dermatitis	↓
Weston et al[107]	Lctbs fermentum	Atopic dermatitis	↓
Hoang et al[108]	Lctbs rhamnosus	Atopic dermatitis	↓
Hattori et al[109]	Bfdbm breve	Atopic dermatitis	↓
Wickens et al[110]	Lctbs rhamnosus, Bb-12	Atopic dermatitis	↓
Niers et al[111]	Bfdbm bifidum, Bfdbm lactis, LL	Atopic dermatitis	↓
Kim et al[112]	Bfdbm bifidum, Bfdbm lactis, Lctbs acidophilus	Atopic dermatitis	↓
Dotterud et al[113]	LGG, Lctbs acidophilus, Bb-12	Atopic dermatitis	↓
Lodinova-Zadnikova et al[114]	*Escherichia coli*	Atopic dermatitis (IgE allergies)	↓
		Eczema	
Brouwer et al[69]	Lctbs rhamnosus	Atopic dermatitis	↔
Taylor et al[87,116]	LGG or Lctbs acidophilus	Atopic dermatitis/(cow's milk allergy) allergic sensitization	↔ / ↑
Boyle et al[99]	LGG	Atopic dermatitis	↔
Kuitunen et al[104]	Lctbs + Bfdbm + Propionibacteria	Atopic dermatitis	↔
van der Aa et al[117]	Bfdbm breve	Atopic dermatitis	↔
Huurre et al[115]	LGG	Atopic dermatitis/allergic sensitization	↔ / ↑
Kopp et al[118]	LGG	Atopic dermatitis (wheezing)	↔, (↑)
Gruber et al[119]	LGG	Atopic dermatitis/allergic sensitization	↔ / ↔
Fölster-Holst et al[120]	LGG	Atopic dermatitis	↔
Soh et al[121]	Bfdbm longum + Lctbcs rhamnosus	Eczema and atopic sensitization	↔
Soh et al[121]	Bfdbm longum + Lctbcs rhamnosus	Eczema and atopic sensitization	↔
Gore et al[122]	Lctbs paracasei + Bfdbm lactis	Atopic dermatitis	↔
		Food allergy and anaphylaxis	
Kim et al[31,55]	Lctbs acidophilus + Bfdbm lactis	Ovalbumin-induced allergic symptoms	↓
Majamaa et al[33]	LGG	Food-sensitized eczema	↓
Pelucchi et al[106]	Bfdbm or Lctbs	Food allergy	↓
Taylor et al[116]	LGG or Lctbs acidophilus	Cow's milk allergy	↔, ↓
Isolauri et al[123]	Bfdbm or Lctbs	Food allergy	↓
Shida et al[127]	VSL#3 + LcS	Anaphylaxis with food allergy	↓
Schiavi et al[128]	VSL#3	Anaphylactic reaction	↓
Zuercher et al[129]	LL	Food allergy symptoms	↓
Rupa et al[130]	LL	Ovomucoid allergy	↓
Hol et al[131]	Lctbs casei + Bb-12	Cow's milk allergy	↔
de Jonge et al[133]	LcS	Peanut allergy	↔
		Perennial allergic rhinitis	
Di Felice et al[126]	VSL#3	Parietaria allergen-specific response	↓
Peng at al[137]	Lctbs paracasei	Dust-mite sensitization	↓
Giovannini et al[138]	Lctbs casei	Health status	↓
Morita et al[139]	LGG + Lctbs gasseri	Allergic rhinitis	↓

(continued)

Table 2. (continued)

References	Probiotic Strain	Allergic Disease Type/Mechanisms	Outcome
Chen et al[140]	Lctbs gasseri	Serum cytokines	↓
Wang et al[141]	Lctbs paracasei	Quality of life	↓
Nishimura et al[142]	Tetragenococcus halophilus	Rhinitis symptoms	↓
		Seasonal allergic rhinitis	
Ivory et al[144]	LcS	Severity of symptoms	↓
Nagata et al[145]	Lctbs plantarum	Symptom-medication score	↓
Kawase et al[146]	LGG and Lctbs gasseri	JCPsis, nasal blockage	↓
Xiao et al[147,148]	Bfdbm longum	JCPsis	↓
Koyama et al[150]	Lctbs paracasei	JCPsis	↓
Tamura et al[151]	LcS	JCPsis	↔
		Allergic rhino-conjunctivitis	
Nagata et al[145]	Lctbs plantarum	Ocular symptom-medication score	↓
Xiao et al[147]	Bfdbm longum	JCPsis	↓
Ouwehand et al[152]	Lctbs acidophilus + Bfdbm lactis	Decreased birch pollen allergy	↓
		Asthma	
Kruisselbrink et al[53]	Lctbs plantarum	Dermatophagoides (Der p1) sensitization	↓
Feleszko et al[82]	Bb-12	Airway reactivity	↓
Giovannini et al[138]	Lctbs casei	Asthmatic response	↔
Blümer et al[154]	LGG	Allergic airway inflammation	↓
Singh and Ranjan Das[155]	LGG and Bb-12	Airway reactivity, pulmonary eosinophilia	↓
Repa et al[156]	LL + Lctbs plantarum	Birch pollen allergen (Bet v1) sensitization, allergen-induced basophil degranulation	↓
Jan et al[157]	Lctbs gasseri	Airway inflammation	↓
Zhang et al[158]	Enterococcus faecalis	Asthmatic response	↓
Karimi et al[159]	Lctbs reuteri	Allergic airway inflammation	↓
Lue et al[160]	Lctbs johnsonii	FVC + FEV_1 improved	↓
Moreira et al,[162] Helin et al[165]	LGG	Asthmatic response	↔
Helin et al[165]	LGG	Pollen allergy	↔

Abbreviations: Lctbs, Lactobacillus; Bfdbm, Bifidobacterium; LGG, Lctbs rhamnosus GG; LL, *Lactococcus lactis*; VSL#3, probiotic mixture; LcS, *Lactobacillus casei* strain Shirota; Bb-12, Bifidobactrium animalis; JCPsis, Japanese cedar pollinosis; FVC, forced vital capacity; FEV_1, forced expiratory volume in 1 second; ↑, increase in symptoms or negative effect; ↓, decrease in symptoms or positive effect; ↔, no change in symptoms or no effect.

pregnancy prevents atopic eczema in children aged from 2 to 7 years. However, a mixture of various bacterial strains did not affect the development of atopic eczema, independent of whether they contain lactobacilli or not.[100]

IgE-sensitized (atopic) eczema therapy and prevention. Until now, several clinical studies have been published that have focused on the use of probiotics for therapy and primary prevention of atopic diseases. To date, the results of at least 20 prospective preventive studies with different Lactobacillus or Bifidobacterium strains (or mixture) in children at high risk for allergic diseases have been published. The first study in the literature by Isolauri et al analyzed a benefit of LGG in mild atopic dermatitis disease in 1997. They observed 27 exclusively breastfed infants (median age 4-6 months) with mild atopic dermatitis, receiving extensively hydrolyzed whey formula with (LGG or Bifidobacterium strain) or without probiotics (placebo) for 8 weeks. They showed a reduction in the SCORAD by 15 points for the LGG and by 16 points for the Bifidobacterium arm, as compared with a reduction of 2 to 6 points in the placebo arm. However, 1 month after therapy, SCORAD scores were comparable with those of placebo. Therefore, the probiotic effect was limited to acceleration of improvement in infants with mild disease.[33] The same investigators subsequently published 2 additional studies. One of these studies compared LGG with *Bifidobacterium lactis*, both of which showed a significant improvement in SCORAD score over placebo. However, after 6 months, the median SCORAD score was zero in all groups, again suggesting that the effect is limited to rapid initiation of improvement. The other study underlined the importance of viability for probiotic species. The use of heat inactivated LGG resulted in adverse gastrointestinal symptoms with diarrhea, and then study recruitment was halted. They concluded that supplementation of infant formulas with viable but not heat-inactivated LGG was found to be a potential approach for the management of atopic eczema and cow's milk allergy.[101]

In a double-blinded, placebo-controlled study of 62 mother–infant pairs by Rautava et al,[102] it is shown that administering probiotics to the pregnant and lactating mother significantly increased the immunoprotective potential of breast milk, as assessed by the amount of anti-inflammatory TGF-β2 in the milk of mothers receiving probiotics versus in mothers receiving placebo. The risk of developing atopic eczema during the first 2 years of life in infants whose mothers received probiotics was significantly reduced in comparison with that in infants whose mothers received placebo (15% and 47%, respectively; relative risk = 0.32; $P = .0098$). The infants most likely to

benefit from maternal probiotic supplementation were those with an elevated cord blood IgE concentration. Administering probiotics during pregnancy and breast-feeding thus offers a safe and effective mode of promoting the immunoprotective potential of breast-feeding and provides protection against atopic eczema during the first 2 years of life.[102]

One of the recently published largest studies to date by Viljanen et al[97] compared LGG or a probiotic mix (LGG, *Lactobacillus rhamnosus*, *Bifidobacterium breve*, and Propionibacterium) with placebo. In this study, 230 Finnish children with atopic dermatitis were treated for 4 weeks with LGG, a mixture of 4 probiotic strains or placebo. With supplementation with probiotic LGG, Viljanen et al found significant improvement on the SCORAD index only in ''IgE-sensitized'' cow's milk allergic infants with the atopic eczema–dermatitis syndrome. Only in the subgroup of IgE-sensitized children did the LGG group show a greater reduction in SCORAD than the placebo group but this effect could have been due to a higher baseline score in this subgroup. Contrary to what would be expected, improvement was seen 4 weeks after discontinuation of therapy rather than during treatment.[97] In a study by Rosenfeldt et al[68] from Denmark, 2 lyophilized probiotic Lactobacillus strains (lyophilized *Lactobacillus rhamnosus* and *Lactobacillus reuteri*) were given in combination for 6 weeks to 1- to 13-year-old (mean age = 5.2 years) children with atopic dermatitis. This study used 2 different Lactobacillus species in older children. A combination of these was beneficial in the management of atopic dermatitis. Statistically significant improvement in SCORAD score was seen only in a subset of children with positive skin prick test results and elevated IgE levels.[66] Another study by Sistek et al[42] showed the efficacy of the probiotics *Lactobacillus rhamnosus* and *Bifidobacterium lactis* in food-sensitized children.[42]

A study by Finnish group used the same probiotic mixture of Viljanen et al with prebiotic. Kukkonen et al,[103] in a trial using probiotic mix (LGG, *Lactobacillus rhamnosus*, *Bifidobacterium breve*, and Propionibacterium) and prebiotic galacto-oligosaccharides demonstrated that the prevention of atopic eczema in high-risk Finnish infants is possible by modulating the infant's gut microbiota with probiotics and prebiotics. Probiotic treatment compared placebo with IgE-associated (atopic) diseases. Probiotic treatment also reduced non-atopic plus atopic eczema.[103] In 2009, in a study by Kuitunen et al,[104] 1223 Finnish mothers were randomized with infants at high risk for allergy to receive the same probiotic mixture (2 Lactobacilli, Bifidobacteria, and propionibacteria) or placebo during the last month of pregnancy and their infants to receive it from birth until age 6 months. Infants also received a prebiotic galacto-oligosaccharide or placebo. At 5 years, the cumulative incidence of allergic diseases (eczema, food allergy, allergic rhinitis, and asthma) and IgE sensitization were evaluated. Frequencies of allergic and IgE-associated allergic disease and sensitization in the probiotic and placebo groups were similar. However, less IgE-associated allergic disease occurred in cesarean-delivered children receiving probiotics. No allergy-preventive effect that extended to age 5 years was achieved with perinatal supplementation of probiotic bacteria to high-risk mothers and children. It conferred protection only to cesarean-delivered children.[104] Similarly, Abrahamsson et al[105] could not confirm a preventive effect of probiotics (*Lactobacillus reuteri*) on infant eczema in a recently published study. However, he observed that the treated infants had less IgE-associated eczema at 2 years. Moreover, skin prick test reactivity was also less common in the treated group than in the placebo group, but this difference reached significance only for infants with allergic Swedish mothers.[105] A current meta-analysis provided evidence in support of a moderate role of probiotics in the prevention of atopic dermatitis and IgE-associated atopic dermatitis in infants. The favorable effect was similar regardless of the time of probiotic use (pregnancy or early life) or the subject(s) receiving probiotics (mother, child, or both).[106]

In conclusion, all these studies taken together demonstrate that probiotics might not be effective and/or therapeutic for all children with atopic dermatitis, but offer benefit in a subset of IgE-sensitized children.

Non-IgE-sensitized (nonatopic) eczema therapy and prevention. In an earlier study by Viljanen et al, probiotics have been suggested to be useful in children with non-atopic and atopic eczema.[97,101] Yet, in 2010, a study by Woo et al[72] was performed to assess the clinical effect of *Lactobacillus sakei* supplementation in children with atopic eczema–dermatitis syndrome. In this study, children aged 2 to 10 years with atopic eczema–dermatitis syndrome with a minimum SCORAD score of 25 were randomized to receive either daily *Lactobacillus sakei* or daily placebo supplementation for 12 weeks. At week 12, SCORAD total scores adjusted by pretreatment values were lower after probiotic treatment than after placebo treatment. There was a 31% improvement in mean disease activity with probiotic use compared with a 13% improvement with placebo use. Therefore, significant differences in favor of probiotic treatment were also observed in proportions of patients achieving improvement of at least 30% and 50%. Interestingly, clinical improvement in this study was not just observed in the subgroup of IgE-sensitized children, contrary to the study by Viljanen et al, and it was regardless of IgE sensitization.[72] Weston et al[107] from Australia published their experience with using *Lactobacillus fermentum* for 8 weeks in 53 infants with atopic dermatitis. After 16 weeks, the probiotic group had significant reduction of SCORAD scores whereas the placebo group did not. *Lactobacillus fermentum* caused a significant reduction in SCORAD scores. Although the change in SCORAD score from baseline in the probiotic group was significant, the difference between the probiotic and placebo groups did not reach significance by week 16.[107] In a study by Hoang et al,[108] the authors followed 14 cases of pediatric patients (age 8-64 months) with a history of resistant eczema for a period of at least 6 months. All these children received *Lactobacillus rhamnosus* cell lysate daily as an immunobiotic supplement. The results of this open label nonrandomized clinical observation showed a substantial improvement in

quality of life, skin symptoms, and daytime and nighttime irritation scores in children with the supplementation of *Lactobacillus rhamnosus* lysate. *Lactobacillus rhamnosus* cell lysate may thus be used as a safe and effective immunobiotic for the treatment and prevention of childhood eczema.[108] Bifidobacterium breve has been reported by Hattori et al[109] to improve cutaneous symptoms of atopic dermatitis patients. Fifteen children with atopic dermatitis who had Bifidobacterium-deficient microflora were selected for this study. Eight subjects in the Bifidobacteria-administered group were given oral administration of lyophilized *Bifidobacterium breve* M-16 V strain. In the Bifidobacteria-administered group, the proportion of Bifidobacterium in the fecal microflora was increased and the proportion of aerobic bacteria was decreased after 1 month of administration. Furthermore, significant improvement of allergic symptoms (in cutaneous symptom and total allergic scores) was also observed in the Bifidobacteria-administered group. The tendency of allergic symptom improvement was remarkable compared with the control group; however there was no correlation between changes in fecal microflora and allergic symptoms.[109]

The Finnish study of Kalliomäki et al[34] was the first report to describe that the frequency of atopic dermatitis in the probiotic group was half that of the placebo. This hallmark study demonstrated that administration of LGG for 1 month before and 6 months after birth to their infants was associated with a significant reduction in the cumulative incidence of eczema during the first 7 year of life. The effect of probiotics on preventing atopic dermatitis has been demonstrated in infants of Finnish pregnant mothers with a strong family history of eczema, allergic rhinitis, or asthma. The frequency of developing atopic dermatitis in the offspring was significantly reduced by 2, 4, and 7 years, by 50%, 44%, and 36%, respectively. But there were no preventive effects on atopic sensitization and onset of respiratory allergic diseases.[34]

Wickens et al[110] studied a differential effect of 2 probiotics in the prevention of eczema and atopy. Infants receiving *Lactobacillus rhamnosus* had a significantly reduced risk of eczema, compared with placebo, but this was not the case for *Bifidobacterium animalis* subsp *lactis*. In a double-blind, randomized placebo-controlled trial of infants at risk of allergic disease, pregnant women were randomized to take *Lactobacillus rhamnosus*, *Bifidobacterium animalis* subsp *lactis*, or placebo daily from 35 weeks' gestation until 6 months if breastfeeding, and their infants were randomized to receive the same treatment from birth to 2 years (n = 474). Infants receiving *Lactobacillus rhamnosus* had a significantly reduced risk of eczema compared with placebo, but this was not the case for *Bifidobacterium animalis* subsp *lactis*. There was no significant effect of *Lactobacillus rhamnosus* or *Bifidobacterium animalis* subsp *lactis* on atopy. *Lactobacillus rhamnosus* (71.5%) was more likely than *Bifidobacterium animalis* subsp *lactis* (22.6%) to be present in the feces at 3 months, although detection rates were similar by 24 months. The authors found out that supplementation with *Lactobacillus rhamnosus*, but not *Bifidobacterium animalis* subsp *lactis*, substantially reduced the cumulative prevalence of eczema, but not atopy, by 2 years.[110]

In a randomized double-blind study by Marschan et al,[74] probiotic bacteria mix (LGG, *Lactobacillus rhamnosus* LC705, *Bifidobacterium breve*, and Propionibacterium) or placebo were given for 1 month before delivery to mothers and for 6 months to infants with a family history of allergy. Infants receiving probiotic bacteria had higher plasma levels of CRP, total IgA, total IgE, and IL-10 than infants in the placebo group. Increased plasma CRP level at age 6 months was associated with a decreased risk of eczema and with a decreased risk of allergic disease at age 2 years, when adjusted with probiotic use. The association of CRP with a decreased risk of eczema at 2 years of age in allergy-prone children supports the view that chronic, low-grade inflammation protects from eczema. Probiotic-induced low-grade inflammation was characterized by elevation of IgE, IgA, and IL-10, the changes typically observed in helminth infection-associated induction of regulatory mechanisms (please see the section Mechanisms of Probiotics' Effects).[74]

In the PandA study of Niers et al[111] administered a mixture of probiotic bacteria (*Bifidobacterium bifidum*, *Bifidobacterium lactis*, and *Lactobacillus lactis* W58; Ecologic Panda) for 6 week prenatally to mothers of high-risk children and to their offspring for the first 12 months of life. Although cumulative incidence of atopic eczema and IgE levels were similar in both treated and placebo groups, the parental reported eczema was significantly lower during the first 3 months of life in infants receiving probiotics. This particular combination of probiotic bacteria showed a preventive effect on the incidence of eczema in high-risk children, which seems to be sustained during the first 2 years of life. In addition to previous studies, the preventive effect appeared to be established within the first 3 months of life in this study.[111] In a trial by Kim et al,[112] a total of 112 pregnant women with a family history of allergic diseases received a mixture of *Bifidobacterium bifidum*, *Bifidobacterium lactis*, and *Lactobacillus acidophilus*, starting at 4 to 8 weeks before delivery and continuing until 6 months after delivery. The cumulative incidence of eczema during the first 12 months was reduced significantly in probiotic group; however, there was no difference in serum total IgE level or the sensitization against food allergens between the 2 groups. Prenatal and postnatal supplementation with a mixture of probiotics is an effective approach in preventing the development of eczema in infants at high risk of allergy during the first year of life.[112]

In a randomized, double-blind trial by Dotterud et al,[113] probiotics were given to pregnant women in order to prevent allergic disease. In this study, children from a nonselected maternal population, women received probiotic milk or placebo from 36 weeks of gestation to 3 months postnatally during breastfeeding. The probiotic milk contained LGG, *Lactobacillus acidophilus*, and *Bifidobacterium animalis*. At 2 years of age, all children were assessed for atopic sensitization, atopic dermatitis, asthma, and allergic rhinoconjunctivitis. Probiotics given to nonselected mothers reduced the cumulative incidence of atopic dermatitis but had no effect on asthma or atopic sensitization.[113]

Of note, another recently published Swedish study demonstrated that administration of *Lactobacillus casei* during weaning significantly reduced the incidence of eczema, indicating that proper timing of the probiotic intervention is a critical factor. This study also supports the notion that there is more than a single window of opportunity to manage allergic diseases. This study evaluated the effects of feeding with Lactobacillus F19 during the weaning period on the incidence of eczema and Th1/Th2 balance. In this intervention trial by West et al,[54] infants were fed cereals with (n = 89) or without Lactobacillus F19 (n = 90) from 4 to 13 months of age. The cumulative incidence of eczema at 13 months was 11% and 22% in the probiotic and placebo groups, respectively ($P < .05$). The higher Th1/Th2 ratio in the probiotic compared with the placebo group suggests enhancing effects of Lactobacillus F19 on the T cell–mediated immune response. As a result, feeding Lactobacillus F19 during weaning could be an effective tool in the prevention of early manifestation of allergy such as eczema.[54]

In a study by Lodinova-Zadnikova et al,[114] intentional colonization of the intestine in the early postnatal period by oral administration of probiotic *Escherichia coli* after birth was found to decrease the incidence of allergies later in life (after 10 and 20 years).

Gerasimov et al[89] conducted a study to assess the clinical efficacy and impact of *Lactobacillus acidophilus* plus *Bifidobacterium lactis* with fructo-oligosaccharide on peripheral blood lymphocyte subsets in preschool children with moderate-to-severe atopic dermatitis. In a randomized, double-blind, placebo-controlled, prospective trial of 90 children aged 1 to 3 years with moderate-to-severe atopic dermatitis who were treated with a mixture of probiotics for 8 weeks versus placebo. At the final visit, the percentage significant decrease in SCORAD was 34% in the probiotic group compared with 19% in the placebo group. Children receiving probiotic showed a greater decrease in the mean SCORAD score than did children from the placebo group at week 8. The administration of a probiotic mixture and fructo-oligosaccharide was associated with significant clinical improvement in children with atopic dermatitis, with corresponding lymphocyte subset changes in peripheral blood.[89]

In conclusion, here probiotics were more likely to be effective in treating moderately severe atopic dermatitis as well as mild atopic disease. Although not every study result above was significant, the effect of probiotics did not seem to be greater just in the IgE-sensitized group than in the non-IgE-sensitized group. Nevertheless, there have been several reports in the literature showing no effect of probiotics, and these are discussed the following sections.

No therapeutic or preventive effect of probiotics in atopic dermatitis regardless of IgE sensitization. It is striking that the proportion of children with atopic dermatitis and allergic sensitization such as in the study of Huurre et al[115] and Taylor et al[116] was significantly higher in the probiotic group. In the trial by Taylor et al, probiotic supplementation postnatally failed to reduce the risk of atopic dermatitis and increased the risk of allergen sensitization in high-risk children. Newborns of women with allergy (n = 231) received either *Lactobacillus acidophilus* or placebo daily for the first 6 months of life. Children were assessed for atopic dermatitis and other symptoms at 6 and 12 months and had allergen skin prick tests at 12 months of age. At 6 and 12 months, atopic dermatitis rates were similar in the probiotic and placebo groups. At 12 months, the rate of sensitization was significantly higher in the probiotic group. The presence of culturable Lactobacilli or Bifidobacterium in stools in the first month of life was not associated with the risk of subsequent sensitization or disease; however, the presence of Lactobacillus at 6 months of age was associated with increased risk of subsequent cow's milk sensitization. Early probiotic supplementation with *Lactobacillus acidophilus* did not reduce the risk of atopic dermatitis in high-risk infants and was associated with increased allergen sensitization in infants receiving supplements. There were 3 major differences between the study by Taylor et al and those by others. The type of probiotic product (*Lactobacillus acidophilus*), the supplementation period (1 year) as well as the timing of the introduction of the probiotic were different. Taylor et al administered the probiotic supplement postnatally, whereas other studies administered probiotics before and after birth. Prenatal supplementation may prove to be crucial for the preventive benefit of probiotics in this disorder. The data from this study point in the same direction regarding allergic sensitization, suggesting that the use of probiotics for primary prevention must be exercised with caution.[116]

In a double-blind, placebo-controlled multicenter trial by van der Aa et al,[117] 90 infants with atopic dermatitis, age <7 months, were randomized to receive an infant formula with Bifidobacterium breve and a mixture of short chain galacto-oligosaccharides and long-chain fructo-oligosaccharides, or the same formula without synbiotics during 12 weeks. With allergen-specific stimuli, they found a significantly decreased IL-12p40/70 and IL-12p70 production in response to egg allergen and decreased IL-12p70 production in response to peanut allergen in the synbiotic compared with the placebo group. This synbiotic mixture did not have detectable effect on plasma levels of the analysed atopic disease markers, ex vivo cytokine production and circulating Treg cell percentage in infants with atopic dermatitis. They concluded that their results did not support the use of this synbiotic in clinical practice.[117]

Similarly, a randomized, double-blind, placebo-controlled prospective trial by Kopp et al[118] of probiotics for primary prevention did show no clinical effects of LGG supplementation. 105 pregnant women from families with ≥1 member (mother, father, or child) with an atopic disease were randomly assigned to receive either the probiotic LGG or pacebo. The supplementation period started 4 to 6 weeks before expected delivery, followed by a postnatal period of 6 months. The primary end point was the occurrence of atopic dermatitis at the age of 2 years. Secondary outcomes were severity of atopic dermatitis, recurrent episodes of wheezing bronchitis, and allergic sensitization at the age of 2 years. Notably, children with recurrent (≥5) episodes of wheezing bronchitis were more frequent in the

LGG group (26%), as compared with the placebo group (9%). As a result, supplementation with LGG during pregnancy and early infancy neither reduced the incidence of atopic dermatitis nor altered the severity of atopic dermatitis in affected children but was associated with an increased rate of recurrent episodes of wheezing bronchitis.[118] Furthermore, prenatal probiotic LGG treatment during pregnancy was not associated with reduced risk of eczema or IgE-associated eczema in a randomized controlled trial by Boyle et al.[99] The study by Grüber et al[119] also did not show any effect for LGG in infants with atopic dermatitis regardless of their IgE sensitization status.

However, a study from the Netherlands by Brouwer et al and another study from Germany by Fölster-Holst et al[120] showed no effect of LGG in infants with atopic dermatitis regardless of their IgE sensitization status. In a study conducted by Brouwer et al,[69] 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 atopic dermatitis received a hydrolyzed whey-based formula as placebo (n = 17), or supplemented with either *Lactobacillus rhamnosus* (n = 17) or LGG (n = 16) for 3 months. No statistically significant effects of probiotic supplementation on SCORAD, sensitization, inflammatory parameters or cytokine production between groups were found. No clinical or immunological effect of the probiotic bacteria used in infants with atopic dermatitis.[69] A similar prospective study by Fölster-Holst et al[120] was performed to reassess the efficacy of orally administered LGG in infants with atopic dermatitis. In a randomized, double-blind, placebo-controlled study, 54 infants aged 1 to 55 months with moderate-to-severe atopic dermatitis were randomized to receive LGG or to placebo during an 8-week intervention phase. At the end of treatment there were no significant differences between the groups with respect to clinical symptoms (SCORAD, pruritus, and sleep loss), immunological parameters, or health-related quality of life of the parents.[120] Additionally, Soh et al,[121] in a clinical trial involving 253 infants with a family history of allergic disease, used probiotic supplementation (*Bifidobacterium longum* + *Lactobacillus rhamnosus*) in the first 6 months of life in Asian infants at risk and evaluated the effects on eczema and atopic sensitization at the age of 1 year. Early life administration of a cow's milk formula supplemented with probiotics showed no effect on prevention of eczema or allergen sensitization in the first year of life in Asian infants at risk of allergic disease.[121]

In a very recent study by Gore et al,[122] it was investigated whether dietary supplementation of infants with eczema at age 3 to 6 months with *Lactobacillus paracasei* or *Bifidobacterium lactis* had a treatment effect or altered allergic disease progression. A total of 208 infants aged 3 to 6 months with physician-diagnosed eczema were recruited. No difference was observed in SCORAD scores between randomized and observational groups. They found no benefit from supplementation with *Bifidobacterium lactis* or *Lactobacillus paracasei* in the treatment of eczema, when given as an adjunct to basic topical treatment, and no effect on the progression of allergic disease from age 1 to 3 years.[122]

In conclusion, LGG was mostly used probiotic species in these studies. First used by Kalliomäki et al[34] with a success, other groups, including Brouwer et al,[69] Boyle et al,[99] Kopp et al,[118] Grüber et al,[119] and Fölster-Holst et al,[120] however, could not demonstrate any benefit in atopic dermatitis. For instance, Kopp et al have shown that the probiotic LGG has no preventive effect on the development or the severity of atopic dermatitis at the age of 2 years in a German population of infants at high risk. Instead, there was a significantly higher risk of ≥5 episodes with wheezing bronchitis during the first 2 years in the LGG group, as compared with placebo. There were several methodological differences between these studies: Kopp et al adapted the protocol of Kalliomäki et al and continued to supplement LGG for 3 months after birth to the breast-feeding mothers and the following 3 months only to the neonates. This modification was made to achieve a more consistent probiotic delivery. Second, Finnish mothers received supplementation during the last 4 weeks of pregnancy, whereas pregnant women in this population commenced with LGG or placebo for 4 to 6 weeks. They extended the prenatal supplementation period, because a 4-week period is thought to possibly be too short for suspected in utero effects of LGG supplementation. Also, the population in this study by Kopp et al was as higher risk compared with the Finnish population, which might account for the differing results. And more infants with older siblings were recruited compared with the Finnish study. Lastly, the Finnish and German populations are of different genetic background.

Food Allergy and Anaphylaxis

Since food allergies are thought to be central in the pathogenesis of atopic diseases, targeting the enteric mucosa, the primary route of food antigen contact and sensitization, with probiotics might influence crucial mechanisms. There have been also rare published human studies showing that oral administration of Bifidobacterium or Lactobacillus strains could alleviate the food allergy.[105] 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.[33] Studies in infants with eczema who received formulas supplemented with LGG have shown benefit in decreasing gastrointestinal symptoms too.[123] However, because of scarcity of clinical and experimental data in the literature, even allergen nonspecific therapies including Chinese herbal therapy, anti-IgE, probiotics, engineered lactic acid bacteria, and helminth therapy have been investigated in recent years.[124,125]

Oral therapy with the probiotic mixture VSL#3 and *Lactobacillus casei* strain Shirota (LcS) were able to reduce anaphylactic symptoms in a food allergy model.[126,127] The therapeutic potential of VSL#3 probiotic mixture on specific immune responses and anaphylactic reaction induced in mice by the major food allergen shrimp tropomyosin was investigated. Oral therapeutic administration of VSL#3 to shrimp tropomyosin-sensitized mice significantly reduces symptom

score and histamine release in the feces following allergen challenge, as well as specific IgE response. Oral therapeutic treatment with the probiotic mixture VSL#3 is effective in redirecting allergen-specific Th2-polarized immune responses toward Th1-Treg responses and in the protection against anaphylactic reactions induced by the allergen in a murine model of food allergy.[128] In another study, *Lactobacillus acidophilus* and *Bifidobacterium lactis* treatments prevented OVA-induced allergic symptoms on the skin and gastrointestinal tract, for example, eosinophilic infiltration.[55] Additionally, *Lactobacillus lactis* decreased subsequent frequency of food allergy symptoms thru reducing Th2 type immune response in neonatal pigs as well as in mice. LL NCC 2287 significantly decreased relative expression levels of the Th2 cytokines; and associated chemokines eotaxin-1 and CCL17 (TARC) in the mice ileum.[129] In a study; newborn pigs pretreated orally with *Lactobacillus lactis* were hypothesized as protected against allergy to ovomucoid. Pigs were assigned to 2 treatment groups. Piglets were pretreated orally on days of age 1 to 7, 10, 12, 14, 21, 28, and 35 with *Lactobacillus lactis* (n = 30) or medium (control, n = 32) and sensitized to ovomucoid by intraperitoneal injection. Pigs were orally challenged with egg white later and assigned scores for allergic signs. Clinical signs and skin test positivity were significantly less frequent in the *Lactobacillus lactis* group. Oral treatment of neonatal pigs with *Lactobacillus lactis* significantly reduced subsequent frequency of allergy to ovomucoid associated with reduced type-2 immune response correlates hence supporting the "hygiene hypothesis" and potential use of *Lactobacillus lactis* as a neonatal immunoregulator.[130]

These early results indicated that some probiotic strains of bacteria, such as LGG or Lactobacillus F19, might reduce allergic sensitization. As expected, several clinical studies reporting significant benefits by probiotics supplementation in food allergy prevention and management but not everyone agree on their effectiveness. Consistently, supplementation of *Lactobacillus casei* and Bifidobacterium Bb-12 to extensively hydrolyzed formula did not accelerate cow's milk tolerance in infants with cow's milk allergy.[131] Similarly, LGG and *Bifidobacterium animalis* MB5 was demonstrated by Finamore et al to induce intestinal but not systemic antigen-specific hyporesponsiveness in OVA-immunized rats.[132] LcS was also shown not to decrease allergic response to peanut extract in Brown Norway rats in a study by de Jonge et al.[133] Moreover, a few randomized controlled trials also showed no effects of probiotics, specifically LGG or *Lactobacillus acidophilus*, in protection against cow's milk allergy in infancy.[97,105,117,121] Osborn and Sinn[134] reviewed 6 studies enrolling 1549 infants and reported no other benefits of probiotics for food hypersensitivity as well.

Allergic Rhinitis

Perennial allergic rhinitis. Previous studies can suggested that probiotic administration can have therapeutic and/or preventive effects on atopic dermatitis in infants; however, its role in allergic airway diseases remains controversial. Probiotic treatment in patients with perennial allergic rhinitis and seasonal allergic rhinitis showed clinical improvement in most of the earlier published studies.[135,136] 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.[126]

The aim of a study by Peng and Hsu[137] was to evaluate the efficacy of heat-killed *Lactobacillus paracasei* (LP33) in the treatment of perennial allergic rhinitis induced by house dust mite in 90 human subjects. The results suggest that heat-killed LP33 can effectively improve the overall quality of life for patients with allergic rhinitis and that it may be efficacious as an alternative treatment.[137] In a study, 12-month consumption of fermented milk containing *Lactobacillus casei* improved the health status of children with allergic rhinitis. To examine whether long-term consumption of fermented milk containing a specific *Lactobacillus casei* may improve the health status of preschool children suffering from allergic rhinitis a randomized, prospective, double-blind, controlled trial by Giovannini et al[138] was conducted in 187 children 2 to 5 years old. The children received for 12 months either fermented milk containing *Lactobacillus casei* or placebo. Long-term consumption of fermented milk containing *Lactobacillus casei* was demonstrated to improve the health status of children with allergic rhinitis.[138] The fermented milk prepared with *Lactobacillus gasseri* TMC0356 was administered at 200 mL per day for 4 weeks to 15 subjects with high serum IgE levels and perennial allergic rhinitis. The serum total IgE concentration was significantly reduced after 28 days' exposure to the fermented milk compared with that before the intervention. The serum IgE specific to Acari and those to Japanese cedar pollen also significantly declined. Th1 cells in the composition of their peripheral blood mononuclear cells significantly increased after 14 and 28 days. These results of this study by Morita et al[139] suggest that the fermented milk prepared with *Lactobacillus gasseri* may alter serum IgE concentration, at least partly by enhancement of Th1 immune responses of the subjects with high concentration of serum IgE. Another randomized, double-blind, placebo-controlled study was conducted by Chen et al[140] on schoolchildren (age = 6-12 years) with allergic rhinitis. The aim in this study was to determine whether daily supplementation with specific *Lactobacillus gasseri* A5 for 8 weeks can improve the clinical symptoms and immunoregulatory changes in children having allergic rhinitis. The study results showed the clinical symptom scores for allergic rhinitis decreased in the probiotic-treated patients as compared to the controls. Furthermore, there was a significant reduction in the TNF-α, IFN-γ, IL-12, and IL-13 production by the peripheral blood mononuclear cells following the probiotic treatment. The researchers concluded that probiotic supplementation may have clinical benefits for schoolchildren suffering from allergic airway diseases such as allergic rhinitis.[140]

The results of a study by Wang et al[141] suggest that ingestion of *Lactobacillus paracasei*-33-fortified fermented milk for 30

days can effectively and safely improve the quality of life of patients with perennial allergic rhinitis, and can possibly serve as an alternative treatment for allergic rhinitis. A halophilic lactic acid bacteria, *Tetragenococcus halophilus* Th221, from soy sauce Moromi, a mixture of Koji and salt solution, and showed that it possesses an immunomodulatory activity that promotes Th1 immunity. To evaluate the antiallergic effects of Th221, a randomized, double-blind, placebo-controlled study was performed by Nishimura et al[142] in 45 subjects with perennial allergic rhinitis treated by oral administration of Th221 or a placebo (15 subjects) for 8 weeks. According to the subjects' diaries, significant improvements in sneezing and rhinorrhea were observed during some periods in the high-dose group. The change in serum total IgE improved significantly at the end of the trial compared with the beginning in this group. Th221 was thought to be expected to safely improve the symptoms of perennial allergic rhinitis.[142]

The majority of the randomized controlled trials showed a reduction in symptom severity and decreased use of relief medications.[137,138] In addition, a meta-analysis by Vliagoftis[135] concluded that all the trials studied in children showed improvement in clinical outcomes. A recent review by Nogueira and Gonçalves Mda[143] showed that probiotics, Lactobacillus and Bifidobacterium appear to prevent allergy recurrences, alleviate the severity of symptoms and improve the quality of life of patients with allergic rhinitis. However, a meta-analysis evaluating 6 relevant studies also reported no other benefits of probiotic use for any allergic disease.[134]

Seasonal allergic rhinitis. PubMed was searched by Vliagoftis et al[135] to identify randomized controlled trials that studied the effects of probiotics on allergic rhinitis (n = 12). Randomized controlled trials that studied the effects of probiotics administration on the treatment but not the prevention of allergic rhinitis were selected for inclusion in this review. Nine of the 12 randomized controlled trials that evaluated clinical outcomes in allergic rhinitis showed an improvement due to the use of probiotics. All the randomized controlled trials that studied perennial allergic rhinitis showed lower symptom scoring and medication use with the use of probiotics compared with placebo. Also, 5 of the 8 randomized controlled trials that referred to seasonal allergic rhinitis suggested an improvement in clinical outcomes. Probiotics may have a beneficial effect in allergic rhinitis by reducing symptom severity and medication use.[135]

The study by Ivory et al[144] was double-blinded, placebo-controlled with 10 seasonal allergic rhinitis sufferers in each group. Volunteers treated with LcS showed a significant reduction in levels of antigen-induced IL-5, IL-6, and IFN-γ production compared with volunteers supplemented with placebo. Meanwhile, levels of specific IgG increased and IgE decreased in the probiotic group. These data show that probiotic supplementation modulates immune responses in seasonal allergic rhinitis and may have the potential to alleviate the severity of symptoms.[144] Randomized, placebo-controlled, double-blind studies of *Lactobacillus plantarum* No. 14 (LP14) in female students with seasonal allergic rhinitis were conducted. For subjects who took LP14, a significant improvement in symptom-medication score was observed.[145]

A double-blind, placebo-controlled study was conducted by Kawase et al[146] to examine the effectiveness of LGG and Lactobacillus gasseri TMC0356 in alleviating Japanese cedar pollinosis, a seasonal allergic rhinitis caused by Japanese cedar pollen. Fermented milk prepared with the tested bacteria or placebo yogurt was administered to 40 subjects with a clinical history of Japanese cedar pollinosis for 10 weeks. Consumption of milk significantly decreased the mean symptom score for nasal blockage after 9 weeks and mean symptom-medication scores after 9 and 10 weeks when compared with the placebo group. The fermented milk prepared with LGG and *Lactobacillus gasseri* was beneficial in Japanese cedar pollinosis because of its effect on nasal blockage.[146]

Intake of *Bifidobacterium longum* supplemented yogurt also relieved Japanese cedar pollinosis symptoms.[147,148] A study investigated the effects of probiotic strain *Bifidobacterium longum* BB536 in the treatment of Japanese cedar pollinosis. In this randomized, double-blind, placebo-controlled trial by Xiao et al,[147] a total of 44 Japanese cedar pollinosis subjects received BB536 or placebo for 13 weeks during the pollen season. Comparison of subjective symptom scores indicated significant decreases in rhinorrhea, nasal blockage, and composite scores in the BB536 group compared with the placebo group. BB536 tended to suppress the decreasing blood levels of IFN-γ and the increasing blood eosinophil rates; a significantly higher IFN-γ level was observed. BB536 tended to suppress elevations of Japanese cedar pollen–specific IgE. These results suggest the efficacy of BB536 in relieving Japanese cedar pollinosis and eye symptoms, probably through the modulation of Th2-skewed immune response.[147]

In addition; the effects of daily intake of *Lactobacillus paracasei* strain KW3110 in patients with Japanese cedar pollinosis were investigated by Yonekura et al[149] in 126 patients who received strain KW3110 or a placebo in a double-blind study. The study began 1 month before the start of the pollen season and lasted for 3 months. A significant reduction of nasal symptoms and the serum level of eosinophil cationic protein and improvement of quality-of-life scores occurred in the patients who received KW3110 when pollen scattering was low. However, the effects were limited during the peak period of pollen scattering. Intake of KW3110 may reduce allergic inflammation, but the effect is limited.[149] Similarly; a mixture with *Lactobacillus rhamnosus* GR-1 and *Bifidobacterium adolescentis* was formulated into a yogurt and tested for its effects in 36 subjects with seasonal allergic rhinitis over 2 pollen seasons in a double-blind, placebo-controlled trial by Koyama et al.[150] However, at the end of the grass pollen season, serum IL-10 and IL-12 levels were increased in the probiotic group compared to the controls. During the ragweed season, the serum TGF-β levels were significantly higher in the probiotic group than in the controls. The novel probiotic formulation had potentially desirable effects on the cytokine profile of patients with seasonal allergic rhinitis, but provided few clinical benefits.[150]

Furthermore; one study suggests that fermented milk containing LcS does not prevent allergic symptoms in patients sensitive to Japanese cedar pollen, although the addition of the strain may delay the occurrence of allergic symptoms in patients with moderate-to-severe nasal symptom.[151]

Allergic rhinoconjunctivitis. Two randomized, placebo-controlled, double-blind studies of *Lactobacillus plantarum* No. 14 (LP14) in female students with seasonal allergic rhinitis were conducted by Nagata et al.[145] For subjects who took LP14, a significant improvement in ocular symptom-medication score was observed.[145] Another study investigated the effects of probiotic strain *Bifidobacterium longum* BB536 in the treatment of Japanese cedar pollinosis. In this randomized, double-blind, placebo-controlled trial by Xiao et al,[147] 44 Japanese cedar pollinosis subjects received BB536 or placebo for 13 weeks during the pollen season. Comparison of subjective symptom scores indicated significant decreases in composite scores in the BB536 group compared with the placebo group. BB536 tended to suppress elevations of Japanese cedar pollen–specific IgE. These results suggested the efficacy of BB536 in relieving Japanese cedar pollinosis and eye symptoms, probably through the modulation of Th2-skewed immune response.[147] However, 47 children with birch pollen allergy were randomized by Ouwehand et al[152] in a study to receive either a probiotic combination of *Lactobacillus acidophilus* NCFM and *Bifidobacterium lactis* or placebo in a double-blind manner for 4 months, starting prior to onset of the birch pollen season. Fewer subjects in the probiotic group reported runny nose, nasal blocking and had infiltration of eosinophils in the nasal mucosa compared to the placebo group. Although eye symptoms tended to be slightly more frequent in the probiotic group during May, this study indicated a trend for reduced nasal symptoms.[152]

Asthma

Perinatal programming, a dominant theory for the origins of some diseases such as cardiovascular disease, proposes that environmental stimuli influence developmental pathways during critical periods of prenatal and postnatal development, inducing permanent changes in metabolism. In a recent article, evidence for the perinatal programming of asthma via the intestinal microbiome was presented. While epigenetic mechanisms continue to provide new explanations for the programming hypothesis of asthma development, it is increasingly apparent that the intestinal microbiota plays an independent and potentially interactive role.[153] Some researchers also demonstrated 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. 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.[154] 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.[155] 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.[53] Co-application of *Lactobacillus lactis* and *Lactobacillus plantarum* with the major birch pollen allergen (Bet v1) caused suppression of allergen-induced basophil degranulation.[156] Oral administration with *Lactobacillus gasseri* attenuated major characteristics of allergen-induced airway inflammation and IL-17 pro-inflammatory immune response in a mouse model of allergic asthma, which may have clinical implication in the preventive or therapeutic potential in allergic asthma.[157] Zhang et al[158] conclude that the oral administration of *Enterococcus faecalis* FK-23 suppresses the asthmatic response and that this is associated with attenuation of Th17 cell development. An interesting systematic study was performed by Aumeunier et al[96] on the disease-modifying effects of a set of natural or synthetic TLR agonists using 2 experimental models, OVA-induced asthma and spontaneous autoimmune type 1 diabetes, presenting the same genetic background of the non-obese diabetes mouse that is highly susceptible to both pathologies. In these same models, the effect of probiotics was also investigated. Probiotics which stimulate TLRs also protect from these two diseases. Multiple TLR agonists prevent from both allergy and autoimmunity when administered parenterally was demonstrated. These results indicated that the TLR-mediated effects involve immunoregulatory cytokines such as IL-10/TGF-β and different subsets of Treg cells, notably CD4+/CD25+/FoxP3+ cells for TLR-4 agonists and NKT cells for TLR-3 agonists. These observations demonstrated that systemic administration of TLR ligands can suppress both allergic and autoimmune responses.[96] Finally, oral administration of live Lactobacillus 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.[95,159]

In a study by Lue et al,[160] the aim was to compare the clinical efficacy of levocetirizine with that of levocetirizine plus *Lactobacillus johnsonii* EM1 for treating perennial allergic rhinitis in children. Sixty-three children aged 7 to 12 years fulfilled the entry criteria for the study and had moderate to severe perennial allergic rhinitis of at least 1year's duration. The effects of the 2 regimens were compared using the Pediatric Rhinoconjunctivitis Quality of Life Questionnaire and the total symptom score from diary cards. After the first 4 months of treatment, total symptom score in both groups had improved progressively. Forced vital capacity and forced expiratory volume in 1 second were improved significantly in both groups at weeks 8 through 24, but there was no significant difference between the 2 groups.[160] A recent study in asthmatic children showed that the interactive treatment by acupuncture and probiotics has a beneficial clinical effect on bronchial hyperreactivity and it might be helpful in the prevention of

acute respiratory exacerbations.[161] Similarly; a randomized, double-blind, placebo-controlled study was conducted by Chen et al[140] on schoolchildren (age = 6-12 years) with asthma. The aim in this study was to determine whether daily supplementation with specific *Lactobacillus gasseri* A5 for 8 weeks can improve the clinical symptoms and immunoregulatory changes in children having asthma. The study results showed the pulmonary function and peak expiratory flow rate increased significantly, and the clinical symptom scores for asthma decreased in the probiotic-treated patients as compared with the controls. Probiotic supplementation seemed to have clinical benefits for schoolchildren suffering from allergic airway diseases such as asthma.[140] Consistently, to examine whether long-term consumption of fermented milk containing a specific *Lactobacillus casei* may improve the health status of preschool children suffering from allergic asthma a randomized, prospective, double-blind, controlled trial by Giovannini et al[138] was conducted in 187 children 2 to 5 years of age. The children received for 12 months either fermented milk containing *Lactobacillus casei*. Long-term consumption of fermented milk containing *Lactobacillus casei* did not have any effect in asthmatic children.[138] In a study allergy in marathon runners and effect of LGG supplementation on allergic inflammatory markers was investigated by Moreira et al.[162] A total of 141 Finnish marathon runners were also randomized to receive either LGG or placebo during the 3 months of the pollen season prior to the marathon. LGG supplementation did not prevent the increase of allergic markers, for example, serum eosinophilic cationic protein or total IgE during the pollen season, or the eosinopenia induced by the marathon.[162] A prospective double-blind study by Rose et al[163] randomly assigned 131 children (age = 6-24 months) with at least 2 wheezing episodes and a first-degree family history of atopic disease to 6 months of *Lactobacillus rhamnosus* or placebo. Fewer sensitizations were found toward aeroallergens after 6 months of LGG and after 6 months of follow-up. In young children with recurrent wheeze and an atopic family history, oral LGG had no clinical effect on atopic dermatitis or asthma-related events, and only mild effects on allergic sensitization.[163] A study by Kukkonen et al[164] aimed at studying the effect of probiotic treatment during the first 6 months of life on airway inflammation at the age of 5 years. In a randomized double-blind allergy prevention trial between 2000 and 2007 in Helsinki, Finland, they gave a probiotic combination, plus prebiotics, or placebo, to 1018 children during 6 months from birth. Early intervention with probiotics and prebiotics did not affect airway inflammation even later in childhood.[164] Correspondingly, in another study, adolescents suffering from pollen allergy did not benefit from LGG administration.[165]

Furthermore, Osborn and Sinn[134] reviewed 6 studies and reported no other benefits for any other allergic disease. PubMed was searched by Vliagoftis et al[135] to identify randomized controlled trials that studied the effects of probiotics on asthma (n = 4). Randomized controlled trials that studied the effects of probiotics administration on the treatment but not the prevention of asthma were selected for inclusion in this review. The randomized controlled trials that studied the effect of probiotic administration on the treatment of asthma showed no positive effects. This 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 cannot be reached, although some positive experimental evidence from animal studies suggest the need for further investigation.[135]

The Role of Probiotics in the Prevention and Treatment of Autoimmune Diseases

In this part of the article, the role of probiotics in the prevention and treatment of mainly 4 autoimmune diseases, including rheumatoid/spondylo-arthritis, type 1 diabetes, multiple sclerosis, and inflammatory bowel disease are discussed in light of recent literature. The various effects of different probiotic strains in autoimmune diseases from crucial clinical trials referred in the text are shown in Table 3.

Probiotic Effect in Clinical Rheumatoid Arthritis and Spondyloarthritis Trials

A pilot double-blind clinical study evaluated the long-term effects of LGG on symptoms of rheumatoid arthritis. Twenty-one patients with rheumatoid arthritis were randomized to receive 2 capsules of LGG or placebo twice daily for 12 months. Rheumatoid arthritis activity was reduced in 71% of patients in the LGG group versus 30% of patients in the placebo group. Although there were no statistical differences in clinical or biochemical parameters, more patients in the LGG group reported a greater feeling of well-being.[166] Furthermore, the effects of an orally administered probiotic LGG on sulfasalazine metabolism in individuals with rheumatoid arthritis were studied in a preliminary study. Even though there were also no statistical significant differences in the activity of rheumatoid arthritis, more subjects in the LGG group reported subjective well-being.[167]

In another pilot study, patients with rheumatoid arthritis who received *Bacillus coagulans* experienced significant improvement in the pain, greater improvement in patient global assessment, patient self-assessed disability, and reduction in total CRP. This randomized, double-blind, placebo-controlled, parallel-design, clinical pilot trial was conducted by Mandel et al[168] to evaluate the effects of the lactic acid bacteria probiotic preparation, *Bacillus coagulans* GBI-30, 6086, on symptoms and measures of functional capacity in patients with rheumatoid arthritis in combination with pharmacological anti-arthritic medications. Forty-five adult men and women with symptoms of rheumatoid arthritis were randomly assigned to receive *Bacillus coagulans* or placebo once a day in a double-blind fashion for 60 days in addition to their standard antiarthritic medications. Compared with placebo, *Bacillus coagulans* treatment resulted in greater improvement in patient global assessment and self-assessed disability; reduction in CRP; as well as the ability to walk 2 miles, reach, and participate in daily activities. Results of this pilot study suggest

Table 3. Probiotic Effects in Essential Clinical Autoimmune Disease Trials.

Reference	Disease	Probiotics	Assessment	Outcome
		Human clinical arthritis trials		
Hatakka et al[166]	RA	LGG	Clinical–biochemical parameters, disease activity/well-being	↔ / ↑
Lee et al[167]	RA	LGG	Disease activity/well-being	↔ / ↑
Mandel et al[168]	RA	Bacillus coagulans	Inflammation, disease activity	↓
Pineda et al[169]	RA	Lctbs rhamnosus + Lctbs reuteri	Clinical–biochemical parameters (ACR20)/functional improvement	↔ / ↑
Garrett et al[170]	Spondyloarthritis	Probiotic	Disease activity	↔
Jenks et al[171]	Spondyloarthritis	Probiotic	Disease activity	↔
		Human clinical autoimmune (T1 diabetes) trials		
Ljungberg et al[15]	IDDM	Probiotic	T1 diabetes-associated autoantibodies	↔
Rozanova et al[174]	IDDM	Probiotic	Severity of T1 diabetes	↓
		Human clinical inflammatory bowel disease trials		
Ulcerative colitis				
Bibiloni et al[177]	Active UC	VSL3#	Disease activity	↓
Rembacken et al[179]	Active UC	*Escherichia coli* Nissle 1917	Inflammation, disease activity/induction of remission	↓ / ↑
Matthes et al[180]	Active UC	*Escherichia coli* Nissle 1917	Inflammation, disease activity/induction of remission	↓ / ↑
Kato et al[181]	Active UC	BbY + Lctbs acidophillus	Disease activity	↓
Ishikawa et al[182]	Active UC	Bfdbm	Disease activity	↓
Venturi et al[183]	UC maintenance	VSL3#	Relapse	↓
Ishikawa et al[182]	UC maintenance	Bfdbm breve, Bfdbm bifidum, Lctbs acidophilus	Disease exacerbations	↓
Zocco et al[184]	UC maintenance	LGG	Disease activity	↔
Naidoo et al[185]	UC maintenance	Various	Remission	↔
Crohn's disease				
Malchow et al[186]	Active CD	*Escherichia coli* Nissle 1917	Inducing remission	↔
Schultz et al[187]	Active CD	LGG	Inducing remission	↔
Guslandi et al[188]	CD maintenance	*Saccharomyces boulardii*	Maintenance of remission	↑
Bousvaros et al[189]	CD maintenance	LGG	Maintenance of remission	↔
Prantera et al[190]	CD maintenance	LGG	Maintenance of surgically induced remission	↔
Van Gossum et al[191]	CD maintenance	Lctbs johnsonii LA1	Maintenance of surgically induced remission	↑
Marteau et al[192]	CD maintenance	Lctbs johnsonii LA1	Maintenance of surgically induced remission	↔
Campieri et al[193]	CD maintenance	VSL#3	Maintaining surgically induced remission	↑
		Human clinical multiple sclerosis trials		
Kidd et al[175]	Multiple Sclerosis	Various	Dysbiosis and disease activity	↓
Fleming et al[176]	Multiple sclerosis	Trichuris suis	Exploratory magnetic resonance imaging, immunological assessments and disease activity	↓

Abbreviations: Bfdbm, Bifidobacterium; Lctbs, Lactobacillus; BbY, Bfdbm breve strain Yakult; LGG, Lactobacillus GG; VSL#3, a mixture of 4 species of lactobacilli, 3 species of bifidobacteria, and *Streptococcus thermophilus*; CD, Crohn's disease; UC, ulcerative colitis; RA, rheumatoid arthritis; IDDM, T1 diabetes, insulin-dependent (autoimmune) diabetes mellitus; ↓, decreased in severity of disease; ↑, increased in severity of disease; ↔, no effect on severity of disease.

that adjunctive treatment with *Bacillus coagulans* appeared to be a safe and effective for patients suffering from rheumatoid arthritis.[168] A 3-month double-blind, placebo-controlled study was performed by Pineda et al[169] using probiotic *Lactobacillus rhamnosus* GR-1 and *Lactobacillus reuteri* RC-14 capsules administered orally in 29 patients with rheumatoid arthritis. Inclusion criteria required at least 4 swollen and 4 tender joints and stable medications with no steroids for at least 1 month prior to and during the study. Fifteen patients were randomized to the probiotic group and 14 to the placebo group. Three subjects in the probiotic (20%) and one in the placebo group (7%) achieved an American College of Rheumatology 20 (ACR20) response ($P = .33$). There was no statistically significant difference between individual components of the ACR20 criteria. There was a significant improvement in the Health Assessment Questionnaire score in the probiotic group from visit 1 to visit 3, but no between-group differences. Although probiotics did not clinically improve rheumatoid arthritis as measured by the ACR20, it is interesting that there was functional improvement seen within the probiotic group compared to placebo.[169]

Nonetheless, in another randomized controlled trial, 63 patients with active spondyloarthritis (enteropathic peripheral arthropathies) were randomized to oral probiotic (n = 32) or placebo (n = 31) for 12 weeks. No significant difference was noted between groups in any of the core domains (pain, spinal mobility, patient global, peripheral joint and entheseal scores, stiffness, CRP, and fatigue).[170] Similarly, in a randomized controlled trial by Jenks et al,[171] the probiotic combination administered did not demonstrate significant benefit over placebo, despite a theoretical rationale for this therapy.

Probiotic Effect in Human Clinical Type 1 (Autoimmune) Diabetes Mellitus Trials

The feature of immune-mediated type 1 diabetes mellitus is T cell–mediated destruction of the insulin-producing β-cell in the islets, which results from an imbalance between disease promoting factors and protective elements. The particular mechanisms of β-cell destruction leading to diabetes remain still unclear.[172] However, the interest and scope for research in the field of probiotics has significantly widened in recent years. In a recent study, the aim was to assess the feasibility of a dietary intervention trial with weaning to casein hydrolyzed formula in infants at increased risk of type 1 diabetes mellitus and to study the effect of the intervention on the emergence of type 1 diabetes mellitus-associated autoantibodies in early childhood. The cumulative incidence of autoantibodies was somewhat smaller in the casein hydrolyzed versus the control formula group. This study provided the first evidence ever in man, despite its limited power, that it might be possible to manipulate spontaneous β-cell autoimmunity by dietary intervention in infancy.[173]

After this dietary interventional experience, another dietary manipulative pilot study of PRODIA (probiotics for the prevention of β-cell autoimmunity in children at genetic risk of type 1 diabetes mellitus) was performed and it included 200 children with genetic risk for type 1 diabetes mellitus. This study was planned to show whether the use of probiotics during the first 6 months of life is safe and feasible and to determine whether the use of probiotics during the first 6 months of life decreases the appearance of type 1 diabetes mellitus–associated autoantibodies. However, the prevalence of autoantibodies among the study subjects at 6, 12, and 24 months of age was at levels close to the expected and the clinical follow-up did not either indicate problems in the feasibility of the study.[15]

A recent article by Rozanova et al[174] also draws attention to a case illustrating an association between the severity of type 1 diabetes mellitus and disorder in the intestinal microbiocenosis (microflora). The authors thought that clinical signs of disbacteriosis are mostly manifested by disturbances in the metabolic processes. Clinical effectiveness of probioticotherapy in the complex treatment of the disease was shown in this study.[174]

Probiotic Effect in Human Clinical Multiple Sclerosis Trials

Much of the epidemiological data in multiple sclerosis is consistent with a role for diet in its initiation, exacerbations, or progression. Some of the dietary factors contributing to the worsening of multiple sclerosis include a high animal-fat diet; food allergies/intolerances; and digestive malfunctions, including malabsorption and dysbiosis. Gut malabsorption and dysbiosis can be corrected using probiotics. Although there is no known clinical data on the use of probiotics in multiple sclerosis patients, probiotics might have an indirect effect in multiple sclerosis thru correcting dysbiosis.[175]

Probiotic treatment strategy based on the hygiene hypothesis, such as administration of ova from the nonpathogenic helminth, *Trichuris suis* (TSO), has recently proven safe and effective in inflammatory bowel disease. To study the safety and effects of TSO in a different autoimmune disease, multiple sclerosis, the phase 1 "helminth-induced immunomodulatory therapy" study was conducted by Fleming et al.[176] Five subjects with newly diagnosed, treatment-naive relapsing–remitting multiple sclerosis were given 2500 TSO orally every 2 weeks for 3 months in a baseline versus treatment control exploratory trial. The mean number of new gadolinium-enhancing magnetic resonance imaging lesions (n-Gd+) fell from 6.6 at baseline to 2.0 at the end of TSO administration, and 2 months after TSO was discontinued, the mean number of n-Gd+ rose to 5.8. In preliminary immunological investigations, increases in the serum level of the cytokines IL-4 and IL-10 were noted in 4 of the 5 subjects. TSO was well tolerated in the first human study of this novel probiotic in multiple sclerosis, and favorable trends were observed in exploratory magnetic resonance imaging and immunological assessments.[176]

Probiotic Effect in Human Clinical Inflammatory Bowel Disease Trials

Studies on the use of probiotics in the treatment of noninfectious inflammatory bowel disease found that 4 strains of Lactobacillus and 1 strain of Streptococcus were effective in maintaining remission of ulcerative colitis and reducing the postoperative recurrence of Crohn's disease. In the randomized controlled trials, 12 of 16 ulcerative colitis but only 2 of Crohn's disease trials of probiotic therapy were successful. No superiority of any probiotic was clearly evident, but a multiagent mixture, VSL3# may be better suited in ulcerative colitis.[177] Studies of probiotics, for example, LGG in Crohn's disease, have been disappointing, and a recent Cochrane systematic review has concluded that their use could not be recommended on the available evidence.[178]

Ulcerative Colitis

Probiotics to treat active ulcerative colitis. In a study comparing the effect of probiotic *Escherichia coli* Nissle 1917 versus mesalamine on induction of remission in ulcerative colitis, both groups had similar time to remission, demonstrating equal

efficacy of treatments. Consistently, several controlled trials have demonstrated that *Escherichia coli* Nissle 1917 has similar efficacy to conventional mesalazine treatment with fewer side effects.[179] Efficacy of direct delivery of the probiotic to the colon with *Escherichia coli* Nissle 1917 enemas in left-sided ulcerative colitis has been demonstrated.[180]

In an open-label trial, VSL#3 was added to current regimen for patients who had failed to respond to conventional therapy for active ulcerative colitis. Addition of VSL#3 for 6 weeks led to either remission or response in 77% of patients as measured by the disease activity index.[177]

Active ulcerative colitis was treated successfully with fermented milk including BbY (*Bifidobacterium bifidum* strain Yakult) and a *Lactobacillus acidophillus* strain.[181] A recent clinical trial demonstrated that treatment of patients with Bifidobacterium fermented milk compared with placebo leads to a significant decrease in a clinical activity index score and a significant decrease in endoscopic and histological scores after 12 weeks of treatment.[182]

Probiotics as maintenance therapy in ulcerative colitis. Treatment with VSL#3 to maintain remission in ulcerative colitis was found to be only 4 of 20 patients had experienced relapse at the end of the study.[183] Several studies examining the use of lactobacilli or bifidobacteria as maintenance treatment in ulcerative colitis have demonstrated conflicting results. Ishikawa et al[182] have demonstrated a reduction in the number of disease exacerbations in a group of Japanese patients receiving fermented milk containing *Bifidobacterium breve*, *Bifidobacterium bifidum*, and *Lactobacillus acidophilus* compared with placebo. However, this clinical benefit was not found to be associated with an increase in steroid-free remission or endoscopic improvement in disease activity.[182] Another open-label trial showed that for maintenance of remission in ulcerative colitis that LGG alone, or in combination with mesalamine, demonstrated equal efficacy to mesalamine alone.[184]

In a Cochrane review by Naidoo et al,[185] the primary objectives were to determine the efficacy and safety of probiotics for the maintenance of remission in ulcerative colitis. Four studies (n = 587) met the inclusion criteria and were included in the review. Three trials compared probiotics with mesalazine and one trial compared probiotics with placebo. The studies ranged in length from 3 to 12 months. There was no statistically significant difference between probiotics and mesalazine for maintenance of remission in ulcerative colitis. Relapse was reported in 40% of patients in the probiotics group compared to 34% of patients in the mesalazine group. A small placebo-controlled trial (n = 32) found no statistically significant difference in efficacy. Seventy-five percent of probiotic patients relapsed at 1 year compared with 92% of placebo patients. Given the relatively small number of patients in the pooled analysis, the small number of events and the high risk and unclear risk of bias in the included studies, there is insufficient evidence to make conclusions about the efficacy of probiotics for maintenance of remission in ulcerative colitis.[185]

Crohn's Disease

Probiotics to treat active Crohn's disease. Previous 2 studies with *Escherichia coli* Nissle 1917 and LGG had evaluated probiotics in active Crohn's disease patients, but neither study has demonstrated convincing efficacy, in part because of small numbers of patients.[186] A recent double-blinded placebo-controlled trial randomized 11 patients with active Crohn's disease to receive either LGG or placebo. There was no difference in the rate of inducing remission for 6 months between the 2 groups.[178,187]

Probiotics to maintain remission in Crohn's disease. Evidence for use of probiotics as maintenance therapy in Crohn's disease is not persuasive, with only a couple of studies reporting positive results. A study comparing *Saccharomyces boulardii* + antibiotic + mesalazine with mesalazine alone has shown fewer relapses in the former group in patients with medically induced remission of Crohn's disease.[188] Another randomized, double-blind study compared LGG versus placebo in addition to standard maintenance therapy in a group of 75 children. These studies did not find any advantage for LGG compared with placebo in maintaining medically induced remission.[189]

Several clinical studies have been performed to analyze the effects of probiotics on maintaining surgically induced remission. Three studies using LGG have not confirmed the effectiveness of this probiotic as a maintenance strategy after surgically induced remission.[190] Another clinical trial using treatment with LGG after surgical resection failed to show prevention of early endoscopic recurrence when compared with placebo. One study suggested modest but not significant improvement in recurrence rates of patients after surgical resection of diseased bowel by *Lactobacillus johnsonii* LA1.[191] However, 2 randomized double-blind placebo-controlled studies have reported no effect of *Lactobacillus johnsonii* LA1 in preventing recurrence of Crohn's disease patients in surgically induced remission.[192] Finally, Campieri et al[193] have shown benefit of VSL#3 in preventing postoperative recurrence in 40 patients randomized to 3 months of rifaximin followed by 9 months of VSL#3 or to 12 months of mesalazine.

Conclusion

As mentioned above, there is a large amount of conflicting data on the preventive/therapeutic effects of probiotics in atopic and autoimmune 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. There are also difficulties of recognizing etiology and pathogenesis of both conditions from atopic dermatitis to inflammatory bowel disease in which have many mechanisms involved. Similarly, with various strains, especially LcS, stimulation of Th1-mediated immune responses has been described as an unwanted effect. Additionally, if probiotics are used in patients with atopic or autoimmune diseases for any reason—therapy or

prevention—cautionary approach ought to be taken.[13] Any probiotic should not be used especially in immune-compromised children. Thus, probiotics cannot be recommended generally for primary prevention of these diseases. Following the guidelines in the literature, Bifidobacteria, particularly *Bifidobacterium lactis*, has a uniquely strong safety profile, making it a good probiotic candidate for newborns and young infants.[32] Finally, there is still insufficient but fairly promising evidence to recommend the addition of probiotics to foods for prevention and treatment of atopic/autoimmune diseases.

Declaration of Conflicting Interests

The author declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author received no financial support for the research, authorship, and/or publication of this article.

References

1. Björkstén B, Sepp E, Julge K, Voor T, Mikelsaar M. Allergy development and the intestinal microflora during the first year of life. *J Allergy Clin Immunol*. 2001;108:516-520.
2. Das RR. Cesarean delivery, antibiotic exposure, and probiotics: relationship with childhood asthma. *J Allergy Clin Immunol*. 2011;128:1133-1134.
3. Newburg DS. Oligosaccharides in human milk and bacterial colonization. *J Pediatr Gastroenterol Nutr*. 2000;30(suppl 2): S8-S17.
4. Matsuki T, Watanabe K, Tanaka R, Fukuda M, Oyaizu H. Distribution of bifidobacterial species in human intestinal microflora examined with 16S rRNA-gene-targeted species-specific primers. *Appl Environ Microbiol*. 1999;65:4506-4512.
5. Harmsen HJ, Wildeboer-Veloo AC, Raangs GC, et al. Analysis of intestinal flora development in breast-fed and formula-fed infants by using molecular identification and detection methods. *J Pediatr Gastroenterol Nutr*. 2000;30:61-67.
6. Yoshioka H, Iseki K, Fujita K. Development and differences of intestinal flora in the neonatal period in breast-fed and bottle-fed infants. *Pediatrics*. 1983;72:317-321.
7. Kalliomäki M, Kirjavainen P, Eerola E, Kero P, Salminen S, Isolauri E. Distinct patterns of neonatal gut microflora in infants in whom atopy was and was not developing. *J Allergy Clin Immunol*. 2001;107:129-134.
8. Kirjavainen PV, Arvola T, Salminen SJ, Isolauri E. Aberrant composition of gut microbiota of allergic infants: a target of bifidobacterial therapy at weaning? *Gut*. 2002;51:51-55.
9. Sepp E, Julge K, Mikelsaar M, Björkstén B. Intestinal microbiota and immunoglobulin E responses in 5-year-old Estonian children. *Clin Exp Allergy*. 2005;35:1141-1146.
10. Özdemir Öner. Gut flora development in infancy and its effect on immune system [in Turkish]. *J Pediatr Infect (Çocuk Enf Derg)*. 2009;3:202-203.
11. Metchnikoff E. *The Prolongation of Life: Optimistic Studies*. London, England: G. P. Putnam; 1907.
12. Food and Agriculture Organization, World Health Organization. Report of Joint FAO/WHO Expert Consultation on evaluation of health and nutritional properties of probiotics in food including powder milk with live lactic acid bacteria. FAO/WHO Report No. 2001;10-1.
13. Özdemir Ö. Any benefits of probiotics in allergic disorders? *Allergy Asthma Proc*. 2009;31:103-111.
14. Cabana MD, McKean M, Wong AR, Chao C, Caughey AB. Examining the hygiene hypothesis: the Trial of Infant Probiotic Supplementation. *Paediatr Perinat Epidemiol*. 2007;21(suppl 3):23-28.
15. Ljungberg M, Korpela R, Ilonen J, Ludvigsson J, Vaarala O. Probiotics for the prevention of beta cell autoimmunity in children at genetic risk of type 1 diabetes—the PRODIA study. *Ann N Y Acad Sci*. 2006;1079:360-364.
16. Vaarala O, Atkinson MA, Neu J. The "perfect storm" for type 1 diabetes: the complex interplay between intestinal microbiota, gut permeability, and mucosal immunity. *Diabetes*. 2008;57: 2555-2562.
17. Bach JF. The effect of infections on susceptibility to autoimmune and allergic diseases. *N Engl J Med*. 2002;347:911-920.
18. Petrovsky N. Immunomodulation with microbial vaccines to prevent type 1 diabetes mellitus. *Nat Rev Endocrinol*. 2010;6: 131-138.
19. Boerner BP, Sarvetnick NE. Type 1 diabetes: role of intestinal microbiome in humans and mice. *Ann N Y Acad Sci*. 2011; 1243:103-118.
20. Prescott SL, Macaubas C, Holt BJ, et al. Transplacental priming of the human immune system to environmental allergens: universal skewing of initial T cell responses toward the Th2 cytokine profile. *J Immunol*. 1998;160:4730-4737.
21. Schwartz RH. Natural regulatory T cells and self-tolerance. *Nat Immunol*. 2005;6:327-330.
22. Billmann-Born S, Till A, Arlt A, et al. Genome-wide expression profiling identifies an impairment of negative feedback signals in the Crohn's disease-associated NOD2 variant L1007fsinsC. *J Immunol*. 2011;186:4027-4038.
23. Walsh KP, Brady MT, Finlay CM, Boon L, Mills KH. Infection with a helminth parasite attenuates autoimmunity through TGF-beta-mediated suppression of Th17 and Th1 responses. *J Immunol*. 2009;183:1577-1586.
24. Sgouroudis E, Kornete M, Piccirillo CA. IL-2 production by dendritic cells promotes Foxp3(+) regulatory T-cell expansion in autoimmune-resistant NOD congenic mice. *Autoimmunity*. 2011;44:406-414.
25. Okada H, Kuhn C, Feillet H, Bach JF. The 'hygiene hypothesis' for autoimmune and allergic diseases: an update. *Clin Exp Immunol*. 2010;160:1-9.
26. Tlaskalová-Hogenová H, Stepánková R, Hudcovic T, et al. Commensal bacteria (normal microflora), mucosal immunity and chronic inflammatory and autoimmune diseases. *Immunol Lett*. 2004;93:97-108.
27. Matsuzaki T, Takagi A, Ikemura H, Matsuguchi T, Yokokura T. Intestinal microflora: probiotics and autoimmunity. *J Nutr*. 2007; 137(3 suppl 2):798S-802S.
28. Kubota A, He F, Kawase M, Harata G, Hiramatsu M, Iino H. Diversity of intestinal bifidobacteria in patients with Japanese

cedar pollinosis and possible influence of probiotic intervention. *Curr Microbiol*. 2011;62:71-77.
29. Canche-Pool EB, Cortez-Gómez R, Flores-Mejía R, et al. Probiotics and autoimmunity: an evolutionary perspective. *Med Hypotheses*. 2008;70:657-660.
30. de Kort S, Keszthelyi D, Masclee AA. Leaky gut and diabetes mellitus: what is the link? *Obes Rev*. 2011;12:449-458.
31. Kim NY, Ji GE. Effects of probiotics on the prevention of atopic dermatitis. *Korean J Pediatr*. 2012;55:193-201.
32. Özdemir Ö. Various effects of different probiotic strains in allergic disorders: an update from laboratory and clinical data. *Clin Exp Immunol*. 2010;160:295-304.
33. Majamaa H, Isolauri E. Probiotics. A novel approach in the management of food allergy. *J Allergy Clin Immunol*. 1997;99:179-185.
34. Kalliomäki M, Salminen S, Poussa T, Isolauri E. 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.
35. Singh B, Rabinovitch A. Influence of microbial agents on the development and prevention of autoimmune diabetes. *Autoimmunity*. 1993:15:209-213.
36. Brugman S, Klatter FA, Visser JT, et al. Antibiotic treatment partially protects against type 1 diabetes in the Bio-Breeding-prone rat. Is the gut flora involved in the development of type 1 diabetes? *Diabetologia*. 2006:49:2105-2108.
37. Sudo N, Sawamura S, Tanaka K, Aiba Y, Kubo C, Koga Y. The requirement of intestinal bacterial flora for the development of an IgE production system fully susceptible to oral tolerance induction. *J Immunol*. 1997;159:1739-1745.
38. Miele E, Pascarella F, Giannetti E, Quaglietta L, Baldassano RN, Staiano A. Effect of a probiotic preparation (VSL#3) on induction and maintenance of remission in children with ulcerative colitis. *Am J Gastroenterol*. 2009;104:437-443.
39. Dotan I, Rachmilewitz D. Probiotics in inflammatory bowel disease: possible mechanisms of action. *Curr Opin Gastroenterol*. 2005;21:426-430.
40. Sawada J, Morita H, Tanaka A, Salminen S, He F, Matsuda H. Ingestion of heat-treated *Lactobacillus rhamnosus* GG prevents development of atopic dermatitis in NC/Nga mice. *Clin Exp Allergy*. 2007;37:296-303.
41. Cebra JJ. Influences of microbiota on intestinal immune system development. *Am J Clin Nutr*. 1999;69:1046S-1051S.
42. Sistek D, Kelly R, Wickens K, Stanley T, Fitzharris P, Crane J. Is the effect of probiotics on atopic dermatitis confined to food sensitized children? *Clin Exp Allergy*. 2006;36:629-633.
43. Pessi T, Isolauri E, Sutas Y, Kankaanranta H, Moilanen E, Hurme M. Suppression of T cell activation by *Lactobacillus rhamnosus* GG-degraded bovine casein. *Immunopharmacology*. 2001;1: 211-218.
44. Kaila M, Isolauri E, Soppi E, Virtanen E, Laine S, Arvilommi H. Enhancement of the circulating antibody secreting cell response in human diarrhea by a human Lactobacillus strain. *Pediatr Res*. 1992;32:141-144.
45. Isolauri E, Sütas Y, Kankaanpää P, Arvilommi H, Salminen S. Probiotics: effects on immunity. *Am J Clin Nutr*. 2001;73(2 suppl):444S-450S.
46. Inoue R, Nishio A, Fukushima Y, Ushida K. Oral treatment with probiotic *Lactobacillus johnsonii* NCC533 (La1) for a specific part of the weaning period prevents the development of atopic dermatitis induced after maturation in model mice, NC/Nga. *Br J Dermatol*. 2007;156:499-509.
47. Salminen SJ, Gueimonde M, Isolauri E. Probiotics that modify disease risk. *J Nutr*. 2005;135:1294-1298.
48. Takahashi N, Kitazawa H, Iwabuchi N, et al. Immunostimulatory oligodeoxynucleotide from *Bifidobacterium longum* suppresses Th2 immune responses in a murine model. *Clin Exp Immunol*. 2006;145:130-138.
49. Braat H, van den Brande J, van Tol E, Hommes D, Peppelenbosch M, van Deventer S. *Lactobacillus rhamnosus* induces peripheral hyporesponsiveness in stimulated CD4+ T cells via modulation of dendritic cell function. *Am J Clin Nutr*. 2004;80:1618-1625.
50. Maassen CB, van Holten-Neelen C, Balk F, et al. Strain-dependent induction of cytokine profiles in the gut by orally administered Lactobacillus strains. *Vaccine*. 2000;18:2613-2623.
51. Shida K, Nanno M, Nagata S. Flexible cytokine production by macrophages and T cells in response to probiotic bacteria: a possible mechanism by which probiotics exert multifunctional immune regulatory activities. *Gut Microbes*. 2011;2:109-114.
52. Niers LE, Timmerman HM, Rijkers GT, et al. Identification of strong interleukin-10 inducing lactic acid bacteria which downregulate T helper type 2 cytokines. *Clin Exp Allergy*. 2005;35: 1481-1489.
53. Kruisselbrink A, Heijne Den Bak-Glashouwer MJ, Havenith CE, Thole JE, Janssen R. Recombinant *Lactobacillus plantarum* inhibits house dust mite-specific T-cell responses. *Clin Exp Immunol*. 2001;126:2-8.
54. West CE, Hammarström ML, Hernell O. Probiotics during weaning reduce the incidence of eczema. *Pediatr Allergy Immunol*. 2009;20:430-437.
55. Kim JY, Choi YO, Ji GE. Effect of oral probiotics (*Bifidobacterium lactis* AD011 and *Lactobacillus acidophilus* AD031) administration on ovalbumin-induced food allergy mouse model. *J Microbiol Biotechnol*. 2008;18:1393-1400.
56. Sunada Y, Nakamura S, Kamei C. Effect of *Lactobacillus acidophilus* strain L-55 on the development of atopic dermatitis-like skin lesions in NC/Nga mice. *Int Immunopharmacol*. 2008;8: 1761-1766.
57. Shida K, Makino K, Morishita A. Lactobacillus casei inhibits antigen induced IgE secretion through regulation of cytokine production in murine splenocyte cultures. *Int Arch Allergy Immunol*. 1998;115:278-287.
58. Watanabe T, Hamada K, Tategaki A, et al. Oral administration of lactic acid bacteria isolated from traditional South Asian fermented milk 'dahi' inhibits the development of atopic dermatitis in NC/Nga mice. *J Nutr Sci Vitaminol (Tokyo)*. 2009;55:271-278.
59. Hayashi A, Kimura M, Nakamura Y, Yasui H. Anti-atopic dermatitis effects and the mechanism of lactic acid bacteria isolated from Mongolian fermented milk. *J Dairy Res*. 2009; 76:158-164.
60. Won TJ, Kim B, Lim YT, et al. Oral administration of Lactobacillus strains from Kimchi inhibits atopic dermatitis in NC/Nga mice. *J Appl Microbiol*. 2011;110:1195-1202.

61. Ogawa T, Hashikawa S, Asai Y, Sakamoto H, Yasuda K, Makimura Y. A new synbiotic, *Lactobacillus casei* subsp. casei together with dextran, reduces murine and human allergic reaction. *FEMS Immunol Med Microbiol*. 2006;46:400-409.
62. Wakabayashi H, Nariai C, Takemura F, Nakao W, Fujiwara D. Dietary supplementation with lactic acid bacteria attenuates the development of atopic-dermatitis-like skin lesions in NC/Nga mice in a strain-dependent manner. *Int Arch Allergy Immunol*. 2008;145:141-151.
63. Segawa S, Hayashi A, Nakakita Y, Kaneda H, Watari J, Yasui H. Oral administration of heat-killed *Lactobacillus brevis* SBC8803 ameliorates the development of dermatitis and inhibits immunoglobulin E production in atopic dermatitis model NC/Nga mice. *Biol Pharm Bull*. 2008;31:884-889.
64. Tanaka A, Jung K, Benyacoub J, et al. Oral supplementation with *Lactobacillus rhamnosus* CGMCC 1.3724 prevents development of atopic dermatitis in NC/NgaTnd mice possibly by modulating local production of IFN-gamma. *Exp Dermatol*. 2009;18: 1022-1027.
65. Thomas DJ, Husmann RJ, Villamar M, Winship TR, Buck RH, Zuckermann FA. *Lactobacillus rhamnosus* HN001 attenuates allergy development in a pig model. *PLoS One*. 2011;6(2): e16577.
66. Pohjavuori E, Viljanen M, Korpela R, et al. Lactobacillus GG effect in increasing IFN-gamma production in infants with cow's milk allergy. *J Allergy Clin Immunol*. 2004;114:131-136.
67. Prescott SL, Dunstan JA, Hale J, et al. Clinical effects of probiotics are associated with increased interferon-gamma responses in very young children with atopic dermatitis. *Clin Exp Allergy*. 2005;35:1557-1564.
68. Rosenfeldt V, Benfeldt E, Nielsen SD, et al. Effect of probiotic Lactobacillus strains in children with atopic dermatitis. *J Allergy Clin Immunol*. 2003;111:389-395.
69. Brouwer ML, Wolt-Plompen SA, Dubois AE, et al. No effects of probiotics on atopic dermatitis in infancy: a randomized placebo-controlled trial. *Clin Exp Allergy*. 2006;36:899-906.
70. Pessi T, Sütas Y, Hurme M, Isolauri E. Interleukin-10 generation in atopic children following oral *Lactobacillus rhamnosus* GG. *Clin Exp Allergy*. 2000;30:1804-1808.
71. Betsi GI, Papadavid E, Falagas ME. Probiotics for the treatment or prevention of atopic dermatitis: a review of the evidence from randomized controlled trials. *Am J Clin Dermatol*. 2008;9: 93-103.
72. Woo SI, Kim JY, Lee YJ, Kim NS, Hahn YS. Effect of *Lactobacillus sakei* supplementation in children with atopic eczema-dermatitis syndrome. *Ann Allergy Asthma Immunol*. 2010;104: 343-348.
73. Inoue R, Otsuka M, Nishio A, Ushida K. Primary administration of *Lactobacillus johnsonii* NCC533 in weaning period suppresses the elevation of proinflammatory cytokines and CD86 gene expressions in skin lesions in NC/Nga mice. *FEMS Immunol Med Microbiol*. 2007;50:67-76.
74. Marschan E, Kuitunen M, Kukkonen K, et al. Probiotics in infancy induce protective immune profiles that are characteristic for chronic low-grade inflammation. *Clin Exp Allergy*. 2008;38: 611-618.
75. Kobayashi T, Suzuki T, Kaji R, et al. Probiotic upregulation of peripheral IL-17 responses does not exacerbate neurological symptoms in experimental autoimmune encephalomyelitis mouse models. *Immunopharmacol Immunotoxicol*. 2012;34:423-433.
76. So JS, Kwon HK, Lee CG, et al. *Lactobacillus casei* suppresses experimental arthritis by down-regulating T helper 1 effector functions. *Mol Immunol*. 2008;45:2690-2699.
77. Lavasani S, Dzhambazov B, Nouri M, et al. A novel probiotic mixture exerts a therapeutic effect on experimental autoimmune encephalomyelitis mediated by IL-10 producing regulatory T cells. *PLoS One*. 2010;5(2): e9009.
78. Niers LE, Hoekstra MO, Timmerman HM, et al. Selection of probiotic bacteria for prevention of allergic diseases: immunomodulation of neonatal dendritic cells. *Clin Exp Immunol*. 2007;149: 344-352.
79. Hart AL, Lammers K, Brigidi P, et al. Modulation of human dendritic cell phenotype and function by probiotic bacteria. *Gut*. 2004;53:1602-1609.
80. Smits HH, Engering A, van der Kleij D, et al. Selective probiotic bacteria induce IL-10-producing regulatory T cells in vitro by modulating dendritic cell function through dendritic cell-specific intercellular adhesion molecule 3-grabbing nonintegrin. *J Allergy Clin Immunol*. 2005;115:1260-1267.
81. Issazadeh-Navikas S, Teimer R, Bockermann R. Influence of dietary components on regulatory T cells. *Mol Med*. 2012;18:95-110.
82. Feleszko W, Jaworska J, Rha RD, et al. Probiotic-induced suppression of allergic sensitization and airway inflammation is associated with an increase of T regulatory-dependent mechanisms in a murine model of asthma. *Clin Exp Allergy*. 2007;37:498-505.
83. Di Giacinto C, Marinaro M, Sanchez M, Strober W, Boirivant M. Probiotics ameliorate recurrent Th1-mediated murine colitis by inducing IL-10 and IL-10-dependent TGF-beta-bearing regulatory cells. *J Immunol*. 2005;174:3237-3246.
84. Hacini-Rachinel F, Gheit H, Le Luduec JB, Dif F, Nancey S, Kaiserlian D. Oral probiotic control skin inflammation by acting on both effector and regulatory T cells. *PLoS One*. 2009;4(3): e4903.
85. Fujimura T, Okuyama R, Ito Y, Aiba S. Profiles of Foxp3+ regulatory T cells in eczematous dermatitis, psoriasis vulgaris and mycosis fungoides. *Br J Dermatol*. 2008;158:1256-1263.
86. Kwon HK, Lee CG, So JS, et al. Generation of regulatory dendritic cells and CD4+Foxp3+ T cells by probiotics administration suppresses immune disorders. *Proc Natl Acad Sci U S A*. 2010; 107:2159-2164.
87. Taylor AL, Hale J, Hales BJ, Dunstan JA, Thomas WR, Prescott SL. FOXP3 mRNA expression at 6 months of age is higher in infants who develop atopic dermatitis, but is not affected by giving probiotics from birth. *Pediatr Allergy Immunol*. 2007;18: 10-19.
88. Weise C, Zhu Y, Ernst D, Kühl AA, Worm M. Oral administration of *Escherichia coli* Nissle 1917 prevents allergen-induced dermatitis in mice. *Exp Dermatol*. 2011;20:805-809.
89. Gerasimov SV, Vasjuta VV, Myhovych OO, Bondarchuk LI. Probiotic supplement reduces atopic dermatitis in preschool children: a randomized, double-blind, placebo-controlled, clinical trial. *Am J Clin Dermatol*. 2010;11:351-361.

90. Chapat L, Chemin K, Dubois B, Bourdet-Sicard R, Kaiserlian D. *Lactobacillus casei* reduces CD8+ T cell-mediated skin inflammation. *Eur J Immunol*. 2004;34:2520-2528.
91. Roessler A, Friedrich U, Vogelsang H, et al. The immune system in healthy adults and patients with atopic dermatitis seems to be affected differently by a probiotic intervention. *Clin Exp Allergy*. 2008;38:93-102.
92. Gareau MG, Sherman PM, Walker WA. Probiotics and the gut microbiota in intestinal health and disease. *Nat Rev Gastroenterol Hepatol*. 2010;7:503-514.
93. Rachmilewitz D, Katakura K, Karmeli F, et al. Toll-like receptor 9 signaling mediates the anti-inflammatory effects of probiotics in murine experimental colitis. *Gastroenterology*. 2004;126: 520-528.
94. Hoarau C, Lagaraine C, Martin L, Velge-Roussel F, Lebranchu Y. Supernatant of *Bifidobacterium breve* induces dendritic cell maturation, activation, and survival through a Toll-like receptor 2 pathway. *J Allergy Clin Immunol*. 2006;117:696-702.
95. Forsythe P, Inman MD, Bienenstock J. Oral treatment with live *Lactobacillus reuteri* inhibits the allergic airway response in mice. *Am J Respir Crit Care Med*. 2007;175:561-569.
96. Aumeunier A, Grela F, Ramadan A, et al. Systemic Toll-like receptor stimulation suppresses experimental allergic asthma and autoimmune diabetes in NOD mice. *PLoS One*. 2010;5: e11484.
97. Viljanen M, Kuitunen M, Haahtela T, Juntunen-Backman K, Korpela R, Savilahti E. Probiotic effects on faecal inflammatory markers and on faecal IgA in food allergic atopic eczema/dermatitis syndrome infants. *Pediatr Allergy Immunol*. 2005;16:65-71.
98. Gore C, Custovic A, Tannock GW, et al. Treatment and secondary prevention effects of the probiotics *Lactobacillus paracasei* or *Bifidobacterium lactis* on early infant eczema: randomized controlled trial with follow-up until age 3 years. *Clin Exp Allergy*. 2012;42:112-122.
99. Boyle RJ, Ismail IH, Kivivuori S, et al. Lactobacillus GG treatment during pregnancy for the prevention of eczema: a randomized controlled trial. *Allergy*. 2011;66:509-516.
100. Doege K, Grajecki D, Zyriax BC, Detinkina E, Zu Eulenburg C, Buhling KJ. Impact of maternal supplementation with probiotics during pregnancy on atopic eczema in childhood—a meta-analysis. *Br J Nutr*. 2012;107:1-6.
101. Kirjavainen PV, Salminen SJ, Isolauri E. Probiotic bacteria in the management of atopic disease: underscoring the importance of viability. *J Pediatr Gastroenterol Nutr*. 2003;36:223-227.
102. Rautava S, Kalliomäki M, Isolauri E. Probiotics during pregnancy and breast-feeding might confer immunomodulatory protection against atopic disease in the infant. *J Allergy Clin Immunol*. 2002;109:119-121.
103. 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.
104. Kuitunen M, Kukkonen K, Juntunen-Backman K, et al. Probiotics prevent IgE-associated allergy until age 5 years in cesarean-delivered children but not in the total cohort. *J Allergy Clin Immunol*. 2009;123:335-341.
105. Abrahamsson TR, Jakobsson T, Böttcher 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.
106. Pelucchi C, Chatenoud L, Turati F, et al. Probiotics supplementation during pregnancy or infancy for the prevention of atopic dermatitis: a meta-analysis. *Epidemiology*. 2012; 23:402-414.
107. Weston S, Halbert A, Richmond P, Prescott SL. Effects of probiotics on atopic dermatitis. A randomised controlled trial. *Arch Dis Child*. 2005;90:892-897.
108. Hoang BX, Shaw G, Pham P, Levine SA. *Lactobacillus rhamnosus* cell lysate in the management of resistant childhood atopic eczema. *Inflamm Allergy Drug Targets*. 2010;9: 192-196.
109. Hattori K, Yamamoto A, Sasai M, et al. Effects of administration of bifidobacteria on fecal microflora and clinical symptoms in infants with atopic dermatitis [in Japanese]. *Arerugi*. 2003;52: 20-30.
110. Wickens K, Black PN, Stanley TV, et al; Probiotic Study Group. A differential effect of 2 probiotics in the prevention of eczema and atopy: a double-blind, randomized, placebo-controlled trial. *J Allergy Clin Immunol*. 2008;122:788-794.
111. Niers L, Martín R, Rijkers G, et al. The effects of selected probiotic strains on the development of eczema (the PandA study). *Allergy*. 2009;64:1349-1358.
112. Kim JY, Kwon JH, Ahn SH, et al. Effect of probiotic mix (*Bifidobacterium bifidum*, *Bifidobacterium lactis*, *Lactobacillus acidophilus*) in the primary prevention of eczema: a double-blind, randomized, placebo-controlled trial. *Pediatr Allergy Immunol*. 2010;21 (2 pt 2): e386-e393.
113. Dotterud CK, Storrø O, Johnsen R, Oien T. Probiotics in pregnant women to prevent allergic disease: a randomized, double-blind trial. *Br J Dermatol*. 2010;163:616-623.
114. Lodinova-Zadnikova R, Cukrowska B, Tlaskalova-Hogenova H. Oral administration of probiotic *Escherichia coli* after birth reduces frequency of allergies and repeated infections later in life (after 10 and 20 years). *Int Arch Allergy Immunol*. 2003; 131:209-211.
115. Huurre A, Laitinen K, Rautava S, Korkeamäki M, Isolauri E. Impact of maternal atopy and probiotic supplementation during pregnancy on infant sensitization: a double-blind placebo-controlled study. *Clin Exp Allergy*. 2008;38:1342-1348.
116. Taylor A, Dunstan J, Prescott S. Probiotic supplementation for the first 6 months of life fails to reduce the risk of atopic dermatitis and increases the risk of allergen sensitization in high-risk children: a randomized controlled trial. *J Allergy Clin Immunol*. 2007;119:184-1891.
117. van der Aa LB, Lutter R, Heymans HS, et al; Synbad Study Group. No detectable beneficial systemic immunomodulatory effects of a specific synbiotic mixture in infants with atopic dermatitis. *Clin Exp Allergy*. 2012;42:531-539.
118. Kopp MV, Hennemuth I, Heinzmann A, Urbanek R. Randomized, double-blind, placebo-controlled trial of probiotics for primary prevention: no clinical effects of Lactobacillus GG supplementation. *Pediatrics*. 2008;121: e850-e856.

119. Grüber C, Wendt M, Sulser C, et al. Randomized, placebo-controlled trial of *Lactobacillus rhamnosus* GG as treatment of atopic dermatitis in infancy. *Allergy*. 2007;62:1270-1276.
120. Fölster-Holst R, Müller F, Schnopp N, et al. Prospective, randomized controlled trial on *Lactobacillus rhamnosus* in infants with moderate to severe atopic dermatitis. *Br J Dermatol*. 2006,155:1256-1261.
121. Soh SE, Aw M, Gerez I, et al. Probiotic supplementation in the first 6 months of life in at risk Asian infants—effects on eczema and atopic sensitization at the age of 1 year. *Clin Exp Allergy*. 2009;39:571-578.
122. Gore C, Custovic A, Tannock GW, et al. Treatment and secondary prevention effects of the probiotics *Lactobacillus paracasei* or *Bifidobacterium lactis* on early infant eczema: randomized controlled trial with follow-up until age 3 years. *Clin Exp Allergy*. 2012;42:112-122.
123. Isolauri E, Arvola T, Sütas Y, Moilanen E, Salminen S. Probiotics in the management of atopic eczema. *Clin Exp Allergy*. 2000;30:1604-1610.
124. Lieberman JA, Wang J. Nonallergen-specific treatments for food allergy. *Curr Opin Allergy Clin Immunol*. 2012;12:293-301.
125. del Giudice MM, Leonardi S, Maiello N, Brunese FP. Food allergy and probiotics in childhood. *J Clin Gastroenterol*. 2010;44(suppl 1): S22-S25.
126. Di Felice G, Barletta B, Butteroni C, et al. Use of probiotic bacteria for prevention and therapy of allergic diseases: studies in mouse model of allergic sensitization. *J Clin Gastroenterol*. 2008;42 (suppl 3 pt 1): S130-S132.
127. Shida K, Takahashi R, Iwadate E, et al. *Lactobacillus casei* strain Shirota suppresses serum immunoglobulin E and immunoglobulin G1 responses and systemic anaphylaxis in a food allergy model. *Clin Exp Allergy*. 2002;32:563-570.
128. Schiavi E, Barletta B, Butteroni C, Corinti S, Boirivant M, Di Felice G. Oral therapeutic administration of a probiotic mixture suppresses established Th2 responses and systemic anaphylaxis in a murine model of food allergy. *Allergy*. 2011;66:499-508.
129. Zuercher AW, Weiss M, Holvoet S, et al. *Lactococcus lactis* NCC 2287 alleviates food allergic manifestations in sensitized mice by reducing IL-13 expression specifically in the ileum. *Clin Dev Immunol*. 2012;2012:485750.
130. Rupa P, Schmied J, Wilkie BN. Prophylaxis of experimentally induced ovomucoid allergy in neonatal pigs using *Lactococcus lactis*. *Vet Immunol Immunopathol*. 2011;140:23-29.
131. Hol J, van Leer EH, Elink Schuurman BE, et al; Cow's Milk Allergy Modified by Elimination and Lactobacilli Study Group. The acquisition of tolerance toward cow's milk through probiotic supplementation: a randomized, controlled trial. *J Allergy Clin Immunol*. 2008;121:1448-1454.
132. Finamore A, Roselli M, Britti MS, Merendino N, Mengheri E. Lactobacillus rhamnosus GG and *Bifidobacterium animalis* MB5 induce intestinal but not systemic antigen-specific hyporesponsiveness in ovalbumin-immunized rats. *J Nutr*. 2012;142: 375-3781.
133. de Jonge JD, Ezendam J, Knippels LM, Penninks AH, Pieters R, van Loveren H. *Lactobacillus casei* Shirota does not decrease the food allergic response to peanut extract in Brown Norway rats. *Toxicology*. 2008;249:140-145.
134. Osborn DA, Sinn JK. Probiotics in infants for prevention of allergic disease and food hypersensitivity. *Cochrane Database Syst Rev*. 2007;(4): CD006475. doi:10.1002/14651858. CD006475.pub2.
135. Vliagoftis H, Kouranos VD, Betsi GI, Falagas ME. Probiotics for the treatment of allergic rhinitis and asthma: systematic review of randomized controlled trials. *Ann Allergy Asthma Immunol*. 2008;101:570-579.
136. Kopp MV, Salfeld P. Probiotics and prevention of allergic disease. *Curr Opin Clin Nutr Metab Care*. 2009;12:298-303.
137. Peng GC, Hsu CH. The efficacy and safety of heat-killed *Lactobacillus paracasei* for treatment of perennial allergic rhinitis induced by house-dust mite. *Pediatr Allergy Immunol*. 2005; 16:433-438.
138. Giovannini M, Agostoni C, Riva E, et al; Felicita Study Group. A randomized prospective double blind controlled trial on effects of long-term consumption of fermented milk containing *Lactobacillus casei* in pre-school children with allergic asthma and/or rhinitis. *Pediatr Res*. 2007;62:215-220.
139. Morita H, He F, Kawase M, et al. Preliminary human study for possible alteration of serum immunoglobulin E production in perennial allergic rhinitis with fermented milk prepared with *Lactobacillus gasseri* TMC0356. *Microbiol Immunol*. 2006;50: 701-706.
140. Chen YS, Jan RL, Lin YL, Chen HH, Wang JY. Randomized placebo-controlled trial of lactobacillus on asthmatic children with allergic rhinitis. *Pediatr Pulmonol*. 2010;45:1111-1120.
141. Wang MF, Lin HC, Wang YY, Hsu CH. Treatment of perennial allergic rhinitis with lactic acid bacteria. *Pediatr Allergy Immunol*. 2004;15:152-158.
142. Nishimura I, Igarashi T, Enomoto T, Dake Y, Okuno Y, Obata A. Clinical efficacy of halophilic lactic acid bacterium *Tetragenococcus halophilus* Th221 from soy sauce moromi for perennial allergic rhinitis. *Allergol Int*. 2009;58:179-185.
143. Nogueira JC, Gonçalves Mda C. Probiotics in allergic rhinitis [in Portuguese]. *Braz J Otorhinolaryngol*. 2011;77:129-134.
144. Ivory K, Chambers SJ, Pin C, Prieto E, Arqués JL, Nicoletti C. Oral delivery of *Lactobacillus casei* Shirota modifies allergen-induced immune responses in allergic rhinitis. *Clin Exp Allergy*. 2008;38:1282-1289.
145. Nagata Y, Yoshida M, Kitazawa H, Araki E, Gomyo T. Improvements in seasonal allergic disease with *Lactobacillus plantarum* No. 14. *Biosci Biotechnol Biochem*. 2010;74: 1869-1877.
146. Kawase M, He F, Kubota A, et al. Effect of fermented milk prepared with two probiotic strains on Japanese cedar pollinosis in a double-blind placebo-controlled clinical study. *Int J Food Microbiol*. 2009;128:429-434.
147. Xiao JZ, Kondo S, Yanagisawa N, et al. Effect of probiotic *Bifidobacterium longum* BB536 [corrected] 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 Investig Allergol Clin Immunol*. 2006;16:86-93.

148. Xiao JZ, Kondo S, Yanagisawa N, et al. Probiotics in the treatment of Japanese cedar pollinosis: a double-blind placebo-controlled trial. *Clin Exp Allergy*. 2006;36:1425-1435.
149. Yonekura S, Okamoto Y, Okawa T, et al. Effects of daily intake of *Lactobacillus paracasei* strain KW3110 on Japanese cedar pollinosis. *Allergy Asthma Proc*. 2009;30:397-405.
150. Koyama T, Kirjavainen PV, Fisher C, et al. Development and pilot evaluation of a novel probiotic mixture for the management of seasonal allergic rhinitis. *Can J Microbiol*. 2010;56: 730-738.
151. Tamura M, Shikina T, Morihana T, et al. Effects of probiotics on allergic rhinitis induced by Japanese cedar pollen: randomized double-blind, placebo-controlled clinical trial. *Int Arch Allergy Immunol*. 2007;143:75-82.
152. Ouwehand AC, Nermes M, Collado MC, Rautonen N, Salminen S, Isolauri E. Specific probiotics alleviate allergic rhinitis during the birch pollen season. *World J Gastroenterol*. 2009;15: 3261-3268.
153. Azad MB, Kozyrskyj AL. Perinatal programming of asthma: the role of gut microbiota. *Clin Dev Immunol*. 2012;2012:932072.
154. Blümer N, Sel S, Virna S, et al. Perinatal maternal application of *Lactobacillus rhamnosus* GG suppresses allergic airway inflammation in mouse offspring. *Clin Exp Allergy*. 2007;37: 348-357.
155. Singh M, Ranjan Das R. Probiotics for allergic respiratory diseases—putting it into perspective. *Pediatr Allergy Immunol*. 2010;21 (2 pt 2): e368-e376.
156. Repa A, Grangette C, Daniel C, et al. Mucosal co-application of lactic acid bacteria and allergen induces counter-regulatory immune responses in a murine model of birch pollen allergy. *Vaccine*. 2003;22:87-95.
157. Jan RL, Yeh KC, Hsieh MH, et al. Lactobacillus gasseri suppresses Th17 pro-inflammatory response and attenuates allergen-induced airway inflammation in a mouse model of allergic asthma. *Br J Nutr*. 2011;14:1-10.
158. Zhang B, An J, Shimada T, Liu S, Maeyama K. Oral administration of *Enterococcus faecalis* FK-23 suppresses Th17 cell development and attenuates allergic airway responses in mice. *Int J Mol Med*. 2012;30:248-254.
159. Karimi K, Inman MD, Bienenstock J, Forsythe P. *Lactobacillus reuteri-induced* regulatory T cells protect against an allergic airway response in mice. *Am J Respir Crit Care Med*. 2009; 179:186-193.
160. Lue KH, Sun HL, Lu KH, et al. A trial of adding *Lactobacillus johnsonii* EM1 to levocetirizine for treatment of perennial allergic rhinitis in children aged 7-12years. *Int J Pediatr Otorhinolaryngol*. 2012;76:994-1001.
161. Stockert K, Schneider B, Porenta G, Rath R, Nissel H, Eichler I. Laser acupuncture and probiotics in school age children with asthma: a randomized, placebo-controlled pilot study of therapy guided by principles of traditional Chinese medicine. *Pediatr Allergy Immunol*. 2007;18:160-166.
162. Moreira A, Kekkonen R, Korpela R, Delgado L, Haahtela T. Allergy in marathon runners and effect of Lactobacillus GG supplementation on allergic inflammatory markers. *Respir Med*. 2007;101:1123-1131.
163. Rose MA, Stieglitz F, Köksal A, Schubert R, Schulze J, Zielen S. Efficacy of probiotic Lactobacillus GG on allergic sensitization and asthma in infants at risk. *Clin Exp Allergy*. 2010;40: 1398-1405.
164. Kukkonen AK, Kuitunen M, Savilahti E, Pelkonen A, Malmberg P, Mäkelä M. Airway inflammation in probiotic-treated children at 5 years. *Pediatr Allergy Immunol*. 2011;22:249-251.
165. Helin T, Haahtela S, Haahtela T. No effect of oral treatment with an intestinal bacterial strain, *Lactobacillus rhamnosus* (ATCC 53103), on birch-pollen allergy: a placebo-controled double-blind study. *Allergy*. 2002;57:243-246.
166. Hatakka K, Martio J, Korpela M, et al. Effects of probiotic therapy on the activity and activation of mild rheumatoid arthritis—a pilot study. *Scand J Rheumatol*. 2003;32:211-215.
167. Lee HJ, Waller RD, Stebbings S, et al. The effects of an orally administered probiotic on sulfasalazine metabolism in individuals with rheumatoid arthritis: a preliminary study. *Int J Rheum Dis*. 2010;13:48-54.
168. Mandel DR, Eichas K, Holmes J. *Bacillus coagulans*: a viable adjunct therapy for relieving symptoms of rheumatoid arthritis according to a randomized, controlled trial. *BMC Complement Altern Med*. 2010;10:1-7.
169. Pineda Mde L, Thompson SF, Summers K, de Leon F, Pope J, Reid G. A randomized, double-blinded, placebo-controlled pilot study of probiotics in active rheumatoid arthritis. *Med Sci Monit*. 2011;17: CR347-CR354.
170. Garrett SL, Kennedy LG, Calin A. Patients' perceptions of disease modulation by diet in inflammatory (rheumatoid arthritis/ankylosing spondylitis) and degenerative arthropathies. *Br J Rheumatol*. 1993;32(suppl 2):43.
171. Jenks K, Stebbings S, Burton J, Schultz M, Herbison P, Highton J. Probiotic therapy for the treatment of spondyloarthritis: a randomized controlled trial. *J Rheumatol*. 2010; 37:2118-2125.
172. Kawasaki E, Abiru N, Eguchi K. Prevention of type 1 diabetes: from the view point of beta cell damage. *Diabetes Res Clin Pract*. 2004;66(suppl 1): S27-S32.
173. Akerblom HK, Virtanen SM, Ilonen J, et al; National TRIGR Study Groups. Dietary manipulation of beta cell autoimmunity in infants at increased risk of type 1 diabetes: a pilot study. *Diabetologia*. 2005;48:829-837.
174. Rozanova GN, Voevodin DA. A case of an effective application of probiotics in the complex therapy of severe type 1 diabetes mellitus and intestinal disbacteriosis [in Russian]. *Klin Med (Mosk)*. 2008;86:67-68.
175. Kidd PM. Multiple sclerosis, an autoimmune inflammatory disease: prospects for its integrative management. *Altern Med Rev*. 2001;6:540-566.
176. Fleming JO, Isaak A, Lee JE, et al. Probiotic helminth administration in relapsing-remitting multiple sclerosis: a phase 1 study. *Mult Scler*. 2011;17:743-754.
177. Bibiloni R, Fedorak RN, Tannock GW, et al. VSL#3 probiotic-mixture induces remission in patients with active ulcerative colitis. *Am J Gastroenterol*. 2005;100:1539-1546.
178. Rolfe VE, Fortun PJ, Hawkey CJ, Bath-Hextall F. Probiotics for maintenance of remission in Crohn's disease. *Cochrane*

Database Syst Rev. 2006;(4): CD004826. doi:10.1002/14651858.CD004826.pub2.
179. Rembacken BJ, Snelling AM, Hawkey PM, Chalmers DM, Axon AT. Non-pathogenic *Escherichia coli* versus mesalazine for the treatment of ulcerative colitis: a randomised trial. *Lancet*. 1999;354:635-639.
180. Matthes H, Krummenerl T, Giensch M, et al. Treatment of mild to moderate acute attacks of distal ulcerative colitis with rectally-administered *E. coli* Nissle 1917: dose-dependent efficacy. *Gastroenterology*. 2006;130(suppl 2): A119.
181. Kato K, Mizuno S, Umesaki Y, et al. Randomized placebo-controlled trial assessing the effect of bifidobacteria-fermented milk on active ulcerative colitis. *Aliment Pharmacol Ther*. 2004;20:1133-1141.
182. Ishikawa H, Akedo I, Umesaki Y, Tanaka R, Imaoka A, Otani T. Randomized controlled trial of the effect of bifidobacteria-fermented milk on ulcerative colitis. *J Am Coll Nutr*. 2003;22: 56-63.
183. Venturi A, Gionchetti P, Rizzello F, et al. Impact on the composition of the faecal flora by a new probiotic preparation: preliminary data on maintenance treatment of patients with ulcerative colitis. *Aliment Pharmacol Ther*. 1999;13:1103-1108.
184. Zocco MA, dal Verme LZ, Cremonini F, et al. Efficacy of Lactobacillus GG in maintaining remission of ulcerative colitis. *Aliment Pharmacol Ther*. 2006;23:1567-1574.
185. Naidoo K, Gordon M, Fagbemi AO, Thomas AG, Akobeng AK. Probiotics for maintenance of remission in ulcerative colitis. *Cochrane Database Syst Rev*. 2011;(12): CD007443. doi:10.1002/14651858.CD007443.pub2.
186. Malchow HA. Crohn's disease and *Escherichia coli*. A new approach in therapy to maintain remission of colonic Crohn's disease? *J Clin Gastroenterol*. 1997;25:653-658.
187. Schultz M, Timmer A, Herfarth HH, Sartor RB, Vanderhoof JA, Rath HC. Lactobacillus GG in inducing and maintaining remission of Crohn's disease. *BMC Gastroenterol*. 2004;4:5-8.
188. Guslandi M, Mezzi G, Sorghi M, Testoni PA. *Saccharomyces boulardii* in maintenance treatment of Crohn's disease. *Dig Dis Sci*. 2000;45:1462-1464.
189. Bousvaros A, Guandalini S, Baldassano RN, et al. A randomized, double-blind trial of Lactobacillus GG versus placebo in addition to standard maintenance therapy for children with Crohn's disease. *Inflamm Bowel Dis*. 2005;11:833-839.
190. Prantera C, Scribano ML, Falasco G, Andreoli A, Luzi C. Ineffectiveness of probiotics in preventing recurrence after curative resection for Crohn's disease: a randomised controlled trial with Lactobacillus GG. *Gut*. 2002;51:405-409.
191. Van Gossum A, Dewit O, Louis E, et al. Multicenter randomized-controlled clinical trial of probiotics (*Lactobacillus johnsonii*, LA1) on early endoscopic recurrence of Crohn's disease after ileo-caecal resection. *Inflamm Bowel Dis*. 2007;13:135-142.
192. Marteau P, Lemann M, Seksik P, et al. Ineffectiveness of *Lactobacillus johnsonii* LA1 for prophylaxis of postoperative recurrence in Crohn's disease: a randomised, double blind, placebo controlled GETAID trial. *Gut*. 2006;55:842-847.
193. Campieri M, Rizzello F, Venturi A, et al. Combination of antibiotic and probiotic treatment is efficacious in prophylaxis of postoperative recurrence of Crohn's disease: A randomized controlled study vs mesalamine. *Gastroenterology*. 2000;118: A781.