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Supplement: Guidance for Assessing Probiotics Beneficial Effects—How to Fill the GAP

Guidance for Substantiating the Evidence for Beneficial Effects of Probiotics: Prevention and Management of Allergic Diseases by Probiotics[1–3]

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Abstract

Allergy is a hypersensitivity reaction mediated by specific antibody-mediated or cell-mediated immunologic mechanisms and clinically manifested as atopic eczema, allergic rhinoconjunctivitis, or asthma. During the recent decades there has been an increase in allergy prevalence, which is attributed to changes in environmental factors. The so-called "hygiene hypothesis" suggests that a lack of exposure to microbial stimulus early in childhood is a major factor involved in this trend. This provides a rationale for using probiotics to modify the gut microbiota and thereby shaping the immune response of the host, especially in infancy. Most success has been obtained in primary prevention of atopic eczema. A limited number of studies also provided evidence for a beneficial effect of different probiotics in the management of allergic diseases (atopic eczema, allergic rhinitis). However, choice of probiotic strains as well as timing of the intervention are important variables. The exact in vivo mechanism of probiotics in shaping the immune response still needs to be determined. Future studies should use uniform criteria for diagnosis and symptom scoring of atopic diseases and may identify the genes predisposing to allergic disease. There is encouraging evidence that specific probiotics can become valuable tools in the prevention and management of allergic diseases. J. Nutr. 140: 713S–721S, 2010.

Characteristic features of allergies

Allergy is defined as a hypersensitivity reaction mediated by specific antibody-mediated or cell-mediated immunologic mechanisms, the clinical manifestation of which is called allergic disease. The term hypersensitivity describes objectively reproducible symptoms or signs initiated by exposure to a defined stimulus at a dose tolerated by normal (i.e. nonallergic) persons (1). The progression of infant allergy to atopic diseases such as atopic eczema, allergic rhinoconjunctivitis, and ultimately asthma is becoming increasingly common and is now referred to as the pediatric allergic march. This is contributing to the so-called epidemic of allergic or atopic diseases that have become more frequent in the Western world over the past several decades (2). Eczema refers to a chronic or relapsing itchy skin inflammation with typical lesions and locations. Eczema is called atopic if it is associated with IgE demonstrated either by positive skin prick tests or elevated antigen-specific IgE antibodies (1). Allergic rhinoconjunctivitis causes nasal and ocular immunologically mediated hypersensitivity symptoms, such as itching, sneezing, increased secretion, and nasal blockage (1). Asthma

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is a chronic inflammatory disorder of the airways, which is associated with airway hyperresponsiveness that leads to recurrent episodes of coughing, wheezing, breathlessness, and chest tightness. Asthma resulting from immunological reactions is called allergic asthma (1). The mechanisms leading to the increased incidence of allergic diseases are not fully understood but are known to involve genetic factors as well as complex interactions between the host and allergen exposure as well as other environmental stimuli such as the intestinal microbiota and infectious agents (3) (**Fig. 1**).

Sensitization to allergens derived from food, pollen, house dust mite, etc. is thought to be a prerequisite for initiating the allergic march. This initial phase is characterized by an acute transient inflammatory immune response associated with the production of allergen-specific IgE antibodies and the influx of activated T cells and other effector cells, e.g. eosinophils and mast cells at the site of allergen exposure (4). In the case of respiratory allergies, continuous allergen exposure and additional triggering factors (e.g. infections, smoking, pollution, and exercise) are contributing to the perpetuation of the inflammation in the mucosa and submucosa. This chronic inflammatory stage is orchestrated by type 2 T helper (Th2)[11] cells. The Th2 cells produce cytokines such as interleukin (IL)-4, IL-5, IL-9, IL-13, and IL-31 that regulate both production of allergen-specific IgE and tissue inflammation characterized by the influx of eosinophils/mast cells and activated CD4+ T-cells (5). The ongoing tissue damage due to eosinophil degranulation products and subsequent remodeling of the mucosa in the case of respiratory allergies further contribute to severity of the disease and the development of irreversible tissue damage (4). As the mechanisms explaining the increasing prevalence of allergic or atopic diseases in developed countries have yet to be fully elucidated, causal therapy is not an option and current research is focused mainly on primary prevention strategies to avoid the onset of the allergic march; some studies also target reduction of allergic symptoms.

There is increasing interest in the role of regulatory T cell (Treg) populations in preventing the sensitization to allergens (3,6–8). Treg are a diverse group of cells that are important in the development of immunological tolerance and comprise the naturally occurring, thymically derived CD4-CD25 Treg that express high levels of the transcription factor Foxp3 and the antigen-specific Treg, which can be induced in vitro and in vivo under particular conditions. The antigen-specific Treg secrete antiinflammatory cytokines such as IL-10 and/or transforming growth factor-β and can potentially suppress IgE production and Th1/Th2 proliferation (7). There is increasing evidence that dendritic cells in the mucosa of the intestine and airways play a role in the differentiation and/or expansion of Treg in vivo, thereby limiting T cell-mediated responses and regulating mucosal tolerance (9). Recent studies indicate that allergen-specific Treg responses may be compromised in allergic diseases that are characterized by an imbalance between allergen-specific Treg and Th1 and Th2 cells (10–12). The mechanisms of tolerance induction and the development of Treg seem to be very complex and depend on many factors, such as the nature and dose of the antigen as well as frequency and route of exposure (5). Moreover, the role of Th17 cells in allergic inflammation is largely unknown (13). There is mounting evidence that the gut microbiota acquired during the early postnatal period is required for the proper development of Treg, of which several subtypes with distinct cytokine secretion pattern have been described (14).

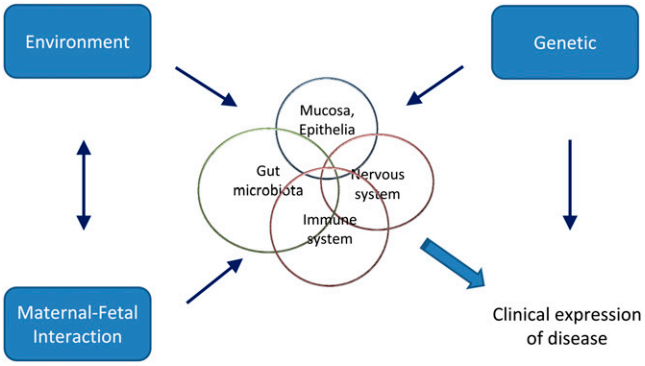

FIGURE 1 Extrinsic and intrinsic factors contributing to the development of allergic diseases. Allergy is a complex and multifactorial disease, the clinical expression of which is determined by the interplay between host (genetic background and maternal-fetal interaction) and environmental influences on gut microbiota, mucosa, and epithelia, the nervous system, and the immune system.

When analyzing results of past and ongoing clinical trials performed with probiotics, it should be kept in mind that allergy is a complex and multifactorial disease whose outcome is strongly influenced by a complex interplay among the host, in particular its genetic background, the status of the immune system and intestinal microbiota, and the environment (Fig. 1). The effects of probiotic preparations thus must be analyzed in this complicated context.

Rationale for use of probiotics in allergy

The steep increase in allergy prevalence during the last decades has been attributed to changes in environmental factors. There is solid evidence from epidemiological studies that Western-type living conditions, e.g. reduced consumption of fermented food, substantial use of antibiotics and other drugs, and increased hygiene, are inversely associated with the rise in allergic diseases. The so-called hygiene hypothesis thus suggests that a lack of exposure to microbial stimulus early in childhood is a major factor involved in this trend (3,15–20).

Recent studies further indicate that certain characteristics of farming, such as farm milk consumption and frequent stay in animal sheds, may be especially protective against the development of allergic diseases (21–23). Anthroposophic lifestyle is characterized by biodynamic agriculture, ample use of organic foods and restrictive use of vaccinations, antibiotics, and antipyretics. Fecal microbiota of both anthroposophic and farm children diverge significantly from that of children with other lifestyles, pointing to the importance of the gut microbiota in the development of allergic disorders (24,25).

The gastrointestinal tract of the newborn baby is sterile. Soon after birth, however, it is colonized by many different microorganisms. Colonization is complete after ~1 wk, but the numbers and species of intestinal bacteria fluctuate markedly during the first several months of life (26). The composition of the gut microbiota differs between healthy and allergic infants and in countries with a high and low prevalence of allergies (27–31). Mode of delivery, either vaginal or through caesarean section, also has a major impact on early colonization patterns of the infant gut (32). The main changes associated with allergic trait

[11] Abbreviations used: IL, interleukin; Th2, type 2 T helper; Treg, regulatory T cell.

are less frequent colonization with lactobacilli and lower counts of bifidobacteria (27–30). These gut microbiota alterations are apparent within the first week of life preceding clinical symptoms, thus suggesting their causative role in allergic disorders (29,30). These differences have even been recorded during pregnancy in the vaginal flora of mothers of children who develop asthma during early childhood (33,34). A recent prospective study from 3 European birth cohorts found, however, no differences in gut microbiota by culture-dependent analysis of fecal samples among infants developing or not developing atopic eczema and food allergy (32). On the contrary, a subgroup analysis of the cohort by cultivation-independent techniques indicated a significantly lower diversity in the gut microbiota of 1-wk-old neonates who later manifested atopic eczema than in neonates remaining healthy during the first 18 mo of life (35), highlighting once more that classical microbiological plating techniques are inappropriate for extensive characterization of the gut microbiota. Similarly, less diverse microbial communities were found among 5-y-old allergic children than among nonallergic children by using another culture-independent technique (36). The same study demonstrated that *Bifidobacterium catenulatum/pseudocatenulatum* prevail in nonallergic children. On the contrary, this particular bifidobacterial species was associated with atopic eczema in a nested case-control study conducted in a different age group, country, and disease population (37), highlighting the complexity of the situation. As the immune modulation properties of bacteria seem to be distinctly strain specific, it cannot be ruled out that the nature of the immune response induced by a specific strain plays a more important role than its classification.

Even though the microbiota hypothesis may not conclusively explain all observations and does not provide specific guidance on how to limit the allergy epidemic, it does provide a strong framework and rationale for using probiotics to modify the gut microbiota and thereby shaping the immune response of the host, especially in infancy. In addition, probiotics might also be considered for treatment of subjects already suffering from allergic disease on the basis of their immune modulation properties. This approach has typically been followed in trials aimed at reducing symptoms of respiratory allergies.

Expectations about developing probiotics to prevent or treat allergic diseases should remain realistic and consistent with the complexity of the studied situation, including the time point of disease progression (**Fig. 2**). However, even a partial but reproducible reduction of symptoms or decrease in the risk of allergy onset would correspond to an important contribution to the management of allergic manifestations.

Effects of probiotics in clinical studies of allergic diseases

Including the first publication in 1997, over 25 randomized, double-blind, placebo-controlled clinical trials have been conducted to study the effects of various probiotics on treatment and prevention of allergic diseases. In total, almost 3000 individuals (including those in placebo groups) have participated in these studies so far (**Table 1**) (38–68). This subject has been covered thoroughly in 3 recent reviews and 1 metaanalysis (37,69–71). Even though these reviews partly diverge in their conclusions, the consensus is that the evidence is stronger for prevention of atopic disease than for treatment of atopic eczema and that the probiotic approach certainly deserves to be further explored. In the case of food allergy, there is definitely a need to find alternative solutions to the currently recommended eviction diet (allergen avoidance). Of note, a systematic review of treatment trials of allergic rhinitis/asthma has been published recently (72).

Management of eczema and atopic eczema by probiotics

To date, randomized clinical trials of probiotics in allergic diseases have mostly focused on children with eczema and atopic eczema. These definitions have recently been revised by an international expert group as described above (1). In many of the studies published before the revision of the nomenclature, different definitions have been used, making direct comparisons between the studies difficult (Table 1). Probiotic strains and doses have also varied considerably between the studies. *Lactobacillus rhamnosus* GG is the strain that has been most studied. The first studies with this strain suggested a therapeutic effect both in eczema and atopic eczema (38,39), whereas the most recent reports show an effect only in patients suffering from atopic eczema (41) or no effect at all (44–46). In conclusion, most of the studies have been conducted in small numbers of patients and results have varied considerably, even with the same strain. This may be due to differences in the

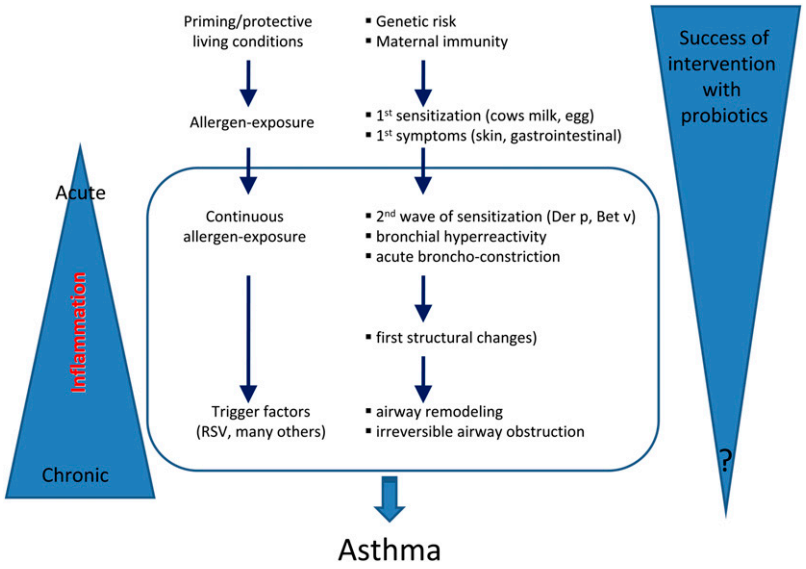

FIGURE 2 Sequence of events in the development of asthma. Priming living conditions leading to allergen exposure which, dependent on genetic and maternal factors, cause sensitization and symptoms of asthma. Following these initial acute inflammatory reactions, continuous allergen exposure leads to worsening of clinical symptoms, including airway remodelling. The window of successful intervention with probiotics is probably during the early stages of the disease, i.e. before exposure to allergens.

TABLE 1 Probiotics in the treatment and prevention of allergic disease[1]

Disease/marker	Reference	Participants	Type of probiotic(s)	Duration	Type of study	Outcome
Probiotics effects in clinical studies of eczema or atopic eczema						
Eczema/atopic eczema	Majamaa et al. (38)	27 infants	*Lactobacillus rhamnosus* GG	1 mo	R, DB, PC	Severity of atopic eczema decreased
Eczema/atopic eczema	Isolauri et al. (39)	27 infants	*L. rhamnosus* GG or *B. bifidum* Bb-12	2 mo	R, DB, PC	Severity of atopic eczema decreased
Eczema/atopic eczema	Rosenfeldt et al. (40)	43 children	*L. rhamnosus 19070 and L. reuteri* DSM122460	6 wk	R, DB, PC	Extent but not severity of atopic eczema decreased
Eczema/atopic eczema	Viljanen et al. (41)	230 infants	*L. rhamnosus* GG or a mixture of 4 probiotics	4 wk	R, DB, PC	Severity of atopic eczema decreased only in IgE-associated eczema in LGG group
Eczema/atopic eczema	Weston et al. (42)	53 infants	*L. fermentum* VRI-033 PCC	8 wk	R, DB, PC	Severity of atopic eczema decreased
Eczema/atopic eczema	Sistek et al. (43)	59 infants	*L. rhamnosus* and *B. lactis*	18 wk	R, DB, PC	Severity of atopic eczema decreased only in children sensitized to food
Eczema/atopic eczema	Brouwer et al. (44)	50 infants	*L. rhamnosus* GG or *L. rhamnosus*	3 mo	R, DB, PC	No effect
Eczema/atopic eczema	F-Ister-Holst et al. (45)	54 infants	*L. rhamnosus* GG	2 mo	R, DB, PC	No effect
Eczema/atopic eczema	Grber et al. (46)	102 infants	*L. rhamnosus* GG	12 wk	R, DB, PC	No effect
Probiotics effects in clinical studies of allergic rhinitis and asthma						
Asthma	Wheeler et al. (47)	15 adults	*L. acidophilus*	1 mo	DB, CO	No effect on clinical parameters
Allergic rhinitis	Helin et al. (48)	36 adults	*L. rhamnosus* GG	5.5 mo	R, DB, PC	No effect
Allergic rhinitis	Wang et al. (49)	80 adults	*L. paracasei-33*	1 mo	R, DB, PC	Quality of life improved
Allergic rhinitis	Peng et al. (50)	90 adults	*L. paracasei-33*	1 mo	R, DB, PC	Quality of life improved
Allergic rhinitis	Ishida et al. (51)	49 adults	*L. acidophilus* L-92	8 wk	R, DB, PC	Decrease in nasal symptoms
Allergic rhinitis	Xiao et al. (52)	44 adults	*B. longum* BB 536	13 wk	R, DB, PC	Decrease in nasal symptoms
Allergic rhinitis	Tamura et al. (53)	109 adults	*L. casei* strain Shirota	10 wk	R, DB, PC	No effect
Asthma and Allergic rhinitis	Giovannini et al. (54)	187 children	*L. casei* DN114001	12 mo	R, DB, PC	Decrease in rhinitis episodes
Serum ECP, Ig E, eosinopenia	Moreira et al. (55)	141 adults	*L. rhamnosus* GG	4 mo	R, DB, PC	No effect
Inflammatory markers in Allergic rhinitis	Ivory et al. (56)	10 adults	*L. casei* strain Shirota	5 mo	R, DB, PC	Decrease in antigen-specific IgE and antigen-induced cytokines
Probiotics effects in preventive studies for atopic disease						
Prevention of eczema/ Atopic eczema	Kalliomôki et al. (57)	132 infants	*L. rhamnosus* GG	1 mo before and 6 mo after birth	R, DB, PC	Incidence of eczema decreased during the first 2 y of life
Prevention of eczema/ Atopic eczema	Kalliomôki et al. (58)	107 infants	Same cohort	Same cohort	same cohort	Incidence of eczema decreased during the first 4 y of life
Prevention of eczema/ Atopic eczema	Kalliomôki et al. (59)	116 infants	Same cohort	Same cohort	same cohort	Incidence of eczema decreased during the first 7 y of life
Prevention of allergic disease	Kukkonen et al. (60,61)	925 infants	4 probiotic strains and galactoolico-saccharide (a prebiotic)	1 mo before and 6 mo after birth	R, DB, PC	Incidence of eczema and atopic eczema decreased during the first 2 y of life. No effect at 5 y (except decrease in atopic eczema in cesarean-delivered children)

(*Continued*)

TABLE 1 Continued

Disease/marker	Reference	Participants	Type of probiotic(s)	Duration	Type of study	Outcome
Prevention of eczema/ Atopic eczema	Taylor et al. (62)	188 infants	*L. acidophilus* (LAVRI-A1)	6 mo postnatally	R, DB, PC	No effect on incidence of eczema, but increased allergic sensitization
Prevention of allergic disease	Abrahamsson et al. (63)	188 infants	*Lactobacillus reuteri* ATCC55730	1 mo before and 12 mo after birth	R, DB, PC	Less atopic eczema during the second year of life
Prevention of eczema/ Atopic eczema	Kopp et al. (64)	94 infants	*L. rhamnosus* GG	1 mo before and 6 mo after birth	R, DB, PC	No effect on atopic eczema or sensitization, but increased risk for recurrent wheezy bronchitis
Prevention of eczema/ Atopic eczema	Wickens et al. (65)	474 infants	*L. rhamnosus* HN001 or *B. animalis* subs. *lactis* strain HN019	1 mo before and 6 mo after birth	R, DB, PC	Lactobacillus decreased risk of atopic eczema, whereas Bifidobacterium had no effect by 2 y. No effect on sensitization
Prevention of eczema/ Atopic eczema	Soh et al. (66)	253 infants	*B. longum* (BL999) and *L. rhamnosus* LPR	6 mo after birth	R, DB, PC	No effect on eczema or sensitization during the first year of life
Prevention of eczema/ Atopic eczema	West et al. 2009 (67)	179 infants	*Lactobacillus paracasei* F19	10 mo (between 4th and 13th mo of life)	R, DB, PC	LF19 decreased the cumulative incidence of eczema and increased the interferon-γ/IL-4 mRNA ratio in polyclonally stimulated peripheral blood T cells at 13 mo.
Prevention of eczema/ Atopic eczema	Niers et al. 2009 (68)	102 infants	Mixture of *B. bifidum* W23, *B. lactis* W52, and *Lc. lactis* W58	6 wk before and 12 mo after birth	R, DB, PC	Reduction of eczema (partly parental reported) during first 3 mo, linked to decreased in vitro IL-5 and IL-13 levels. After 3 mo, incidence of eczema and IgE levels similar in the 2 groups. No reduction of cumulative incidence of atopic eczema.

[1] CO, cross-over; R, randomized; DB, double blinded; PC, placebo controlled.

clinical set-up (different target populations, countries, and intervention schemes and, importantly, additional treatments such as topical treatment or feeding hydrolyzed infant formulae) but also, and this should be stressed, different probiotic preparations or formulations. Thus, at present, a specific probiotic strain cannot be recommended for the general treatment of eczema or atopic eczema.

Management of allergic rhinitis and asthma by probiotics

Apart from a small trial with *Lactobacillus acidophilus* in adult asthmatics (47), a Finnish study with allergic marathon runners using *Lactobacillus* GG (55) and an Italian study with children between the ages of 2 and 5 y supplemented with *Lactobacillus casei* DN-114 001 (54), all the other randomized, placebo-controlled clinical trials of probiotics in respiratory allergic diseases (48–53,56) have been conducted in teenagers and adults with allergic rhinitis (Table 1).

A few studies suggest that certain probiotic strains (*B. longum* BB536, *L. paracasei* Lp33, and *L. acidophilus* L92) may alleviate symptoms of patients and improve their quality of life (49–52). The only strain with an antiinflammatory effect, *Lactobacillus casei* strain Shirota (56), offered no relief of symptoms in another trial (53). The Italian study found that *Lactobacillus casei* DN-114 001 supplementation decreased the number of rhinitis episodes in children with allergic rhinitis (54). However, these episodes were reported by parental diary only and their cause (i.e. viral or allergic) was not studied. Other methodological shortcomings mean that firm conclusions cannot be drawn about the possible therapeutic effects of probiotics in these studies. These flaws include small study populations, use of nonvalidated symptom scores, and no reporting of the possible use of antiallergic medications during the study period. Additional comments on these studies can be found in the review of Vliagoftis et al. (72).

Preventive studies for atopic disease

From a theoretical point of view, it would be an ideal situation if probiotics could be used in the prevention of allergic diseases. Therefore, it is not surprising that there are several ongoing preventive trials to be completed during the next few years (69). To date, the results of 8 prospective preventive studies with different *Lactobacillus* or *Bifidobacterium* strains (or mixture) in children at high risk for allergic diseases have been published (57–59,62–66). In addition, 1 trial was conducted with a mixture of 4 probiotic strains and prebiotic galactooligosaccharides (60,61) (Table 1). The hallmark Finnish study demonstrated that administration of *L. rhamnosus* GG for 1 mo before and 6 mo after birth was associated with a significant reduction in the cumulative incidence of eczema during the first 7 y of life (57–59). There were no preventive effects on atopic sensitization and onset of respiratory allergic diseases. A subgroup analysis of the cohort found that maternal probiotic supplementation during pregnancy and breast-feeding increased the immunoprotective potential of breast milk, as assessed by the amount of TGFβ2 in the milk, and decreased the risk of developing atopic eczema during the first 2 y of life (73). The Finnish study conducted with a mixture of 4 probiotics and prebiotics reported a similar although not so distinct preventive effect on eczema and atopic eczema (60). This effect, however, lasted up to the age of 5 y only in children delivered by caesarean section (61). Nevertheless, in a very recent German study, *Lactobacillus* GG supplementation was not associated with a decreased risk of eczema but with an increased risk for recurrent ($\geq$5) episodes of wheezing bronchitis during the first 2 y of life (64). Two recent studies with different lactobacilli also produced conflicting results. Use of *Lactobacillus reuteri* ATCC55730 for 1 mo before and 12 mo after birth was associated with a reduced risk of atopic eczema during the second year of life. This probiotic strain also reduced atopic sensitization among infants from allergic mothers (63). On the contrary, administration of *Lactobacillus acidophilus* LAVRI-A1 during the first 6 mo of life did not reduce the risk of atopic eczema and increased the risk of atopic sensitization in high-risk children (62). In a preventive study in high-risk babies, 2 different probiotic preparations were compared and it was found that supplementation with *Lactobacillus rhamnosus* HN001, but not *Bifidobacterium animalis subsp lactis* HN019, substantially reduced the cumulative prevalence of eczema by 2 y (65). A mixture of 3 probiotics strains, *Bifidobacterium bifidum* W23, *Bifidobacterium lactis* W52, and *Lactococcus lactis* W58 selected in vitro, was used by Niers et al. (68) for primary prevention of allergic disease. Probiotics were administered 6 wk prenatally to mothers of high-risk children and to their offspring for the first 12 mo 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 mo of life in infants receiving probiotics. The preventive effect on the incidence of eczema was reported to last for 2 y and seemed to be established during the first 3 mo of life. Of note, a recently published Swedish study demonstrated that administration of *Lactobacillus casei* F19 during weaning significantly reduced the incidence of eczema, indicating that proper timing of the probiotic intervention is a critical factor (67). This study also supports the notion that there is more than a single window of opportunity to manage allergic diseases.

Allergy animal models: what can we learn from them?

Although there is a general consensus that probiotic effects have to be demonstrated in human trials conducted in the final target population, research in the allergy area may still benefit from preclinical work performed in animal models (**Table 2**). The number of available probiotics strains, the range of allergic manifestations, and the uncertainty about the best window of intervention (i.e. prenatal, neonatal, weaning, early childhood, adult) often hampers the decision to directly proceed with a clinical intervention study. In addition, the increasing ethical constraints may limit the possibility to perform human studies, especially in infants, without preclinical data. Moreover, it is unlikely that a single strain or a combination of specific strains will protect against all manifestations of the allergic syndrome at different periods of life.

Different animal models, including guinea pigs, monkeys, dogs, rats, and mice, and numerous sensitization protocols to food, contact, and aeroallergens are used to establish an allergic/asthma-like phenotype. They have been used as tools in an attempt to provide insights into the relationship between microbiota and/or intervention with probiotics to prevent or manage allergies. Rodent models have been widely used to gain further knowledge of the mechanisms leading to tolerance induction or allergy onset. Many of the immune cells and mediators involved in the development of allergy and hypersensitivity reactions in humans have a counterpart in experimental animals. As mentioned above, the interaction of the developing immune system with the microbiota seems to play a decisive role for the generation of appropriate immune responses later in life.

TABLE 2 Basis for studying probiotic interventions in mouse models

Basis for studying probiotic interventions in mouse models	
Advantages	Drawbacks
Establish preclinical data for more than a few strain or mixes.	Mice do not develop allergies spontaneously, therefore use of potent and rather artificial sensitization protocols and large number of mice
Head-to-head comparison of performance of new candidate strains	Difficulty in comparing similar models from different laboratories
Possibility to conduct dose-response curves	Mouse microbiota differs substantially from the human one
Investigation of different time windows for intervention	Extrapolation of effective probiotic dose to humans
Dissect key signaling pathways for tolerance induction by probiotics (mechanistic studies)	Difficulty to link clinical symptoms to biological/immunological markers (in some models, no individual correlation between all markers), in particular IgE levels. In this respect, similar situation in humans.
Discover key immune players in tolerance induction/allergy onset and leverage to human studies; take advantage of genetically modified mice lines	Predictive value not truly established
Clarification of the immune modulation capacity of an antiallergy candidate	
Identification of the active compounds of the probiotic strains	
Analyze the impact of the genetic background	
Long-term observations remain short in time	
Obtain approval of ethical committee for human trials.	

However, animal studies have mostly been performed in young adult mice with administration of probiotics starting around weaning. Interestingly, recent papers have begun to investigate the impact of different intervention windows, i.e. comparing perinatal and postnatal treatment (74,75).

Recommendations and gaps in human trials with probiotics in preventing and managing allergy

The current evidence summarized above suggests that certain probiotic strains may play a role in the prevention and management of atopic disease. To consolidate these observations, additional studies are needed where the following points should be considered carefully: *1*) Diagnosis of atopic diseases should be based on uniform criteria in different studies and clusters of subpopulations should be identified. *2*) Genotyping of study patients in relation to different genes predisposing to allergic diseases may help to find patients that might especially benefit from probiotic intervention. For example, 2 independent mutations in the gene encoding the epidermal protein filaggrin have been shown to be strong predisposing factors for childhood eczema (76). Of note, these same mutations have recently been demonstrated to be associated not only with eczema-associated asthma susceptibility but also with asthma severity independent of eczema status (77). More generally, any means to better stratify or select defined subpopulations of subjects (e.g. patients with food allergy as a separate group) would help in clarifying the potency and limits of probiotic interventions against allergic diseases. *3*) Symptom scores of allergic diseases in different studies should be similar and thoroughly validated. *4*) Antiallergic and other medications such as antibiotic use should be closely monitored and reported, as well as other possible confounding factors, including living conditions (rural vs. urban, siblings, pets, weaning habits, etc.).

The following knowledge gaps have been identified: *1*) Effects of different probiotic strains or combinations thereof on different intervention windows should be studied and compared. *2*) Despite numerous data coming from in vitro and animal studies, mechanisms of probiotic action in clinical studies remain to be elucidated. More studies such as the one conducted by Roessler et al. (78) to examine the effect of probiotics on the immune system of different types of populations should be initiated. *3*) In addition to atopic sensitization, other objective markers of allergic diseases are lacking. It should, however, be pointed out that atopic sensitization is considered more likely a marker rather than a definite causative factor for allergic respiratory diseases and atopic eczema, and its central role in allergic diseases has been at least partly brought into question lately (79–81). Therefore, more specific and better markers based on pathogenesis of these disorders are urgently needed.

Conclusions

After a decade of clinical research in the field of allergy and probiotics, no general recommendations for their use in clinical practice can be given. There are a few clinical trials with outstanding findings but also some studies reporting negative results. To date only a limited number of strains have demonstrated benefits, mostly in the area of preventing allergic diseases. It should be kept in mind, however, that this area of research is relatively new, as the first probiotic intervention trial dates back to 1997 (38). The current state of the art most probably reflects the inherent complexity of the allergic syndrome, the difficulty in taking confounding factors into account (69), the varying characteristics and potentials of different probiotics strains, and the still-insufficient understanding of how specific probiotics may counteract different types of immune dysfunction found in allergic diseases in vivo. Better alignment of clinical designs as suggested above would help to render results of studies conducted with different strains, possibly in different populations and at different time points of disease progression, more comparable. This would allow us to reduce controversy in the area and promote rapid progress in this promising field while allowing to perform metaanalyses on adequate data sets. Keeping in mind realistic expectations and the recommendations proposed above and by other experts, we postulate that in the future, probiotic strains properly selected for specific allergic manifestations in well-defined target populations might become an efficient tool in the fight against allergic diseases.

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