

Probiotics for the prevention or treatment of allergic diseases

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This review addresses the effects of probiotic bacteria on immune development and the role in the treatment and prevention of allergic disease. Although there is a sound theoretical basis for anticipating benefits, there are currently insufficient data to recommend probiotics as a part of standard therapy in any allergic conditions. Furthermore, although there have been several studies to show a benefit in prevention of atopic eczema, other studies have failed to support this. None of the studies has shown any clear preventive effect on sensitization, nor any allergic disease other than eczema. The term “probiotic” is often used loosely to include bacterial strains with little documented immunomodulatory capacity or controlled studies to support the claims. It is not known whether effects in experimental systems have any clinical relevance. Finally, very little is known about this large, complex internal ecosystem. Explanations for the varied results between studies include host factors (including genetic differences in microbial responses and allergic predisposition) and other environmental factors, such as general microbial burden, individual microbiota, diet (including consumption of prebiotic substances), and treatment with antibiotics. As more studies are completed, these factors are likely to make robust meta-analyses problematic to perform. (*J Allergy Clin Immunol* ■■■■;■■■;■■■-■■■.)

Key words: Allergic disease, gut microbiota, probiotics, prebiotics, immune development, allergy prevention, atopic dermatitis, oral tolerance

An apparent decline in microbial exposure during early childhood is one of the most plausible causes of the escalating rates of allergic disease. Epidemiologic support for this hypothesis has been progressively consolidated by a growing understanding of effects of microbial factors on immune development. These observations have logically

Abbreviations used

DC: Dendritic cell
SCORAD: Scoring Atopic Dermatitis
TLR: Toll-like receptor

led to the experimental use of microbial products to prevent or inhibit allergic immune responses and associated disease. As summarized in Table I, the interest in using intestinal microbionics is based on key observations that these are essential to normal immune development and oral tolerance, and that early differences in colonization have been noted in neonates that go on to develop allergic disease (see review¹). Together with observations that presymptomatic immunologic differences are also evident in subsequently allergic neonates (see review²), this provided a strong basis for using live intestinal strains to influence early colonization and subsequent patterns of immune development. These concepts appeared to be supported by the initial studies that reported benefits using probiotics (strains with other documented health benefits in human beings) in both prevention³ and treatment⁴ of early allergic disease.

THE ROLE OF MICROBIOTA IN EMERGING MODELS OF ALLERGY PATHOGENESIS

It is now proposed that allergic disease results from a fundamental failure of underlying immune regulation. Microbial exposure arguably provides the strongest environmental signal for normal postnatal maturation of the immune system and also induces the maturation of antigen presenting cells and T-regulatory cells, which are essential for programming and regulating the T-cell response. It appears likely that microbial activation of regulatory pathways through microbial pattern recognition molecules (Toll-like receptors [TLRs]) plays a central role in reducing the risk of immunologically mediated disease, including T_H2-mediated allergic responses, and possibly also T_H1-mediated autoimmune disease, such as type I diabetes. Thus, reduced microbial exposure may be contributing to the rising rates of this wide spectrum of immune diseases. This is likely to be of greatest relevance in early life when immune programming is initiated and less significant in relation to a mature immune system in older children and adults.

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TABLE I. Basis for using probiotics in allergic disease

Observations supporting a role for probiotics in inhibiting allergic responses in early life

1. Epidemiologic links between less exposure to microbes and allergic disease, and protective effects of higher microbial burden
2. Intestinal microbiota are the largest source of microbial exposure through early immune development
3. Intestinal microbiota appear to be essential for development of oral tolerance
4. Changing patterns of microbiota with progressive Westernization and links with allergic disease (see review¹)
5. Differences in perinatal colonization in children who go on to develop allergic disease (see review¹)
6. Perinatal administration of probiotics associated with anti-inflammatory and immunoregulatory effects on immune function (Table II)
7. Presymptomatic immune dysregulation evident in infants and newborns who later develop allergic disease, suggesting that allergy prevention should be initiated early²
8. Initial studies with probiotics suggested promise in the prevention³ and early treatment of allergic disease⁴

The gut microbiota is the major source of microbial exposure, composed of 10^{14} microorganisms, or 10 times the number of cells in the entire body with a 30 times larger total genome than the human genome. Microbial colonization of the gastrointestinal tract, linked with life-style and/or geographic factors, may be important a determinant of the heterogeneity in disease prevalence throughout the world,⁵ and ongoing cohort studies are focusing in detail on this complex question. These suggestions are supported by observations that germ-free mice do not develop tolerance in the absence of a gut microbiota in addition to the observed differences in the composition of the gut microbiota between infants living in countries with a high and a low prevalence of allergy and between healthy infants and infants with allergy (see summary⁵).

PROBIOTICS: MECHANISMS OF ACTION

Probiotics are defined as living microorganisms which, on ingestion in certain numbers, exert health benefits beyond inherent general nutrition. There is now good evidence that certain strains of lactobacilli and bifidobacteria can influence immune function through a number of different pathways (summarized in Table II) including effects on enterocytes, antigen presenting cells (including both circulating monocytes and local dendritic cells [DCs]), regulatory T cells, and effector T and B cells. Importantly, however, the relationship between the various reported effects (Table II) and clinical consequences of treatment are unknown. Because there are very few studies in which several allegedly probiotic strains have been compared, it is not known to what extent a finding using a certain bacterial strain is relevant for other strains, even of the same species. To date, there are only a few strains, limited to lactobacilli, that have been reasonably well documented in clinical studies, mostly against infectious gastroenteritis and lactose intolerance.

Locally in the gut, there is evidence that commensal gut bacteria help reduce local inflammation,⁶ and at least 1 probiotic strain has the capacity to maintain the integrity of the intestinal barrier,⁷ potentially reducing systemic antigen load. At least some of the anti-inflammatory effects appear to be mediated through TLR, including TLR⁹ and possibly TLR2 and TLR4 expressed on enterocytes. Intestinal microbiota also promote enterocyte production

of TNF- β and prostaglandin E₂, which promote the development of tolerogenic DCs.⁹ Other studies have also shown that probiotics directly enhance the activity of human DC populations^{10,11} to promote T_H1 differentiation.¹² Consistent with notions that bacteria promote regulatory function, there is also preliminary evidence that probiotics promote immunoregulatory activity in the gut. In animal studies, probiotic supplementation can induce regulatory T-cell populations (bearing TGF- β),¹³ and human studies also suggest an increase in the *in vitro* production of regulatory cytokines (IL-10) after probiotic ingestion.¹⁴ The effects may be limited to certain species, as indicated by a recent study in which *Lactobacillus reuteri* and *Lactobacillus casei*, but not *Lactobacillus plantarum*, primed monocyte-derived DCs to drive the development of regulatory T cells.¹⁵ These regulatory T cells produced increased levels of IL-10 and were capable of inhibiting the proliferation of bystander T cells in an IL-10-dependent fashion. Interestingly, the 2 former species, but not *L. plantarum*, bound the C-type lectin DC-specific intercellular adhesion molecule 3-grabbing nonintegrin, and blocking antibodies to DC-specific intercellular adhesion molecule 3-grabbing nonintegrin inhibited the induction of the regulatory T cells by these probiotic bacteria.

Intestinal microbiota also influences IgA production in distal sites (respiratory tract). The gastrointestinal tract makes up a critical part of the integrated common mucosal immune system, which includes mucosal surfaces across anatomically remote locations (namely the gastrointestinal tract and respiratory tract). It is well recognized that mucosa-homing IgA-producing B cells and effector T cells mature in the gut mucosa before seeding to distal mucosal sites in the respiratory tract. This provides a possible explanation for how gut microbiota appear to enhance systemic T_H1 responses^{16,17} and IgA production in remote tissues.¹⁸

It is less clear how probiotics influence other bone marrow-derived populations of cells that do not traffic directly through the gut. Circulating monocytes in infant animals mature at significantly different rates depending on enteric microbiota exposure,¹⁹ with 2-fold lower function in germ-free animals.²⁰ Potential marrow effects are supported by studies showing that changes in gut microbiota have effects on bone marrow CD34⁺ progenitor populations entering the circulation.²¹ Clearly a better understanding of the systemic effects of gut microbiota is

TABLE II. Immunologic pathways affected by probiotics

Pathway	Documented effects in human beings and/or animals	Proposed mechanism of immunomodulation
Local effects		
Effects on mucosal barrier	Repair and maintenance of intestinal barrier and tight junctions Increased mucous production	Reduced permeability and reduced systemic penetration of allergens/antigens ⁷
Enterocytes	Reduced cell signaling via nuclear factor- κ B local inflammation ⁶ Increased production of TGF- β and prostaglandin E ₂ , which promote tolerogenic DCs ⁹	Reduced local inflammation/promotion of tolerogenic conditions
Innate mucosal recognition (TLR)	Anti-inflammatory effects of probiotics mediated by TLR9 ⁸ Possible changes in TLR2 <i>in vitro</i> ³⁷	Inhibition of T _H 2 allergic responses: mechanisms unclear TLR2/4 agonists shown to reduce inflammation in murine lung
DCs	Increased activity of DCs in human gut ¹⁰	Promotes tolerogenic DC (IL-10 production)
Effector T cells	T _H 1 skewed responses observed ¹²	Inhibition of T _H 2 differentiation? Effects of T-cell trafficking?
Treg	CD4 ⁺ CD28 ⁺ T cells associated with oral tolerance T-cell-producing IL-10 and TGF- β associated with oral tolerance Probiotics: Increased TGF- β (T _H 3) Treg ¹³	TGF- β produced locally (including by enterocytes) promotes tolerogenic DC, local IgA, and Treg activity
B cells and antibodies	Colonization: increased lymphoid tissue Probiotics: increased local IgA production	Promotes tolerogenic microenvironment (as above); IgA may reduce systemic antigen load
Systemic effects		
Monocytes	Probiotics: increased circulating monocytes ^{19,20}	Mechanisms not known
T cells	Probiotics: increased T _H 1 differentiation	Secondary to effects on T cells trafficking through gut?
B cells/IgA	Probiotics: increased IgA production in other tissues (respiratory tract) ¹⁸	Secondary to effects on B cells trafficking through gut?
Stem cells	Probiotics: increased circulating bone marrow derived CD34 ⁺ stem cells ²¹	Mechanisms not known

Treg, Regulatory T cells.

necessary to explore causal pathways and the potential of probiotics as preventive and therapeutic agents.

EVIDENCE OF CLINICAL BENEFITS OF PROBIOTICS IN TREATMENT OF ALLERGIC DISEASE

Most studies to explore the role of probiotics in the treatment of allergic disease have focused on early manifestations of allergy, namely food allergy and atopic dermatitis. Studies in older individuals with established respiratory disease have failed to show any improvement in asthma²² or allergic rhinitis,²³ although one larger study reported improved quality of life in patients with allergic rhinitis.²⁴ This is consistent with findings in animal studies in which microbial products have more significant effects when immune responses are still developing than once sensitization is established.

There are now a number of studies that have addressed use of probiotics in young children with atopic dermatitis with encouraging (but not strong) effects.^{4,25-28} The studies are limited to 3 species of lactobacilli. The first study to address this demonstrated a clinical improvement (> 50% reduction in Scoring Atopic Dermatitis [SCORAD] index) in infants with atopic dermatitis and cow's milk allergy when fed probiotic-fortified hydrolyzed whey formula (n = 13) during the 1-month treatment period compared with a placebo group (which also subsequently improved).²⁵ The second study included children with mild disease (median SCORAD of 16 at inclusion) and documented a complete resolution in all participants after 6 months, although this occurred more rapidly in the group receiving probiotics (*Lactobacillus* GG [n = 9] or *Bifidobacterium lactis* [n = 9]).⁴ These were both very small studies and only included infants with mild disease who are less likely to be atopic and less likely to develop persistent cutaneous disease or new respiratory allergy.

More recently, a further study in a larger cohort²⁶ reported a slightly greater reduction in SCORAD (-26.1 vs -19.8 ; $P = .036$) after 4 weeks of treatment in IgE sensitized infants with atopic dermatitis (age around 6 months) receiving the same probiotic strain (*Lactobacillus* GG). It is of note that clinical effects of this probiotic were only seen in children with evidence of allergic sensitization and not in children with atopic dermatitis but no sensitization who received the same probiotic. This suggests that atopic dermatitis is a heterogeneous condition and that the effect of immune modifying agents such as probiotics will depend on the pattern of disease. A number of subsequent studies with other strains of lactobacilli have also suggested some favorable effects on atopic dermatitis extent and severity. In one of the studies,²⁷ in which *Lactobacillus rhamnosus* and *L reuteri* were given in combination, 56% of the patients experienced improvement of the eczema compared with 15% in the placebo group ($P = .001$). The second study demonstrated improved SCORAD in 92% of the children receiving a *L fermentum* strain compared with 63% in the placebo group ($P = .01$).²⁸ In general, however, the effects are not strong or not evident at all.²⁹

In 2 studies, probiotic administration (*Lactobacillus rhamnosus* GG¹⁷ and *Lactobacillus fermentum* PCC¹⁶) was associated with increased polyclonal T_H1 IFN- γ responses in the infants. Of note, the improvement in atopic dermatitis was directly proportional to the increase in IFN- γ responses to *Staphylococcus enterotoxin* B ($r = 0.445$; $P = .026$).¹⁶

In summary, although there are studies suggesting favorable effects of probiotics on atopic dermatitis, it is generally accepted that larger, controlled studies with well defined probiotic bacteria and perhaps mixtures of several such strains are needed to determine the role of these products in therapy. The lack of effect of these products in older individuals (with asthma and allergic rhinitis)²²⁻²⁴ suggests that any beneficial effects could be limited to early life before allergic disease is established.

ROLE OF PROBIOTICS IN PREVENTION OF ALLERGIC DISEASE

It is logical from an immunologic standpoint to explore the benefits of probiotics very early in life when immune responses are still developing, and there are now a number of studies addressing the role of probiotics in primary allergy prevention. The first study to assess the role of probiotics in this context administered *L rhamnosus* to mothers (starting 2-4 weeks before delivery) and to infants in the first 6 months of life. This was reported to reduce the incidence of eczema at 2 years by around 50%.³ Although the cumulative effect on eczema was still evident at 4 years, there was no reduction in respiratory allergy, IgE levels, or allergic sensitization.³⁰ Effects on underlying immune response were not reported, and a number of methodologic concerns have been raised about the study.³¹ A major concern was that many of the

children (28 out of 64) included in the probiotic supplement group did not receive probiotics directly, because the supplement was given to the mother if babies were breast-fed. These issues have made the results difficult to interpret.

There are now 3 other published studies and at least 7 other studies still in progress (summarized in Table III) to examine the effects of various probiotic strains for allergy prevention, most using direct infant supplementation. The first of these (using *Lactobacillus acidophilus*) failed to show any reduction in allergic disease despite changes in colonization.³² Rather, there was a concerning increase in sensitization and in IgE-associated atopic eczema. The second showed a reduction in atopic eczema (odds ratio, 0.66; 95% CI, 0.46-0.95; $P = .025$) but no effects on sensitization or other allergic disease.³³ Of note, this study used a combination of strains and prebiotic galacto-oligosaccharides (as detailed in Table III). The third study showed no effect of *L reuteri* on the prevention of allergic disease or sensitization.³⁴ However, subgroup analyses showed that probiotics were linked with less IgE-associated atopic eczema (8% vs 19% in placebo-treated group; $P < .05$) and less sensitization in a subgroup with atopic mothers (17% vs 31%; $P < .05$). Prospective analysis of these populations is necessary to assess long-term outcomes, particularly any possible effects on respiratory allergy. The results of the other studies (Table III) are awaited with interest. At this stage it is not appropriate to recommend probiotics for allergy prevention. Despite all of the immunomodulatory effects described in experimental models, so far none of these studies has shown any clear effect on preventive sensitization or any allergic disease other than eczema.

FACTORS THAT MAY ACCOUNT FOR VARIED EFFECTS OF PROBIOTICS IN DIFFERENT STUDIES

Possible explanations for the varied results include differences in the bacterial strains used, host factors that could influence microbial responsiveness and allergic propensity, and other environmental factors that could influence colonization or immune development (Fig 1). First, there are significant variations in the strains claimed to be probiotic. It is also of note that the studies that suggested preventative effects started supplementation in pregnancy,^{3,33,34} whereas the study that showed increased sensitization did not.³² This may indicate that the supplementation to the mothers in late pregnancy is of a crucial importance. It is of interest to note that in 1 study, the levels of IL-10 were higher and TGF- β lower in colostrum of mothers receiving a probiotic compared with placebo-treated mothers.³⁵ Second, there are differences in host susceptibility to microbial influence and to colonization with a particular strain of bacteria. Functional genetic polymorphisms in microbial recognition pathways are well described (including TLR), and it is likely that this could result in individual variation in the effects of probiotics.

TABLE III. Summary of probiotic primary prevention studies (completed and in progress)

Investigators and location of study	Study protocol				Outcomes			
	Population characteristics	Organisms and dosage	Prenatal duration	Postnatal duration	Reduction in eczema	Reduction in sensitization	Reduction in other AD	Effect on colonization
Kalliomäki, Isolauri, and others, Turku, Finland ^{3,33}	Any first-degree relative with allergic disease n = 132 completed (of initial 159)	<i>L. rhamnosus</i> GG, 1×10^{10} CFU daily Only to mother if breast-feeding postnatally	Yes 2-4 wk before delivery	6 mo *only directly to baby if not breast-feeding	Yes (at 2 and 4 y)	No	No	Yes
Taylor, Prescott, and others, Perth, Australia ³²	Mother with SPT ⁺ allergic disease n = 189 completed (of initial 230)	<i>L. acidophilus</i> (3×10^8 CFU daily)	No	6 mo (direct to infant)	No (at 1 y)	No†	No	Yes
Kukkonen, Kuitunen, and others, Helsinki/Tampere, Finland ³³	One or both parents with allergic disease n = 925 completed (of initial 1223)	<i>L. rhamnosus</i> GG and LC705 (both 5×10^9 CFU twice daily); and <i>Bifidobacterium breve</i> and <i>Propionibacterium freudenreichii</i> (both 2×10^9 CFU twice daily)	Yes 2-4 wk before delivery	6 mo (direct to infant)*	Yes (at 2 y)	No	No	Yes
Abrahamsson, Oldaeus, and others, Linköping, Sweden ³⁴	Any first-degree relative with allergic disease n = 188 completed (of initial 232)	<i>L. reuteri</i> (1×10^8 CFU daily)	Yes 2-4 wk before delivery	12 mo (direct to infant)	No‡ (at 2 y)	No‡	No	Not known
Kopp and others, Germany	Any first-degree relative with allergic disease n = 94 completed (of initial 102)	<i>L. rhamnosus</i> GG, 1×10^{10} CFU daily To mother if breast-feeding postnatally for 3 mo and then to the neonates for additional 3 mo	Yes 4-6 wk before delivery	6 mo	Study complete Clinical analysis complete (awaiting publication)			
					No difference in proliferative response or T-cell reactivity in cord blood and in maternal blood between serum and placebo groups			

TABLE III. (Continued)

Investigators and location of study	Study protocol				Outcomes			
	Population characteristics	Organisms and dosage	Prenatal duration	Postnatal duration	Reduction in eczema	Reduction in sensitization	Reduction in other AD	Effect on colonization
Thornton, Morgan, and others, Swansea, United Kingdom	Any first-degree relative with allergic disease n = 600 intended	<i>Lactobacillus salivaris</i> (6.25×10^8 CFU daily) and <i>Lactobacillus paracasei</i> (1.25×10^8 CFU daily) and <i>Bifidobacterium infantis</i> (1.25×10^8 CFU daily) and <i>Bifidobacterium bifidum</i> (1.25×10^8 CFU daily)	Yes 2-4 wk before delivery	6 mo (direct to infant regardless of feeding method)	Study not complete Outcomes will be assessed at 6 mo, 2 and 5 y			
Wickens, Crane, and others, Wellington and Auckland, New Zealand	One or both parents with allergic disease n = 450 intended	<i>L rhamnosus</i> (1×10^{10} CFU daily) or <i>B lactis</i> (1×10^{10} CFU daily)	Yes 2-5 wk before delivery	2 y (to infant regardless of feeding method)	Study not complete Outcomes will be assessed at 3,6, 12, 18, and 24 mo			
Tang and others, Melbourne, Australia	Any first-degree relative with allergic disease n = 200 intended	<i>L rhamnosus</i> (2×10^{10} CFU daily)	Yes 2-4 wk before delivery	No (only to mother)	Study not complete Outcomes will be assessed at 3,6, 12, and 24 mo			
Skek, Aw, and others, Singapore	Any first-degree relative with SPT ⁺ allergic disease n = 300 intended	<i>L rhamnosus</i> (1×10^9 CFU daily) and <i>Bifidobacterium longum</i> (6×10^8 CFU daily)	No	6 mo (in infant formulae)	Study not complete Outcomes will be assessed at 1, 3, 6, 12, and 24 mo and 5 y			
Niers, Rijkers, Hoekstra, and others, Utrecht, The Netherlands	Past or present atopic disease in either mother or father plus at least 1 sibling n = 120 intended	<i>Lactococcus lactis</i> <i>Bifidobacterium infantis</i> <i>Bifidobacterium bifidum</i> (all 1×10^9 CFU daily)	Yes 4 wk before delivery	12 mo (direct to infant)	Initial assessment at 3 mo now completed (awaiting publication) Study not complete			

TABLE III. (Continued)

Investigators and location of study	Study protocol				Outcomes			
	Population characteristics	Organisms and dosage	Prenatal duration	Postnatal duration	Reduction in eczema	Reduction in sensitization	Reduction in other AD	Effect on colonization
Lau, Wahn, Hamelmann, Berlin, Germany	Infants at age 4 wk with at least 1 atopic parent n = 650	<i>Streptococcus faecalis</i> DSM 16440 and <i>Escherichia coli</i> DSM 17252 (combined at 1.5-4.5 × 10 ⁷ daily)	No	6 mo (wk 5 to end of 7th mo) (direct to child)	Primary outcome: effect on eczema at age 7 and 12 mo; follow-up period after 6-mo treatment period up to age 3 y Secondary outcome: sensitization and other allergic symptoms; gut flora will be studied§			

AD, Allergic disease; CFU, Colony-forming units.

*Probiotic group also received prebiotic supplement (galacto-oligosaccharides).

†Sensitization more common in probiotic group.

‡Probiotics: less IgE-associated eczema in the second year, and less sensitization in subgroup with atopic mothers.

§This study is using heat-killed (rather than live) bacteria.

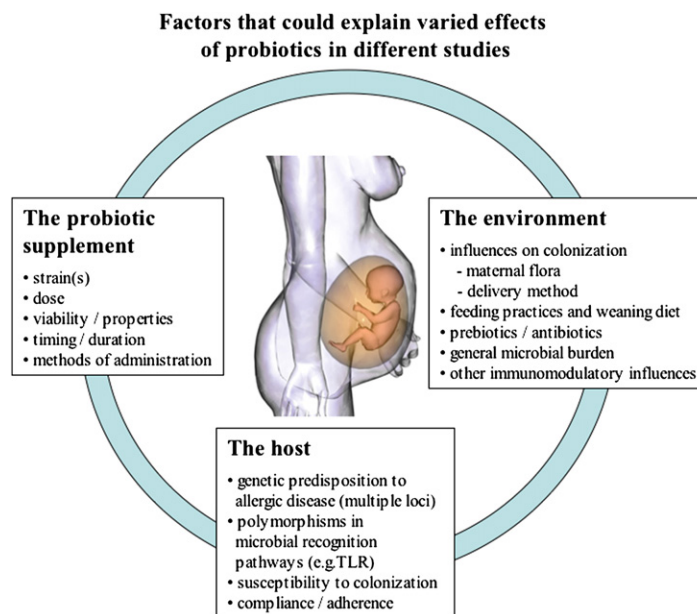


FIG 1. Factors that could explain varied effects of probiotics.

Similarly, there is some heterogeneity in the level of allergic risk in these studies. Third, there are likely to be many environmental factors that influence both colonization (such as maternal microbiota and other sources of microbial exposure, delivery method, antibiotics, prebiotics in the diet, and general microbial burden) and immune development. All of these factors are likely to make robust meta-analyses problematic to perform as more studies are completed.

FUTURE DIRECTIONS: PREBIOTICS?

Although some studies have reported benefit in the treatment and prevention of atopic eczema, none has had

any clear effects on the development T_H2 mediated allergic responses. It appears unlikely that supplementation with a single probiotic strain would be sufficient to have a major influence on the very diverse intestinal microbiota and the complex interaction between the gut bacteria and the host. This has led to a shift in interest to dietary substrates that could have a more global effect on gut microbiota—namely, *prebiotics* (nondigestible, fermentable oligosaccharides that stimulate the growth of *Bifidobacterium* and *Lactobacillus* species). Altering the intake of foods containing these products can directly influence the composition and activity of intestinal microbiota. This could explain some of the protective effects of grains and cereals that have been seen in epidemiologic studies. At this stage, there are still very little data to confirm directly the

immunologic or therapeutic effects of prebiotic supplements, but a number of studies are underway.

CONCLUSION

Although there is a sound theoretical basis for anticipating benefits of probiotic supplementation in allergic disease, there is currently insufficient data to recommend this as a part of standard therapy in any allergic conditions or for prevention. Although there has been early promise in atopic dermatitis, it is generally accepted that more studies are needed to confirm this, and that any benefits are not likely to be great. However, faced with the stress and severe discomfort that can be associated with atopic dermatitis, many families are still choosing to try probiotics in conjunction with their prescribed treatment. Although the microbiotica in probiotic preparations are generally safe, it is possible that some products could contain milk products and may cause anaphylaxis in children with milk allergy.³⁶ Furthermore, although only 1 prevention study has reported adverse outcomes in relation to sensitization (with increased risk³²), the significance of this needs to be examined in further studies. These observations provide a cautionary note amid the continuing public enthusiasm for probiotics.

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