CME Review

Gut microbiota and allergic disease in children

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ARTICLE INFO

Article history:
Received for publication August 21, 2015.
Received in revised form September 30, 2015.
Accepted for publication October 2, 2015.

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Release Date: February 1, 2016
Expiration Date: January 31, 2018

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- Describe associations between infant gut microbiota and childhood allergic disease
- Summarize research and published guidelines on pediatric allergy prevention and management strategies involving the gut microbiota

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Disclosure of Relevant Financial Relationships:
M.H. Grayson has received research grants from Children’s Research Institute/Medical College of Wisconsin, Merck, National Institutes of Health (NIH), and Polyphor. G.D. Marshall has received research grants from Amgen, AstraZeneca, HRSA and National Institutes of Health.
(NIH). J.J. Oppenheimer has been a consultant/advisor for AstraZeneca, GlaxoSmithKline, Meda, Mylan, and Sunovion; has received research grants from AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline and Novartis. A.K. Ellis has received research grants from Circassia, Sun Pharma Advanced Research, Merck, Novartis, Pfizer, and GlaxoSmithKline; has also been a consultant/advisor for Circassia, Merck, Novartis, and GlaxoSmithKline; and has been a speaker for Merck, Novartis, Takeda and AstraZeneca. J.A. Bernstein, G. Krishnaswamy, M.B. Azad, A.B. Becker, S.L. Bridgman, A.L. Kozyrskyj, and J.A. Scott have nothing to disclose. Reviewers and Education/Editorial staff have no relevant financial relationships to disclose. No unapproved/investigative use of a product/device is discussed.

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**Introduction**

With the advancement of technologies for genomic sequencing and molecular biology, our understanding of the human gut microbiome structure, function, and relation to human health and disease is rapidly expanding. It is currently estimated that 500 to 1,000 different bacterial species inhabit the mature gastrointestinal tract, with bacterial cells ultimately outnumbering host cells 10-fold. The micro-organisms colonizing the gut perform different functions vital for human health, including processing of dietary constituents, regulation of host metabolism, immune system maturation, and development of oral tolerance. To date, numerous metabolic and immune disorders have been associated with gut microbiota dysbiosis in childhood, including inflammatory bowel disease, celiac disease, obesity, allergy, and asthma.

As we learn more about the importance of microbiota to human health, there is growing interest in unearthing microbiome-based biomarkers that predict later disease and could be used to develop future therapeutic targets. This review article provides an overview of the association between gut microbiota and childhood allergic disease and related conditions, including allergic sensitization, atopic dermatitis, allergic rhinitis, asthma, and summarizes research, guidelines, and recommendations to date on prevention and management strategies involving the gut microbiome. A glossary of common terms in the microbiome literature is presented in Table 1.

**Development of the Human Gut Microbiome**

The earliest gut colonizers encompass a mixture of cutaneous and enteric facultative anaerobes dominated by lactic acid bacteria (eg, species of *Lactobacillus, Enterococcus, and Streptococcus*) and coagulase-negative staphylococci. Populations of these non-specialists become incrementally displaced by obligate anaerobes (eg, species of *Bifidobacterium, Bacteroides, Clostridium, and Eubacterium*). Ultimately, this succession process culminates in the establishment of a stable “climax community” of microbes resembling the adult microbiota by 3 years of age, with studies in Western populations demonstrating maturation as soon as 1 year.

There is convincing evidence that gut microbiota have coevolved with the infant immune system. Early colonizers play an important role in the development of adaptive and innate immunity; commensal microbes contribute toward intestinal barrier function, produce antimicrobial factors that inhibit colonization by pathogenic bacteria, and enhance regulatory B- and T-cell responses. The temporal succession of the intestinal microbiota is strongly influenced by different dietary and medical exposures, and disruption in early life can have long-term consequences for child health. Method of birth and infant feeding are 2 key factors determining early colonization patterns. Vaginal delivery provides the neonate with a critical “inoculation” of maternal microorganisms, while breastfeeding transfers additional microbes and supplies prebiotic human milk oligosaccharides that drive selection of the gut microbiota. Backhed et al recently showed that mother-to-infant transmission of important bacterial taxa, including *Bacteroides* and *Bifidobacterium* species, were less frequent in infants born by cesarean section. This study also found the microbiota of non-breastfed infants to be associated with enrichment of bacteria typically found in adult microbiota, suggesting that cessation of breastfeeding (rather than the introduction of solid food) drives maturation of the gut microbiota.

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**Table 1**

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
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<tr>
<td>16S rRNA amplicon sequencing</td>
<td>Reconstruction of taxonomic composition of a microbial community based on sequences of a single taxonomically distinctive portion of the ribosomal gene.</td>
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<tr>
<td>Community Culture-independent methods</td>
<td>Techniques used to study microbiota that are not dependent on traditional bacterial plate culturing; examples include qPCR, DGGE, FISH, and NGS.</td>
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<tr>
<td>α-diversity</td>
<td>Overall biological variety within an individual environment or a set of environments, also called “richness”; common metrics include Chao1, Shannon, and Simpson indices.</td>
</tr>
<tr>
<td>β-diversity</td>
<td>Comparative similarity of biological composition between 2 environments or sets of environments.</td>
</tr>
<tr>
<td>Dysbiosis Microbiome NGS OTU (operational taxonomic unit)</td>
<td>Imbalance in compositional or functional homeostasis of a normally stable, polymicrobial environment. Methods for simultaneous sequencing of large numbers of DNA fragments, also known as high-throughput sequencing; examples include Illumina sequencing and 454 pyrosequencing. Group of highly similar or identical sequences representing a group of organisms related at some taxonomic level (eg, species, genus, etc). Group of non-digestible carbohydrates that stimulate the growth and/or activity of beneficial gut bacteria. Live micro-organisms that, when administered in adequate amounts, confer a health benefit on the host; probiotics evaluated for allergy prevention primarily include <em>Bifidobacteria</em> and <em>Lactobacilli</em> species. Reconstruction of whole genomes of multiple organisms from a single sample by assembling many overlapping short sequences. Relation between ≥2 different species in which ≥1 of the partners benefits in some way.</td>
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Abbreviations: DGGE, denaturing gradient gel electrophoresis; FISH, fluorescence in situ hybridization; NGS, next-generation sequencing; q-PCR, quantitative polymerase chain reaction.
From microbial profiling of meconium, the infant’s first stool, there is evidence that the first microbes to colonize the gut influence community composition later in infancy.9,9 Exactly when colonization of meconium occurs is the subject of current investigation. For well over a century, Escherich’s10 proposition that the fetal gastrointestinal tract is absent of microbial colonization has been generally accepted despite reports to the contrary as long ago as the 1930s.8 In 2008, Jimenez et al11 confirmed the non-sterility of infant meconium using careful culture techniques. With the continued application of next-generation sequencing methods to profile meconium microbiota,12 we will gain a better understanding of the early temporal succession of gut microbiota and the environmental factors that influence this developmental process.

Intestinal Microbiota Biomarkers in Allergic Disease and Related Conditions

The widely recognized “hygiene hypothesis” theorizes that lack of exposure to external micro-organisms and infection in childhood inhibits natural immune development and predisposes to chronic disease in later life.13 More recently, this theory has been expanded to encompass the “microflora hypothesis,” placing emphasis on alteration of the commensal gut microbiota during infancy as a potential cause of immune dysregulation and allergic disease.14 Epidemiologic evidence supporting this concept has shown that children with greater microbial exposure in early life, through farming environments, pets, older siblings, and daycare settings, have a lower risk of developing asthma, rhinoconjunctivitis, and atopic dermatitis.15–17 Natural exposure to maternal microbiota through vaginal delivery and breastfeeding also has been associated with a lower incidence of allergic conditions.18–20

The first study exploring the hypothesis that allergic disease is associated with an aberrant microbiota in childhood was conducted in Sweden in the 1990s.21 Using traditional culture-based techniques, gut microbiota were compared between children in Estonia, where the prevalence of allergic disease is low, and Sweden, where allergy prevalence is relatively high. Allergic children in the 2 countries (confirmed by clinical history and positive skin prick test reaction to egg or cow’s milk) were less frequently colonized with lactobacilli, had larger counts and proportions of aerobic bacteria, and smaller proportions of Bacteroidetes than nonallergic children. More recently, studies using culture-independent next-generation sequencing techniques have identified several potential microbial biomarkers of allergic disease, including members of the Bacteroidaceae family and Clostridium genus as recently reviewed by Melli et al.22 Bacteroidetes and Faecalibacterium prausnitzii are often decreased after cesarean section delivery7,25 and have a lower risk of developing asthma, rhinoconjunctivitis, and atopic dermatitis.15–17 Natural exposure to maternal microbiota through vaginal delivery and breastfeeding also has been associated with a lower incidence of allergic conditions.18–20

Recently published prospective studies investigating associations between intestinal microbiota and allergic disease and related conditions from the past 5 years are presented in Table 2.29–41 In a cross-sectional study, Ling et al42 reported smaller proportions of Bacteroidetes and larger proportions of Firmicutes (including Clostridiales) in 5-month-old food–allergic infants. Providing evidence that these changes might precede the development of disease, a prospective study by Nylund et al43 found lower abundance of Bacteroidetes and greater abundance of Clostridium clusters IV and XVb at 18 months in children subsequently diagnosed with eczema. Similar results from a Swedish cohort of 40 infants associated atopic eczema at 2 years with a lower diversity of Bacteroidetes at 1 month of age.40 In the KOALA birth cohort of nearly 1,000 infants, colonization with C difficile at 1 month of age was associated with an increased risk of eczema, recurrent wheeze, allergic sensitization, and asthma by 7 years of age.31 Colonization with Clostridium cocoides subcluster XIVa also has been associated with an increased risk of asthma at 3 years of age.35 Recent findings from the Canadian Healthy Infant Longitudinal Development (CHILD) general population cohort study, using next-generation Illumina sequencing to profile the gut microbiota of 166 infants, identified a higher ratio of Enterobacteriaceae to Bacteroidaceae at 3 months of age to be predictive of food sensitization at 1 year.33 The ratio of Enterobacteriaceae to Bacteroidaceae could be a marker of gut microbiota immaturity because Bacteroidaceae tend to become more dominant with age. Importantly, these associations were still evident in analyses excluding infants with major microbiota-disrupting exposures (cesarean delivery, antibiotics, or formula feeding). A nested case–control study examining the gut microbiota of 319 infants enrolled in the same CHILD cohort found that children with a high risk of asthma at school age (classified as those with atopy and wheeze at 1 year) exhibited transient gut microbiota dysbiosis during the first 100 days of life. The relative abundances of Lachnospira, Veillonella, Rothia, and Faecalibacterium prausnitzii were significantly decreased in children with asthma.34 Another recent study demonstrated deficiency in Bacteroides in pregnant mothers of infants with IgE-associated eczema,35 although this deficiency was not confirmed in infant microbiota. This study of 20 mother–infant dyads further showed a depletion of Ruminococcaceae in infants developing IgE-associated eczema and demonstrated correlations between specific microbial taxa and inflammatory cytokine responses.

Although compelling evidence for microbiota associations with allergic disease and related conditions is emerging, some studies have failed to find differences in infant microbiota according to later allergic status46,47 or have found associations with some allergic phenotypes but not others.7,38 Heterogeneity in study design, including sampling time points, methods used to characterize microbiota, and different allergic phenotypes under study, make it difficult to establish a causal relation between specific bacterial taxa and development of allergy. To date, no specific bacterial taxon has been consistently associated with allergic disease or other related conditions. With this in mind, some studies have suggested that early diversity of gut microbiota might be more important than the presence or absence of specific taxa.48,49–51 Several prospective studies have found decreased microbial diversity to precede the development of eczema,36,50,64,45 atopie sensitization and allergic rhinitis,36 and asthma.35 Some studies measuring microbial diversity in older infants (>3 months) have not found similar associations,49,52,53 suggesting that very early infancy could be a critical period for microbe–host interactions contributing to immune system development. Other studies are conflicting51 or have not found associations between early gut microbial diversity and allergic sensitization,50 eczema,35,52 or asthma.35

Despite a wealth of studies, continued investigation in this area focusing on data from large longitudinal cohorts is required to confirm which deviations in microbial development in early infancy are important in the later development of atopic disease, including those that might present novel targets for intervention.

Probiotics and Prebiotics for the Prevention and Management of Allergic Disease

Probiotics are defined as live micro-organisms that, when administered in adequate amounts, confer a health benefit on the host. Given their potential to regulate gut microbiota and modulate immune responses, there is increasing interest in the application of probiotics to prevent or manage allergic disease. To date, probiotics evaluated in clinical trials for allergy prevention or treatment...

### Overall Evidence and Recommendations for Probiotics in Allergic Disease

Recent guidelines and systematic reviews addressing the use of probiotics for allergy prevention or management are presented in Table 3.46–55

### Table 2

<table>
<thead>
<tr>
<th>Allergic disease</th>
<th>Association with gut microbiota</th>
<th>Study</th>
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<tbody>
<tr>
<td>Atopic dermatitis or eczema</td>
<td>Lower relative abundance of gram-positive Ruminococcaceae at 1 wk of age in infants developing IgE-associated eczema by 2.5 y of age. Greater diversity at 18 mo of age; lower abundance of <em>Bacteroidetes</em> and greater abundance of <em>Clostridium</em> clusters IV and XIVa (Firmicutes phylum) at 18 mo in infants with eczema at 2 y of age. Lower microbiota diversity at 1 wk in infants with eczema at 12 mo of age. Lower microbiota diversity at 1 mo; lesser diversity of phylum <em>Bacteroidetes</em> and genus <em>Bacteroides</em> at 1 mo; lower abundance of <em>Proteobacteria</em> at 12 mo in children with IgE-associated eczema at 2 y of age. Colonization by <em>Clostridium difficile</em> at 1 mo associated with eczema throughout the first 6 y of life. Colonization with <em>Lactobacillus paracasei</em> at 1 mo inversely associated with risk of atopic dermatitis at 2 y of age.</td>
<td>West et al, 20155,0 Nylund et al, 201320,b Ismail et al, 20120,b Abrahamsson et al, 201230 van Nimwegen et al, 201111 Penders et al, 20109</td>
</tr>
<tr>
<td>Allergic sensitization</td>
<td>Lower microbiota richness at 3 mo; higher <em>Enterobacteriaceae/Bacteroidaceae</em> ratio at 3 and 12 mo in food-sensitized children at 1 y. Fewer <em>Lactobacilli</em> in the first weeks of life; lower colonization with <em>Bifidobacterium bifidum</em> at 1 wk of age in food-sensitized children at 5 y of age. Lower microbiota diversity at 1 and 12 mo in sensitized children during the first 6 y of life. Lower levels of <em>Escherichia coli</em> at 4 mo and 1 y, higher levels of <em>Bifidobacterium longum</em> at 1 y, and lower levels of <em>Bacteroides fragilis</em> at 2 y of age in sensitized infants. Decreased relative abundances of <em>Lachnospira</em>, <em>Veillonella</em>, <em>Rothia</em>, and <em>Faecalibacterium</em> during first 100 d in children classified as high risk of developing asthma in childhood (children with atopy and/or wheeze at 1 y). Lower microbiota diversity at 1 wk and 1 mo in children developing asthma by 7 y of age. Colonization by <em>Clostridium difficile</em> at 1 mo of age associated with asthma at 6 y of age. Colonization with <em>Bacteroides fragilis</em> group and/or to <em>Clostridium cocoides</em> subcluster XIVa at 3 wk associated with increased risk of asthma at 3 y of age.</td>
<td>Azad et al, 201535 Johansson et al, 201141 Bisgaard et al, 20115,9 Storro et al, 201157 Arrieta et al, 201554 Abrahamsson et al, 201436 van Nimwegen et al, 201111 Vael et al, 201115</td>
</tr>
<tr>
<td>Asthma or asthma risk</td>
<td>Decreased relative abundances of <em>Lachnospira</em>, <em>Veillonella</em>, <em>Rothia</em>, and <em>Faecalibacterium</em> during first 100 d in children classified as high risk of developing asthma in childhood (children with atopy and/or wheeze at 1 y). Lower microbiota diversity at 1 wk and 1 mo in children developing asthma by 7 y of age. Colonization by <em>Clostridium difficile</em> at 1 mo of age associated with asthma at 6 y of age. Colonization with <em>Bacteroides fragilis</em> group and/or to <em>Clostridium cocoides</em> subcluster XIVa at 3 wk associated with increased risk of asthma at 3 y of age.</td>
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*Includes studies from past 5 years in which microbiota were analyzed before allergic disease outcome.

*Infants at high risk of allergic disease.

### Table 3

<table>
<thead>
<tr>
<th>Guideline (study)</th>
<th>Statement or recommendation</th>
<th>Main findings (number of studies; participants included)</th>
</tr>
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<tbody>
<tr>
<td>World Allergy Organization and McMaster University guidelines for allergic disease prevention: probiotics (Fiocchi et al, 201555)</td>
<td>Probiotics recommended for (1) pregnant women at high risk of having an allergic child, (2) women who are breastfeeding a high-risk infant, and (3) infants at high risk of developing allergy; there is likely a net benefit resulting primarily from prevention of eczema. No guidance on specific probiotic strains or dosage.</td>
<td>There is no evidence to support the use of prebiotics or probiotics for food allergy prevention in pregnant women, breastfeeding mothers, or infants.</td>
</tr>
<tr>
<td>European Academy of Allergy and Clinical Immunology food allergy and anaphylaxis guidelines (Muraro et al, 201445–49)</td>
<td></td>
<td>No specific recommendations about the use of probiotics in pregnant women or infants.</td>
</tr>
<tr>
<td>Food and Agriculture Organization and World Health Organization guidelines on probiotics (Morelli and Capurso, 201224)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Probiotics and allergy prevention (Cuello-Garcia et al, 201546)</td>
<td>Probiotics used by pregnant women or breastfeeding mothers and/or given to infants decreased risk of eczema in infants (very low quality evidence); no effect on prevention of other allergic conditions (29 studies; 4927 pregnant women, breastfeeding mothers or infants).</td>
<td>Probiotics decreased risk of AD in general and high-risk populations; supplementation in pre- and postnatal periods was required; postnatal supplementation alone had no effect (16 trials; 3,495 pregnant women, breastfeeding mothers, or infants).</td>
</tr>
<tr>
<td>Prebiotics and allergy prevention (Osborn and Sinn, 201350)</td>
<td>Probiotics added to infant formula decreased risk of eczema; no evidence for prevention of other allergic conditions (4 trials; 1,428 infants).</td>
<td>Probiotics decreased risk of AD in general and high-risk populations; supplementation in pre- and postnatal periods was required; postnatal supplementation alone had no effect (16 trials; 3,495 pregnant women, breastfeeding mothers, or infants).</td>
</tr>
<tr>
<td>Probiotics and AD prevention (Panduru et al, 201555)</td>
<td></td>
<td>Probiotics decreased AD symptoms in adults and children, but no benefit for infants (25 trials; 1,599 infants, children, or adults).</td>
</tr>
<tr>
<td>Probiotics and long-term AD prevention (Cao et al, 201551)</td>
<td>Probiotics decreased long-term risk of AD (6 trials with &gt;5-y follow-up; 1,955 pregnant women, breastfeeding mothers, or infants).</td>
<td>Probiotics had no effect on risk of diagnosed asthma or childhood wheeze (20 trials; 4,866 pregnant women, breastfeeding mothers, or infants).</td>
</tr>
<tr>
<td>Probiotics and asthma prevention (Azad et al, 201352)</td>
<td>Probiotics improved Rhinitis Quality of Life scores, but had no effect on Rhinitis Total Symptom scores or total IgE levels (23 studies; 1,919 children or adults).</td>
<td>Probiotics improved Rhinitis Quality of Life scores, but had no effect on Rhinitis Total Symptom scores or total IgE levels (23 studies; 1,919 children or adults).</td>
</tr>
<tr>
<td>Probiotics and allergic rhinitis treatment (Zajac et al, 201449)</td>
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pregnancy (pooled relative risk [RR] 0.71, 95% confidence interval [CI] 0.60–0.84), by breastfeeding mothers (RR 0.57, 95% CI 0.47–0.69), or when given to infants (RR 0.80, 95% CI 0.68–0.94). Evidence did not support an effect on asthma, food allergy, allergic rhinitis, or adverse events. Consistent with other recent reviews, the WAO panel found there was insufficient evidence to generally support the use of probiotic supplementation in the primary prevention of allergic disease, but reported modest evidence for net beneficial effects in the prevention of eczema in high-risk children with a family history of allergic disease.46,47,58 Despite acknowledging the low or very low quality of evidence, the panel concluded that the potential benefits of probiotics in this population outweigh any potential harms and made conditional recommendations for the use of probiotics by (1) pregnant women at high risk of having a child with allergy, (2) women who are breastfeeding a high-risk infant, and (3) infants at high risk of developing allergy.47 No recommendation was made regarding the type or dose of probiotic to be used in these populations.

**Probiotics and Atopic Dermatitis**

Supporting the WAO Guidelines, a new meta-analysis by Cao et al39 reviewed the long-term effect of early-life probiotic use on the prevalence of atopic dermatitis. In 6 trials with a minimum follow-up duration of 5 years, probiotic supplementation during pregnancy or early infancy decreased the development of atopic dermatitis by 14% (RR 0.86, 95% CI 0.77–0.96). Probiotic treatment of atopic dermatitis also is an active area of research.59 A 2014 meta-analysis of 25 probiotic trials reported significant improvement in symptoms in adults and children receiving probiotics, although no benefit was shown for infants.48 A new study of 43 children found that a 4-week course of *L salivarius* significantly improved clinical parameters from baseline, and a randomized trial of 40 infants found that 4 weeks of treatment with *B bifidum* significantly improved symptoms compared with placebo.60

**Probiotics and Other Allergic Conditions**

Evidence for probiotics in the prevention or management of other allergy-related conditions remains low and inconclusive. Recent reviews do not recommend probiotics for the prevention or treatment of asthma, allergic rhinitis, or food allergy.49,50,56,59,62–64 A meta-analysis of 20 trials found no decrease in the incidence of wheeze (RR 0.97, 95% CI 0.87–1.09) or physician-diagnosed asthma (RR 0.99, 95% CI 0.81–1.21) after early-life probiotic supplementation.50 In a systematic review of 23 studies evaluating probiotics for the treatment of allergic rhinitis, Zajac et al51 found significant improvement in quality-of-life scores, but no effect on total symptom scores or IgE levels. In the new European Academy of Allergy and Clinical Immunology guidelines for food allergy and anaphylaxis, the prevention taskforce found no evidence to support the use of probiotics for food allergy prevention.49 Studies are ongoing to evaluate the potential effect of probiotics for the treatment of food allergy, with a recent trial by Tang et al62 showing promising results for a coadministration strategy combining probiotic supplementation with oral immunotherapy for peanut allergy.

**Prebiotics for the Prevention and Management of Allergic Disease**

Prebiotics are nondigestible food ingredients that benefit the host by selectively stimulating the growth or activity of intestinal microbiota. Human milk is rich in prebiotic oligosaccharides, and synthetic oligosaccharides are increasingly being added to infant formulas, with the goal of stimulating “healthy” gut microbiota development.55 Recent animal studies have suggested that prebiotic supplementation could attenuate food allergy symptoms, prevent allergic asthma, or diminish allergic sensitization in offspring when provided to pregnant or lactating mothers.68 However, clinical evidence is lacking. A 2013 Cochrane review identified 4 randomized trials providing probiotics to infants and found a significant decrease in eczema (RR 0.68, 95% CI 0.48–0.97) but no effect on other allergic outcomes.52 A new trial by Sierra et al69 found no difference in allergic manifestations (wheezing, atopic dermatitis, food allergy) after prebiotic supplementation of healthy formula-fed infants for the first year of life.

**Summary**

The use of probiotics and prebiotics for allergic disease prevention and management is an active area of clinical research; however, current evidence is limited and conflicting. Thus far, these microbiota-targeting supplements have shown more promise for primary prevention vs treatment of established allergic disease.62 Evidence summaries are complicated by significant heterogeneity between studies in outcome measurements, study design, and especially probiotic strain, dose, and timing of administration.49–51,53,59–61,64 The absence of a pooled effect from different probiotics does not exclude the possibility that a certain strain or combination could be effective and effects might depend critically on the timing of administration. Several studies have found that prenatal supplementation is more effective than postnatal use, with combined strategies having the greatest impact.53,59,64 Moreover, the physiologic response to probiotic supplementation is likely affected by host immunity and the existing microbiota. For example, in the trial conducted by Abrahamsson et al70 of maternal and infant supplementation with *L reuteri*, levels of this probiotic strain unexpectedly decreased over the course of supplementation and were surprisingly lower in breastfed vs formula-fed infants, despite detection of *L reuteri* in maternal milk. These findings suggest that resident microbiota might “out compete” probiotic strains over time, and that enhanced immunity (eg, resulting from breastfeeding) could prohibit permanent colonization by probiotic bacteria. Thus, although significant progress has been made toward understanding the potential application of probiotics and prebiotics in allergic disease and related conditions, much remains unknown and further research is required to identify the most effective probiotic strains and optimize the dose and timing of administration.

**Future Directions**

Rapid advances in gene sequencing technology have improved our ability to characterize the human microbiome in leaps and bounds. However, we still do not know what constitutes a healthy gut microbiota in the infant and which microbes are crucial in the development of specific atopic phenotypes. This will require further research in well-designed longitudinal cohorts combined with experimental studies in animal models to characterize complex host–microbe interactions.

At the same time, disappointing results with probiotic interventions have led to a search for other therapies that can repair “dysbiosis” of gut microbiota, such as fecal microbial transplantation. Although fecal microbial transplantation has proved quite effective in the treatment of recurrent *C difficile* infection,71 individuals with this refractory condition are prime candidates for fecal microbial transplantation because repeated exposure to antibiotics has wiped out their gut microbial community. It remains to be determined whether this approach can be applied for the prevention or treatment of allergic disease. Improved characterization of the human microbiome also has led to the discovery of the airway microbiome with dysbiosis observed in adults with asthma.72 The idea that asthma could result from disruption of early airway colonization also might explain why ingested probiotics are ineffective in preventing its development.
Evidence is accumulating for an early developmental window during infancy when gut microbes program our immune system. Repairing microbiota dysbiosis at an older age might be ineffective in restoring a healthy immune phenotype; thus, it will be important to carefully study the timing of gut colonization, microbiota succession, and immune development to identify optimal time windows for intervention. Conversely, the programming of host immunity might not be driven directly by microbiota, but rather by the metabolites they produce (e.g., short-chain fatty acids). Despite dramatic shifts in taxonomy with advancing age during infancy, the metabolic capacity and metabolite content of the gut are relatively stable, indicating redundancy in microbial function. This thesis opens up the possibility of using microbial metabolites to prevent atopic disease.

**Conclusion**

There is mounting evidence from observational studies that disruption of early gut colonization and microbiota diversity precede the development of allergic disease and related conditions. Clinical trials have demonstrated that manipulation of the gut microbiota with prebiotics or probiotics might be effective in the primary prevention of atopic dermatitis, but currently there is no consensus that adding microbiota with prebiotics or probiotics might be effective in the prevention of atopic disease.

**Acknowledgment**

The authors thank Amy Dynterski for her assistance in conducting literature searches for this review.

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[33] Almqvist C, Oberg AS. The association between caesarean section and asthma during infancy is associated with increased risk of allergic disease. BMC Microbiol. 2013;13.


