Recent advances in understanding environmental risk factors for allergic diseases in children have led to renewed efforts aimed at prevention. Factors that modify the probability of developing allergies include prenatal exposures, mode of delivery, diet, patterns of medication use, and exposure to pets and farm animals. Recent advances in microbial detection techniques demonstrate that exposure to diverse microbial communities in early life is associated with a reduction in allergic disease. In fact, microbes and their metabolic products might be essential for normal immune development. Identification of these risk factors has provided new targets for prevention of allergic diseases, and possibilities of altering microbial exposure and colonization to reduce the incidence of allergies is a promising approach. This review examines the rationale, feasibility, and potential effect for the prevention of childhood allergic diseases and explores possible strategies for enhancing exposure to beneficial microbes. (J Allergy Clin Immunol 2015;136:23-8.)

Key words: Allergy, prevention, IgE, prebiotics, probiotics, diet, intervention

More and more children have allergic diseases and other inflammatory disorders.1,2 These are lifetime diseases that can be severe and progressive and are associated with significant morbidity and some mortality. These disturbing trends, together with skyrocketing health care costs, have redoubled national and international efforts to prevent allergic diseases in childhood. The National Institutes of Health has sponsored conferences on prevention and birth cohort studies to review what is known about the origins of allergic diseases and to develop an evidence-based map for research priorities. Furthermore, the US Centers for Disease Control and Prevention has developed an initiative entitled “National prevention strategy: America’s plan for better health and wellness,” which emphasizes 4 elements: (1) building healthy and safe community environments, (2) expanding quality preventive services in both clinical and community settings, (3) empowering people to make healthy choices, and (4) eliminating health disparities.3 There are corresponding multifaceted strategies for preventing cardiovascular disease, obesity, and chronic lung disease, but interventions to prevent allergic diseases are noticeably absent. New developments in understanding disease pathogenesis and the early-life origins of allergic disease raise hope that prevention of allergic disease is achievable. This review will evaluate promising candidates for primary prevention of allergic disease. Given the recent advances in understating how the microbiome affects immune development and the risk of allergy, potential strategies for altering microbial exposures in early life to prevent childhood allergy are explored in detail.

ASSESSMENT OF RISK FACTORS: WHAT ARE THE OPPORTUNITIES FOR INTERVENTION?

Genetics, environmental exposures, age of exposure, and lifestyle and child-rearing practices all contribute to the risk of allergic diseases in childhood. Genetic variations can modify the risk of allergy by altering the expression or development of immunoregulatory pathways that promote type 2 immunity (receptor for IL-33 [IL1RL1] and signal transducer and activator of transcription 6 [STAT6]), by regulating immune tolerance (forkhead box protein 3 [FOXP3]), or by affecting epithelial integrity and permeability (filagrin [FLG]).6-8 Furthermore, genetic studies have implicated additional variants in genetic regions (eg, loci in 11q13.5 and 5q22.1) that promote allergic sensitization through unknown mechanisms.7,9 Thus genetic studies have affirmed longstanding paradigms and also have prompted investigations into novel mechanisms of allergy pathogenesis.

There is convincing evidence that environmental exposures markedly influence the risk of allergic diseases. In Western Europe growing up on a dairy farm reduces the risk of allergic diseases by up to half compared with that seen in nonfarm families.10 Moreover, Amish children in Indiana have very low rates of birch pollen allergy (2% vs 27%).12 Russian Karelia (2%) versus Finnish Karelia (27%) have different lifestyles. For example, schoolchildren growing up in Russian Karelia (2%) versus Finnish Karelia (27%) have dramatically lower rates of birch pollen allergy (2% vs 27%).12 Effects of environmental exposures can be genotype dependent. For example, the CD14 genotype can determine the effects of exposures to diverse stimuli, including endotoxin, farm milk, and household dogs, on outcomes such as allergic sensitization, atopic dermatitis, and total serum IgE levels.13-15 Collectively, this information provides evidence that environmental factors contribute to the incidence of allergic diseases in children.

Epidemiologic and birth cohort studies have identified a lengthy list of specific environmental risk factors for allergic diseases in childhood. Examples of prenatal factors associated...
with childhood allergic diseases include maternal diet and use of antibiotics. Mode of delivery can influence allergy; children delivered by means of cesarean section are at increased risk. Postnatal dietary factors that can affect the risk of allergic diseases include breast-feeding, nutrient content (eg, folate, vitamin D, and n-3 polyunsaturated fatty acids), age of introduction of specific foods (eg, peanut), and consumption of foods containing microbes (eg, raw farm milk). Relationships between diet and allergic diseases can be complex. In the National Health and Nutrition Examination Survey population, folate levels were inversely related to risk of atopy and serum IgE levels in both children and adults, although in other studies prenatal folate intake was associated with childhood asthma, and early-life serum folate levels were positively associated with risk of sensitization. Allergen avoidance to prevent allergies has been extensively studied, and multifaceted interventions that included dust mite avoidance have demonstrated reduced incidence of allergies, asthma, or both. Several recent studies have fueled a change in prevailing opinions, and the value of allergen avoidance in early life, which was once a cornerstone of preventive recommendations, is now questionable.

For example, an interventional study of high-risk infants was successful in reducing exposure to dust mite allergens in the home, but rates of sensitization to dust mite or Aeroallergens in general were increased, rather than reduced, at age 3 years. Treatment of infants with medications, such as antibiotics, acetaminophen, and antihistamines, are associated with increased risk of allergic diseases, although whether these effects are causal or confounded by association with underlying illnesses is difficult to determine.

Finally, there is intense interest in how early-life exposures to microbes affect the development of tolerance mechanisms and allergic sensitization. As mentioned previously, growing up in environments with rich microbial exposures is associated with lower risks of allergic disease. Within the farming environment, contact with stable and consumption of farm milk are associated with favorable clinical outcomes. Recently, there are data to indicate that diverse microbial exposures and gastrointestinal colonization in early life are associated with a reduced risk of allergic disease.

WHEN TO INTERVENE?

The influence of environmental and lifestyle factors can begin in very early life and even before birth. For example, exposure to environmental tobacco smoke might have the greatest effect on incident asthma when exposure occurs during the prenatal period. This conclusion is also supported by observations within immigrant populations in Western countries. For example, immigrants have lower rates of allergy and asthma in the United States, and rates of allergy increase together with the length of time that a child has resided in the United States. These findings indicate that exposures in the first few years of life are critically important in determining the risk of allergic diseases.

Immune mechanisms in allergy

Recent advances help to explain how environmental factors can influence the process of allergic sensitization in childhood, as reviewed by Holt. Historically, identification of Th1 and Th2 cells 30 years ago represented a major advance, and soon afterward, allergy and asthma were found to have skewed Th1 cell responses characterized by overproduction of type 2 cytokines (eg, IL-4 and IL-13). More recent discoveries have shed light on how environmental processes influence patterns of T-cell differentiation and allergy. For example, epithelial cells are now recognized as important links in the chain of events leading to allergic sensitization. Reduced epithelial barrier function can promote greater penetration of allergens into the subepithelial layers, which are involved in antigen recognition mechanisms. In addition, epithelial damage or stimulation by proteases induces the release of alarmins (eg, thymic stromal lymphopoietin and IL-33). These cytokines in turn act on antigen-presenting cells and innate and adaptive lymphoid cells to promote Th2 differentiation and allergic sensitization.

Some allergens can influence local immune responses through their functional properties or by means of molecular mimicry to promote sensitization. The major dust mite allergen Der p 2 has structural homology with an LPS-binding protein and can activate Toll-like receptor 4, which might serve as an adjuvant to sensitization. Moreover, some allergens are proteases and can activate allergic effector cells and degrade epithelial barrier function.

Microbes play an essential role in directing the development and function of the immune system at mucosal surfaces, such as the gastrointestinal tract. These microbes stimulate immune development through effects on epithelial cells and antigen-presenting cells that ultimately modulate T-cell differentiation, including stimulation of regulatory T-cell development. Accordingly, mice raised in germ-free environments have disordered immune development that predisposes toward allergic and inflammatory diseases, and repopulation of the gut with specific microbes affects immune development. For example, segmented filamentous bacteria can promote development of IL-17 responses, and bacteria that produce short-chain fatty acid metabolites promote differentiation of regulatory T cells. Microbes can exert effects through several mechanisms, including modulation of immune responses and inhibition of growth of pathogenic bacteria. Some microbes produce metabolites (eg, short-chain fatty acids, α-galactosylceramide, and tryptophan metabolites) that influence immune development. The strong influence of gastrointestinal flora on the development of systemic immune responses might be due to the large surface area of the gastrointestinal tract, heavy bacterial colonization, and the large amount of both lymphoid and myeloid cells and tissues in proximity to the intestinal mucosa. Less is known about how microbes on the skin and respiratory tract affect local immunity, but it is clear that commensal bacteria on the skin can modify local immune responses independent of effects of gastrointestinal microbes. It is likely that microbes in the respiratory tract have similar functions.

The importance of understanding immune development in healthy children

As discussed above, allergic sensitization represents a breakdown of tolerance and the development of immune responses that are biased toward type 2 cytokine responses and overproduction of IgE. This implies that prevention of allergy could be accomplished by fostering the development of tolerance mechanisms and by promoting the development of balanced immune responsiveness. Conceptually, this sounds straightforward; however, interventions in early childhood that affect immune development could have unintended consequences.
From the perspective of an allergist, type 2 responses should be suppressed; however, in patients with other inflammatory diseases, overproduction of interferons or IL-17 family cytokines have been implicated in disease processes, and restoration of type 2 responses can be a goal. Thus rebalancing the immune system in early life must be considered with caution so that immune modulation to prevent allergy does not inadvertently increase the risk of other inflammatory diseases or chronic infectious disease, perhaps decades later. These concerns, although theoretical, underscore the need to develop a comprehensive understanding of the developmental ecology of the microbiome of healthy children will be necessary to guide interventional studies intended to promote development of a well-balanced immune system.

**Opportunities for altering the microbiome to prevent childhood allergic diseases**

Altering the microbiome in early life has exceptional promise as a strategy to prevent allergic diseases during childhood. This conclusion is based on (1) strong epidemiologic data demonstrating microbial exposures and colonization in early life affect the risk of atop, (2) animal models demonstrating that microbes can have marked effects on immune development and especially the development of tolerance mechanisms, and (3) feasibility of several different types of interventions to influence the early-life microbiome (Fig 1). Challenges to this approach are also sizeable and include microbe selection, safety assessment, and intervention design (route of administration and dose, timing, and duration).

**Selection of microbes.** Intervention studies with probiotics have tested a number of different species of bacteria within the *Lactobacillus* and *Bifidobacterium* genera. *Lactobacillus rhamnosus* GG, a strain commonly used in probiotics, was originally isolated from the gastrointestinal tract of healthy human subjects, and bifidobacteria are the predominant organisms in the stool of breast-fed infants. There are well over 20 studies testing for preventive effects of probiotics on allergic sensitization, serum IgE levels, eczema, wheezing illnesses, and asthma. Results are mixed and depend on when the probiotic was administered, the specific organism used, and the outcomes. Meta-analyses indicate that there are small but significant effects (odds ratio, 0.85-0.90) on prevention of eczema, allergic sensitization, and serum IgE levels but not wheezing or asthma. Effects on allergic sensitization and serum IgE levels might be stronger when probiotics are started prenatally and continued during the postnatal period.

**Safety.** Probiotic bacteria, such as *Lactobacilli* and *Bifidobacteria* are considered generally safe because they are part of the normal human gastrointestinal microflora and have been used extensively in the cheese and yogurt industry. Even so, infectious complications are occasionally reported. As information accumulates about the immunoregulatory effects of additional bacteria that are selected for study because of inverse associations with allergic diseases, it is likely that we will move beyond the “yogurt bacteria” and conduct studies with a new generation of probiotics that are selected for specific immunologic effects. To accomplish this goal with a high degree of safety, a better understanding of the developmental ecology of the microbiome of healthy children will be necessary to guide interventional studies intended to promote development of a well-balanced immune system.

**Intervention studies and the microbiome.** Once candidate bacteria are identified, there are several possible approaches to designing an intervention. There are a number of environmental sources of microbes and nutritional and lifestyle factors that influence microbial composition and persistence and function (Fig 1). Thus the intervention could be in the form of a traditional therapeutic or could instead focus on changing lifestyle or child-rearing practices that secondarily affect the microbiome and clinical outcomes. These topics are discussed in the following sections.

**Environmental sources of microbial colonization.** The human microbiome evolves rapidly in the first few months of life, and microbial composition stabilizes by age 2 years. Many sources can contribute to colonization of the gastrointestinal tract, skin, and respiratory tract of the infant. During the perinatal period, maternal vaginal flora and skin flora, as well as mode of delivery, influence colonization. In early life other influences likely include airborne microbes that affect the upper and lower airways during respiration and are then swallowed. House dust and soil also contribute to microbial colonization, although in early life, house dust probably predominates in westernized societies. Pets can affect the home microbiome and, together with unwanted animals in the home (eg, mice and cockroaches), shape microbial exposures in the home. Ecological factors, such as temperature, humidity, and the amount of green space in a neighborhood, also affect microbial composition. In turn, babies eat dust and soil, a fact well documented in the toxicology literature with respect to exposures to lead and other environmental toxins. Although current parenting customs seem to discourage ingestion of soil, in fact, this appears to be normal behavior for infants and could be an important source for establishment of the microbiome. Finally, food can influence microbes in the gastrointestinal tract through several mechanisms; microbes present in or on foods can directly affect the gastrointestinal microbiome.
whereas nutrient content can shape microbial content and composition.

Prebiotics. Prebiotics are nutritional supplements designed to promote the growth and function of bacteria with beneficial effects. By altering the composition of the gastrointestinal microbiome, prebiotics have the potential to modify immune development in early life. In a German study addition of oligosaccharides to formula for the first year led to a 44% reduction in atopic dermatitis but no reduction in allergic sensitization.55 In mice short-chain fatty acids can promote development of regulatory T cells and tolerance mechanisms, and fiber and oligosaccharides in the diet can be digested by subsets of intestinal bacteria to increase concentrations of short-chain fatty acids.56 These studies suggest that for maximum benefits, prebiotics can be administered together with microbes with corresponding metabolic functions to maximize effects on metabolites with beneficial effects on immune development.

Active versus passive interventions. As an alternative to a traditional probiotic approach, interventions could instead be directed toward the environment in early life or toward child-rearing, dietary, or lifestyle changes. Identifying major sources of microbial colonization for truly healthy children and defining natural mechanisms for microbial colonization could inform this type of intervention strategy. An example of this approach would be to enrich the environment for key bacteria (perhaps a probiotic powder), which would then be acquired by the infant through natural routes, including inhalation, skin contact, and swallowing of house dust.

A third approach might be to focus on child-rearing practices. Epidemiologic studies have identified associations with reduced allergy risk that, if causality is proved, could lead to recommendations for changes in parenting practices. Examples include cleaning the pacifier in the mother’s mouth,50 consumption of fermented foods,50 and washing dishes by hand instead of in a dishwasher.

Individual versus community-level interventions. Some of the most effective public health measures are passive and aimed at the community rather than the individual. For example, altering building codes to require window guards led to a 50% reduction in children falling from windows in New York City,57 and adding vitamin D to milk virtually eliminated childhood rickets. Are there passive or community-level interventions that could promote a healthy microbiome? There are opportunities for assessing whether community interventions could improve health. For example, large urban areas are extensively paved and have a paucity of animal and green space. As a result, many inner-city neighborhoods might be especially poor in microbial exposures and can be thought of as “microbial deserts.” In some neighborhoods, however, the city landscape is changing. A number of city and nonprofit organizations and the US Environmental Protection Agency have organized programs to raze dilapidated housing and turn these properties into parks or community gardens.50-52 Consequently, the number of urban gardens in Detroit has increased from less than 100 to 1400 since the year 2000.53 These programs are increasing green space and enhancing opportunities for young mothers and children to work in soil that is rich in microbes to grow nutritious crops for local consumption. Other programs have been organized to bring urban youth to rural areas to experience farming and rural environments.64,65 Will these programs lead to health benefits, including less allergy, in part by enhancing colonization with sources of diverse and beneficial microbes? The question is ripe for study.

CONCLUSIONS

As detailed in articles by Drs Platts-Mills1 and Holt32 in this issue, the causes for the increase in childhood allergic diseases and asthma in the past century are multifactorial. The complexity of multifactorial pathogenesis offers a number of potential interventions. The microbiome is one of the more promising targets for intervention studies based on strong immunologic effects of microbes in animal studies and a wealth of data from epidemiologic studies implicating changes in microbial colonization with the risk of allergic diseases and other disorders of chronic inflammation. In particular, ongoing work across the globe to identify keystone microbes that promote colonization with a community of organisms that promote optimal immune development is likely to translate into development of new probiotics. These investigative efforts in microbial effects, diet, and lifestyle are likely to advance a multitude of new preventive approaches that each lead to incremental reductions in the risk for allergy and asthma.

These conceptual advances also highlight a number of research priorities and remaining questions related to the prevention of allergic diseases in childhood.

1. Prevention must be safe. These interventions would be administered to pregnant women, babies, or both, with the goal of altering lifelong immune development. Therefore the priority is to develop a clear understanding of immune development in healthy babies and to define how immune development deviates from normal (optimal).

2. The focus of this review has been the microbiome; however, there are opportunities in many areas to identify effective strategies to prevent allergic diseases. Continued research into timing of exposure to foods and allergens, diet and nutrients, and child-rearing practices are needed to develop a palate of preventive measures. Immunologic studies should be included in clinical studies to provide insights into mechanisms of action and effects on developmental biology. This information would enable multifaceted interventional studies in the future to optimize strategies for allergy prevention.

3. Interventional studies for prevention of allergic diseases in children are by definition large, time-consuming, and expensive. Even for outcomes that can be measured as early as age 2 years (eg, food allergies and atopic dermatitis), the time required for recruitment, birth, active study participation, and analysis is at least 5 years. Given the large sample size, expense, time commitment, and limitations on available funding sources, research efforts at prevention need to be carefully coordinated at the national or international level. Recent consensus conferences are a step in this direction,1 and follow-up meetings could help promote collaborative efforts to prevent allergic diseases.

REFERENCES


