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Promising Candidates for Prevention of Allergy

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Abstract

Recent advances in understanding environmental risk factors for allergic diseases in children has 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 may 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 impact for the prevention of childhood allergic diseases, and explores possible strategies for enhancing exposure to beneficial microbes.

Keywords

Allergy; prevention; IgE; prebiotics; probiotics; diet; intervention

Introduction

More and more children are developing allergic diseases and other inflammatory disorders (Platts-Mills TAE – this issue, and ¹). 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 NIH has sponsored conferences on prevention² and on birth cohort studies³ to review what is known about the origins of allergic diseases, and to develop an evidence-based map for research priorities. Furthermore, the Centers for Disease Control has developed an initiative entitled “National Prevention Strategy: America’s Plan for Better Health and Wellness”, which emphasizes four elements: 1) building healthy and safe community environments, 2) expanding quality preventive services in both clinical and community settings, 3) empowering people to make

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healthy choices, and 4) eliminating health disparities.⁴ 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 early life origins of allergic disease raise hope that prevention of allergic diseases 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 (*IL1RL1* (receptor for IL-33), *STAT6*), by regulating immune tolerance (*FOXP3*), or by affecting epithelial integrity and permeability (*FLG* [filaggrin]).⁵⁻⁷ Further, genetic studies have implicated additional variants in genetic regions (e.g. loci in 11q13.5 and 5q22.1) that promote allergic sensitization through unknown mechanisms.^{6, 8} 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 to non-farm families.⁹ Moreover, Amish children in Indiana have very low rates of allergic sensitization (7%), allergic rhinitis (0.6%) and asthma (5.2%).¹⁰ In addition, the prevalence of allergy can be quite different among populations of similar heritage who have different lifestyles. For example, schoolchildren growing up in Russian Karelia (2%) vs. Finnish Karelia (27%) have dramatically lower rates of birch pollen allergy (2% vs. 27%).¹¹ Effects of environmental exposures may be genotype-dependent. For example, 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.¹²⁻¹⁴ 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.¹⁵ Mode of delivery can influence allergy; children delivered by Caesarian section are at increased risk.¹⁶ Postnatal dietary factors that may affect the risk of allergic diseases include breastfeeding, nutrient content (e.g. folate, vitamin D, n-3 polyunsaturated fatty acids [PUFA]), age of introduction of specific foods (e.g. peanut), and consumption of foods containing microbes (e.g. raw farm milk).^{9, 17, 18} Relationships between diet and allergic diseases can be complex. In the NHANES population, folate levels were inversely related to risk of atopy and serum IgE in both children and adults,¹⁹ while in other studies prenatal folate intake was associated with childhood asthma²⁰ and early life serum folate levels were

positively associated with risk of sensitization.²¹ Allergen avoidance to prevent allergies has been extensively studied, and multifaceted interventions that included dust mite avoidance have demonstrated reduced incidence of allergies and/or asthma.²² 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.²³ 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.²⁴ 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.²⁵

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 diseases. Within the farming environment, contact with stables and consumption of farm milk are associated with favorable clinical outcomes. Recently, there are data to indicate that diverse microbial exposures^{26, 27} and gastrointestinal colonization in early life is 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 may have the greatest effect on incident asthma when the exposure occurs during the prenatal period.²⁸ 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 US, and rates of allergy increase together with the length of time that a child has resided in the US.^{29, 30} 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 in this issue (reference Holt paper). Historically, identification of Th1 and Th2 cells 30 years ago represented a major advance,³¹ and soon afterwards allergy and asthma were found to have skewed T-helper cell responses characterized by overproduction of type 2 cytokines (e.g. IL-4, 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.³² Reduced epithelial barrier function can promote greater penetration of allergens into the sub-epithelial layers that are in antigen recognition mechanisms.³² In addition, epithelial damage or stimulation by proteases induces the release of alarmins (e.g. TSLP, IL-33). These cytokines in turn act on antigen presenting cells, and innate and adaptive lymphoid cells to promote Th2 differentiation and allergic sensitization.^{33, 34}

Some allergens can influence local immune responses via their functional properties or by molecular mimicry to promote sensitization. The major dust mite allergen Der p2 has structural homology with an LPD-binding protein and can activate TLR4, which may serve as an adjuvant to sensitization.³⁵ Moreover, some allergens are proteases, and can activate allergic effector cells and degrade epithelial barrier functions.^{36–38}

How does the human microbiome affect immune development?: Microbes play an essential role in directing the development and function of the immune system at mucosal surfaces such as the gastrointestinal tract.³⁹ These microbes stimulate immune development through effects on epithelial cells and antigen presenting cells that ultimately modulate T cell differentiation, including stimulation of T regulatory cell development.^{39, 40}

Accordingly, mice raised in germ-free environments have disordered immune development that predisposes towards 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 T regulatory cells.^{40, 41} Microbes can exert effects via several mechanisms, including modulation of immune responses and inhibiting growth of pathogenic bacteria.⁴² Some microbes produce metabolites (e.g. short chain fatty acids, α -galactosylceramide and tryptophan metabolites) that influence immune development.⁴³ The strong influence of gastrointestinal flora on development of systemic immune responses may 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 in the 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.⁴⁴ It is likely that microbes in the respiratory tract have similar functions.⁴⁵

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 towards 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 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, though theoretical, underscore the need to develop a comprehensive understanding of immune responses that are associated with long-term health throughout childhood and beyond.⁴⁶ In this context, the definition of “health” goes beyond “no allergic disease”, and instead refers to immunologic responses of children who are not only free of allergic diseases, but are also devoid of other inflammatory disorders, and deal effectively

with acute and chronic infections. Using new systems based approaches to define immune development in truly healthy children would be an invaluable asset in understanding immune deviation associated with allergic disease and other disorders with immunologic origins.

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: a) strong epidemiologic data demonstrating microbial exposures and colonization in early life affect the risk of atopy, b) animal models demonstrating that microbes can have marked effects on immune development, and especially the development of tolerance mechanisms, and c) feasibility of several different types of interventions to influence the early life microbiome (Figure 1). Challenges to this approach are also sizeable, and include the selection of microbes, assessment of safety, and design of the intervention (route of administration, 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 rhamnosis* GG, a strain commonly used in probiotics, was originally isolated from the GI tract of a healthy human,⁴⁷ 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-analysis indicate that there are small but significant effects (OR 0.85–0.90) on prevention of eczema, allergic sensitization and serum IgE, but not wheezing or asthma.^{48, 49} Effects on allergic sensitization and serum IgE may be stronger when the probiotics are started prenatally and continued during the postnatal period.⁴⁸

Safety: Probiotic bacteria such as *Lactobacilli* and *Bifidobacteria* are considered as 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.⁵⁰ As information accumulates about 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. In order 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 (Figure 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 the age of two 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 impact 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,⁵¹ and together with unwanted animals in the home (e.g. mice and cockroaches),²⁷ 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,⁵² a fact well documented in the toxicology literature with respect to exposures to lead and other environmental toxins. Though 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 may directly affect the GI microbiome, while nutrient content can shape microbial content and composition.

Prebiotics: Prebiotics are nutritional supplements designed to promote the growth and function of bacterial 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.⁵³ In mice, short chain fatty acids (SCFA) can promote development of T regulatory cells and tolerance mechanisms, and fiber and oligosaccharides in the diet can be digested by subsets of intestinal bacteria to increase concentrations of SCFA.⁴⁰ These studies suggest that for maximum benefits, prebiotics might be administered together with microbes with corresponding metabolic functions to maximize effects on metabolites with beneficial effects on immune development.

Active vs. passive interventions: As an alternative to a traditional probiotic approach, interventions could instead be directed towards the environment in early life, or towards 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 proven, could lead to

recommendations for changes in parenting practices. Examples include cleaning the pacifier in the mother's mouth,⁵⁴ consumption of fermented foods,⁵⁵ and washing dishes by hand instead of in a dishwasher.⁵⁶

Individual vs. 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 may 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 Environmental Protection Agency have organized programs to raze dilapidated housing and turn these properties into parks or community gardens.^{58, 59, 60} Consequently, the number of urban gardens in Detroit has increased from less than 100 to 1400 since the year 2000.⁶¹ 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.^{62, 63} 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 papers by Drs. Platts Mills and Holt 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 the development of new probiotics. These investigative efforts in microbial effects, diet and lifestyles 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 and/or babies 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 aeroallergens, 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 (e.g. food allergies, atopic dermatitis), the time required for recruitment, birth, active study participation and analysis is at least five 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,³ and follow-up meetings could help promote collaborative efforts to prevent allergic diseases.

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Abbreviations

SCFA short chain fatty acid

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Figure 1.

Sources of microbial exposure in early life and relationship to immune development and clinical outcomes. Abbreviation: SCFA, short chain fatty acids.