Environmental determinants of allergy and asthma in early life

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Overall Purpose/Goal: To provide excellent reviews on key aspects of allergic disease to those who research, treat, or manage allergic disease.

Target Audience: Physicians and researchers within the field of allergic disease.

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Activity Objectives:

1. To describe the effect of microbial exposure and childhood infections on the risk of allergic disease.
2. To understand the link between indoor allergen exposure and the risk of atopy.
3. To determine the effect of environmental exposure from tobacco smoke and air pollution on allergic disease.

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Allergic disease prevalence has increased significantly in recent decades. Primary prevention efforts are being guided by study of the exposome (or collective environmental exposures beginning during the prenatal period) to identify modifiable factors that affect allergic disease risk. In this review we explore the evidence supporting a relationship between key components of the external exposome in the prenatal and early-life periods and their effect on atopy development focused on microbial, allergen, and air pollution exposures. The abundance and diversity of microbial exposures during the first months and years of life have been linked with risk of allergic sensitization and disease. Indoor environmental allergen exposure during early life can also affect disease development, depending on the allergen type, dose, and timing of exposure. Recent evidence supports the role of ambient air pollution in allergic disease inception. The lack of clarity in the literature surrounding the relationship between environment and atopy reflects the complex interplay between cumulative environmental factors and genetic susceptibility, such that no one factor dictates disease development in all subjects. Understanding the effect of the summation of environmental exposures throughout a child's development is needed to identify cost-effective interventions that reduce atopy risk in children. (J Allergy Clin Immunol 2017;140:1-12.)

Key words: *Environment, allergy, asthma, exposure, microbiome, infection, endotoxin, allergen, air pollution, tobacco smoke*

Like many chronic health conditions, allergic disease likely results from complex gene-environment interactions. Mapping of the human genome has advanced our understanding of genetic risk factors for allergic diseases. However, the increase in the

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prevalence of allergic disease over the past few decades has occurred too rapidly to be accounted for by changes in the genome alone and is more likely to be the result of changes in environmental factors that are in some cases accompanied by epigenetic changes. These observations have led to increasing interest in understanding the effect of the exposome on the development of atopic disease. In 2005, Christopher Wild framed our understanding of the exposome concept to include 3 types of exposures: (1) the general external environment, including factors such as urban-rural residence, climate, air pollution, social capital, and education; (2) one's specific external environment, including diet, physical activity, tobacco exposure, infection, and occupation; and (3) the internal environment, which includes the biological and metabolic/toxicological manifestations of these exposures in the body.[1] In this review we explore the effect of a variety of environmental exposures in early life that have been found to influence the development of allergic disease, with particular focus on exposures to microbes, allergens, and ambient air pollutants.

MICROBIAL EXPOSURE

The increase in the prevalence of allergic disease, particularly in the Western world, has coincided with significant environmental changes that have reduced microbial exposure in early life, such as improved sanitation and increased rates of immunization. Many have proposed that among genetically susceptible subjects, these changes in environmental conditions might alter normal development of the immune system and thus affect susceptibility to allergic disease, the basis of the hygiene hypothesis.[2] In this section we will discuss key findings from studies examining both endogenous and exogenous microbial exposures.

The host microbiome

The human microbiome consists of all microbial communities within the body, including the gut, airways, skin, and others. Alteration of the host microbiome is suspected to play a role in susceptibility to allergic disease, particularly during early life, coinciding with maturation of the immune system. Establishment of the microbiome begins *in utero* and is likely the result of maternal transmission.[3-5] During infancy, differences in the gut microbial environment between those who go on to have atopy and those who do not are apparent in the first few months of life. Reduced diversity of stool flora at age 1 month was predictive of atopic eczema at age 2 years and allergic sensitization and allergic rhinitis at age 6 years.[6]

Similarly, diversity of microbial species in the infant gut was shown to be inversely related to risk of atopic sensitization, allergic rhinitis, and eosinophilia.[7] Atopic children showed reduced early life colonization with *Lactobacillus* species,[8] *Bifidobacterium* species,[8,9] and *Bacteroides* species and increased colonization with *Clostridia* species[8] and yeasts.[9] A greater abundance of *Bacteroides* and *Lactobacillus* species has been associated with protection against allergy, whereas abundance of *Clostridia* species has been associated with wheezing, allergic sensitization, and atopic eczema.[10,11]

Microbial colonization of the airways also begins early in life. Colonization with *Streptococcus* species at age 2 months was associated with increased risk for earlier first lower respiratory tract illness, which has been linked to later asthma development.[12] Similarly, in a study from the Copenhagen Prospective Studies on Asthma in Childhood birth cohort, asymptomatic 1-month-old neonates colonized with *Streptococcus pneumoniae*, *Moraxella catarrhalis*, or *Haemophilus influenzae* through hypopharyngeal aspirate were at greater risk of a first wheezing episode, persistent wheeze, severe exacerbation of wheeze, and hospitalization for wheeze.[13] Lower airway colonization with these organisms was also associated with higher blood eosinophil counts and total IgE levels but not specific IgE levels at 4 years and with bronchodilator reversibility and development of asthma at age 5 years. In a study of children younger than 3 years hospitalized for virus-induced wheezing, 60% demonstrated nasopharyngeal colonization with *Streptococcus pneumoniae*, *Moraxella catarrhalis*, or *Haemophilus influenzae*, and this was associated with increased risk of recurrent wheezing episodes during the following year.[14] Importantly, antibiotic use might select for these organisms.[12]

Many factors can affect microbial colonization in infants and young children, including prenatal and postnatal antibiotic exposure, mode of delivery, and early diet. Wu et al[15] identified dose-dependent relationships between risk of childhood asthma and maternal urinary tract infections during pregnancy or infant antibiotic use during the first year of life. The increase in risk is presumably due to changes in the abundance and diversity of the host's commensal microbes, as demonstrated by Penders et al,[16] who reported that antibiotic use in infancy was associated with decreased abundance of *Bifidobacterium* and *Bacteroides* species.

Mode of delivery is also an important determinant of the infant microbiome,[17] although the effect of vaginal versus caesarean delivery on development of allergic disease is debated. Vaginally delivered infants tended to be colonized with vaginal (*Lactobacillus* species) and fecal (*Prevotella* species) flora, whereas infants born by means of caesarean section tended to be colonized by skin flora (*Staphylococcus* and *Corynebacterium* species),[17] with increased abundance of *Clostridium difficile* and reduced *Bifidobacterium* and *Bacteroides* species.[16] Meta-analyses of studies examining the association between delivery mode and allergic disease in Western countries found an increased risk of childhood asthma,[18,19] allergic rhinitis,[18] and food allergy[18] in children born by means of caesarean section compared with vaginal births. However, studies from outside the United States and Europe have not consistently shown these effects.[20-22]

Diet during early life can also be important for establishing the infant's microbiome. Breast-feeding was associated with greater microbial diversity compared with formula feeding,[23] and a recent study reported that breast-feeding was associated with a trend toward increased *Bifidobacterium* and reduced *Clostridia* species at 3 to 6 months of age.[24]

Despite this evidence, it remains unclear whether these differences in the infant microbiome promote development of allergy or merely serve as a marker of immune dysregulation early in life that leads to allergic disease.

The external microbial environment

Exposure to abundant and diverse microbes in the environment appears to augment the risk of allergic disease. The "biodiversity

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