Published in final edited form as:

Curr Opin Allergy Clin Immunol. 2017 April ; 17(2): 116–122. doi:10.1097/ACI.0000000000000338.

Microbes, Allergic Sensitization and the Natural History of Asthma

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Abstract

Purpose of review—Understanding factors that lead to asthma development in early life is essential to developing strategies aimed at primary or secondary prevention.

Recent findings—This article will review current evidence addressing the development of early life allergic sensitization in relation to microbes and the gut and airway microbiome. Wheezing illnesses, particularly viral, remain a significant risk factor for asthma inception; however, bacterial pathogens have recently emerged as an additional important contributor to asthma risk, either alone or as cofactors with viral infections. The combined influence and interaction of early life viral wheezing and aeroallergen sensitization is important, with allergic sensitization preceding the onset of viral wheeze. Lastly, we review recent data from longitudinal studies regarding the development of irreversible airway obstruction and its impact on the natural history of asthma.

Summary—The development of asthma remains complex and incompletely understood. There is interplay between genetic predisposition and environmental exposures, including allergens and microbes. Interventions aimed at these risk factors during the preschool years may prevent the longitudinal course of asthma progression to irreversible airway obstruction.

Keywords

children; asthma development; aeroallergen sensitization; wheezing illnesses; microbiome; rhinovirus; RSV; bacteria

Introduction

The inception and natural history of asthma has been an area of active research over the past several decades. (1–7) Understanding factors that lead to asthma development is essential to developing strategies aimed at primary or secondary prevention. The development of allergic sensitization and wheezing respiratory tract illnesses have been identified as clear risk factors for asthma inception. Not only have they been shown to be independent risk factors,

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Conflicts of interest

Dr. Jackson reports receiving consulting honoraria from Novartis, GlaxoSmithKline, and Vectura. Dr. Anderson reports no conflicts of interest.

there is also evidence to suggest they are synergistic in the development of asthma. While there are a multitude of contributing factors, both genetic and environmental, that occur at a critical developmental window in time, this article will review current evidence addressing the role of allergic sensitization, microbes and their interaction, as it relates to the inception and natural history of asthma.

Early life allergic sensitization

Allergic sensitization, most notably to perennial aeroallergens, is a major risk factor for childhood asthma development. (4, 8) The development of allergic sensitization has the greatest impact on later asthma inception when sensitization occurs early (in the first few years of life) and to multiple aeroallergens. (8, 9) Children sensitized to multiple aeroallergens at an early age have a remarkable increase in risk for asthma and severe exacerbations leading to hospitalization. Recently, Havstad et al utilized latent class analysis to identify specific patterns of serum specific IgE in early life. Those that are “highly sensitized” (i.e. sensitized to multiple allergens, both food and inhalant) are more at risk for numerous allergic manifestations, including a doctor-diagnosis of asthma, compared to those with low to no sensitization or primarily food sensitization. (10) Children involved in the Pollution and Asthma Risk: an Infant Study (PARIS), a population-based prospective birth cohort demonstrated three profiles of increasing severity with regard to allergic sensitization to foods and aeroallergens(11). The two profiles with increased allergic sensitization by age 18 months demonstrated increased prevalence of doctor-diagnosed asthma, rhinitis, eczema, food allergy and multimorbidity at 2 years, as well as symptoms of current asthma, rhinitis, eczema and multimorbidity at age 6 years.

In the Childhood Origins of Asthma (COAST) cohort, allergic sensitization at year 1 to food or aeroallergen is associated with increased asthma risk at year 6 (aeroallergen: OR, 2.7; food: OR, 2.0) and aeroallergen sensitization at year 1 intensifies as a risk factor for asthma at age 13 (OR, 6.1). (12) Developmental patterns of allergic sensitization and their relationship to subsequent asthma risk were examined in this study as well and found that children who were sensitized to 1 or more aeroallergens by age 1, had the highest rate of asthma at year 13 (65%); children who were not sensitized at year 1 but sensitized to 1 or more aeroallergens by age 5 years had a 40% rate of asthma at age 13 years and the remaining children were not sensitized by age 5 years and had an asthma rate of 17% at age 13 years. Importantly, children in the cohort who developed allergic sensitization after age 5 had an asthma risk at age 13 that was no different than age-matched children without aeroallergen sensitization. Taken together, the timing, etiology and magnitude of allergic sensitization are critical factors in the link of allergic sensitization to subsequent asthma risk.

The development of allergic sensitization in early life is also associated with measurable and persistent differences in lung function. Illi and colleagues showed that children who are sensitized and exposed to perennial allergens have reduced lung function at school age. (13) The Perth Infant Asthma follow-up cohort extended these observations, demonstrating that early sensitization (19% of the infants in their cohort) was longitudinally associated with a persistent reduction in lung function from 1 month to 24 years of age when adjusted for in utero smoke exposure. (14) Early sensitization in this cohort was also associated with a 3-

fold increased risk for asthma at age 6 and increased risk for current wheeze to 18 and 24 years of life.

The mechanism by which early sensitization impacts asthma risk is not fully understood. However, in a study of preschool age children with severe recurrent wheezing, airway smooth muscle area (ASM) was higher in preschoolers with atopy than without atopy (13.1% vs. 7.7%; $P = 0.01$), while differences in other features of remodeling were not observed. (15) Additionally, increased ASM mass was the only reported feature to be a predictor of future asthma.

Microbial exposure, the microbiome and the impact on sensitization and wheezing

Since early allergic sensitization is an important risk factor for later asthma development, it is important to understand what may put a child at risk for early sensitization. While there are likely many factors, recent epidemiologic studies in Central Europe have demonstrated a significant protective effect on the development of asthma and allergic disease in children raised on traditional dairy farms that have high microbial exposures (both bacterial and fungal). (16). Recently, Stein et al found that despite similar genetic ancestries and lifestyle, Amish children who are raised amidst traditional farming techniques are exposed to significantly (6.8 times) higher endotoxin levels and also had an allergic sensitization rate that was 6 times lower when compared to Hutterite children raised with modern farming practices. (17) Interestingly, in mouse models for allergic asthma, inhalational exposure to Amish house dust with higher endotoxin levels led to less airway hyper-responsiveness and eosinophilia compared to Hutterite house dust-exposed mice, and Amish children had enhanced innate immune responses compared to Hutterite children. The results suggest that certain microbial environmental exposures, namely close contact of children to the Amish farming environment, promote maturation of the innate immune system, which in turn conveys protection against allergic sensitization and asthma.

Data collected from the Urban Environment and Childhood Asthma (URECA) study examined a birth cohort at high-risk for asthma in Baltimore, Boston, New York, and St. Louis similarly suggests that exposure to “bacterial richness” may be protective against the development of allergic sensitization and wheezing. (18) While cumulative allergen exposure over the first 3 years of life is associated with allergic sensitization, a surprising finding in this study was that children in homes with high levels of cockroach, mouse and cat in the first year have less recurrent wheeze at age 3 years. Furthermore some of the “protective” bacterial taxa were positively associated with mouse and cockroach levels. This suggests that pests may actually enhance the microbial exposure in the urban environment and perhaps promote favorable clinical outcomes.

While we speculate that the microbial diversity we are exposed to in the environment is important to instruct a well-adapted immune response, at this time, very little is known about how the environmental microbiome might shape the human microbiome. However, recent studies have suggested that alterations in the microbiome of infants and children may be associated with increased asthma risk and perhaps the early multiple sensitization phenotype. (19, 20) The Copenhagen Prospective Study on Asthma in Childhood (COPSAC) high-risk birth cohort first reported the importance of asymptomatic bacterial

colonization of the hypopharynx in infants. *Streptococcus pneumoniae*, *Haemophilus influenzae*, and/or *Moraxella catarrhalis* colonization at 4 weeks of age was associated with a persistent wheezing phenotype, asthma diagnosis, positive bronchodilator response, and the development of atopic biomarkers (elevated peripheral eosinophil count and total serum IgE) at age 5. (21) Despite this association, it remains unknown whether asymptomatic bacterial colonization promotes the development of asthma or rather if it is a marker for immune dysregulation early in life. Prospective data from the same cohort implicated bacterial pathogens as potential independent causal factors for wheezing episodes. (22) In children between the ages of 4 weeks to 3 years, wheezing episodes were not only associated with viral illnesses (OR=2.8), as expected, but also with bacterial infection (OR=2.9). The associations of bacteria and viruses were independent of each other.

More recently, the Childhood Asthma Study (CAS) high-risk birth cohort used 16s sequencing to assess nasopharyngeal (NP) samples from infants at planned healthy visits and with illness to further elucidate the NP microbiome during the first year of life. (23) Early colonization (around 2 months) with *Streptococcus* was associated with asthma risk at age 5. Other independent risk factors for later chronic wheeze in their study included: febrile lower respiratory illnesses and RV-C lower respiratory illnesses with wheezing, especially in participants with allergic sensitization. Another study evaluating children raised in farming environments compared to those not raised on farms found that *Moraxella* abundance was associated with asthma in the non-farm children. (24) Children living on farms seem to not be susceptible to the disadvantageous effect of *Moraxella*. Notably, the non-farm children also had lower diversity of nasal microbiota.

The gut microbiome is increasingly recognized as an important instructor of immune maturation. Most findings about the potential role of the gut microbiome stem from experimental studies in mice, and little is known from human studies; however, a recent study of racially and socioeconomically diverse participants from the Wayne County Health, Environment, Allergy and Asthma Longitudinal Study (WHEALS) birth cohort found that distinct differences in the gut microbiota of infants at age 3 months are differentially associated with atopy at age 2 years. (25) The highest risk group demonstrated a lower relative abundance of certain bacteria and a higher relative abundance of particular fungi and a fecal metabolome enriched with pro-inflammatory metabolites. Furthermore, the highest-risk fecal fluid induced IL-4 production by adult CD4 T cells in *ex vivo* culture. These findings suggest that gut microbiome alterations (bacterial and fungal) in early life may drive T cell production of Th2 cytokines, which may be associated with early childhood allergic sensitization.

Virus and Bacteria Infections

Viral respiratory wheezing illnesses are common in early childhood, and many children who wheeze subsequently develop asthma. The risk of asthma seems to be most closely associated with the occurrence and frequency of virus-induced wheezing illnesses. (26) Respiratory syncytial virus (RSV) historically has been considered the most important respiratory pathogen for asthma inception risk. Many studies have supported that infant RSV bronchiolitis is associated with recurrent wheeze or asthma throughout childhood and even

into early adulthood. (27, 28) In population based cohorts from Northern California Kaiser Permanente (KPNC) and Tennessee Medicaid (TennCare), the proportion of children who developed asthma was almost two times higher in children with a history of infant bronchiolitis during RSV season as compared to the children who did not have a history of infant bronchiolitis during RSV season. (29) Supportive mechanistic animal studies demonstrate infection with RSV induced a Th2-like effector phenotype in T regulatory cells and this may in turn suppress tolerance to unrelated antigens, including allergens. (30) Furthermore treatment with anti-RSV monoclonal antibody, in otherwise healthy pre-term infants, resulted in significant lower frequency of wheezing illnesses in the first year of life, implicating RSV as an important factor for recurrent wheeze. (31)

The role of rhinovirus (RV) infections in early life wheezing was previously underappreciated because of poor growth of RV using standard culture techniques; however, with the advent of sophisticated molecular sequencing techniques, the ability to identify RV more robustly, including novel RV-C types, has led to the recognition that RV is a major etiologic risk factor for early life wheezing and asthma inception. (32) RV-wheezing illnesses have been associated with an approximately 10-fold increase in asthma risk by 6 years of age, regardless of aeroallergen sensitization or other risk factors.(26)

The COPSAC high-risk birth cohort has recently reported that the number of lower respiratory episodes in the first three years of life, as opposed to a specific viral or bacterial etiology, is associated with asthma risk, and suggested that the specific microbiologic trigger is not important for the risk of later asthma development. (33) However, in the COAST cohort, the number of early life wheezing illnesses, irrespective of etiology, is also found to be important for asthma risk; however, the number of rhinovirus wheezing illnesses is the most robust asthma predictor in children to age 13. (34) Wheezing with RSV in the first 3 years of life was associated with an increased risk of asthma at ages 6, 8, and 11 years, but this was no longer significant at 13 years (OR, 2.8, 2.6, 2.9, and 1.6).(12) Wheezing with RV during the first 3 years of life was associated with a greater increased risk of asthma at age 6, 8, and 11 years that, unlike RSV, persisted out to the 13th year of age (OR, 7.9, 7.5, 6, and 3.4) In a multivariate model adjusted for wheezing with other viruses, RSV wheezing in the first 3 years of life was not associated with an increased asthma risk at any age. In contrast, RV wheezing was associated with a persistent increase in the risk of asthma at 6, 8, 11, and 13 years.

While strongly associated with asthma risk, the question has remained as to whether RV is causal in asthma inception. A recent mechanistic study has supported the concept that recurrent RV infections can contribute to aspects of airway remodeling. (35) Rhinovirus-infected airway epithelial cells produce chemoattractants, primarily CXCL10 (IP-10) and CXCL8 (IL-8) that drive fibroblast migration. Additionally, RV-C is highly virulent and has been associated with increased lower respiratory tract illnesses, emergency department visits and hospitalization and may occur more frequently in children with allergic sensitization. (36, 37) RV-C has a unique receptor, recently identified as cadherin related family member 3 (CDHR3) that enables RV-C binding and replication. A coding single nucleotide polymorphism that has previously been linked to wheezing illnesses and hospitalizations for childhood asthma, also mediates enhanced RV-C binding. Therefore, infants with this risk

locus may have more susceptibility to RV-C infections and illnesses, which may negatively affect the developing lung and increase asthma risk. (38)

Allergy-Virus Interactions

The combined influence of early life viral wheezing and aeroallergen sensitization has been clearly linked to an even greater risk for the development of asthma. (7, 26) Recent findings from COAST demonstrate that aeroallergen sensitization at year 3 without RV wheezing in the first 3 years of life and RV wheezing without concomitant aeroallergen sensitization was each associated with increased risk of asthma at age 6, 8, 11, and 13 years (OR, 3.9 and 7.8, 2.9 and 8.1, 2.9 and 6.2, 2.7 and 3, respectively). However, children with both RV wheezing and aeroallergen sensitization by age 3 years had the highest incidence of subsequent asthma at 6, 8, 11, and 13 years (OR, 45, 20, 14, and 7.9)

More specifically, there is likely a sequential relationship with allergic sensitization preceding viral wheezing. In fact allergic sensitization may lead to more severe RV-induced lower respiratory illnesses. (39) A variety of mechanisms support this interaction, including the findings that children with allergic asthma have impaired antiviral responses. (40) A recent clinical trial studied the use of omalizumab (anti-IgE) to prevent seasonal virus-induced asthma exacerbations. (41) Omalizumab reduced virus-induced exacerbations, which also coincided with reduced type I interferon response ex vivo in rhinovirus-stimulated mononuclear cells. Interestingly, the participants with larger increases in type I interferon response with omalizumab treatment had the greatest protection from virus-induced exacerbations. (42) These findings provide some of the most direct evidence supporting the importance of allergen-virus interactions in asthma exacerbations.

Natural History of Asthma

Longitudinal studies evaluating the natural history of persistent childhood asthma have demonstrated that the period between birth and 6 years of age is a critical developmental window for the development of airflow limitation. (43) Furthermore, patterns of growth and decline in lung function in persistent childhood asthma suggest that ~17% of children with mild or moderate asthma at school age will meet criteria for COPD by their third decade of life. (44) Patients with COPD at age 50, who had a history of severe childhood asthma, had acquired their reduced lung function in their childhood years. (45)

Historically it was felt that chronic airway inflammation was the cause of structural airway remodeling, but randomized prospective trials did not show a change in prognosis despite treatment with controller inhaled corticosteroid. (46, 47) Structural airway changes have been observed to occur early in life. In infants, eosinophilic inflammation and reticular basement membrane thickening are not yet present despite presence of reversible airflow obstruction. However, at 3 years of age, both are present in children with severe persistent wheezing. (48) Increased angiogenesis, epithelial shedding and increased airway smooth muscle mass are also reported. (15) Bronchial hyperresponsiveness can be present as early as 6 years of age and persist into adulthood and bronchoconstriction itself, irrespective of airway inflammation, may promote airway remodeling as well. (49, 50) It also has been

observed that recurrent severe wheezing exacerbations during early life lead to airway remodeling and are associated with progressive reductions in lung function in school-age children and adults. (51, 52). All of these observations suggest that prevention of lower airway inflammation, bronchoconstriction and recurrent severe lower respiratory tract illnesses in early life may have a long-term positive impact on lung growth and development.

Conclusion

The inception and natural history of asthma remains complex and incompletely understood. There is interplay between genetic predisposition and environmental exposures, including allergens and microbes. Early life allergic sensitization and wheezing respiratory illnesses (both viral and bacterial) can be independent and/or synergistic risk factors for asthma development. Interventions aimed at these risk factors during the preschool years may prevent the longitudinal course of asthma progression to irreversible airway obstruction. Further study of the interactions among the host and microbes (viruses, bacteria and fungi) will be important in further elucidating the development and progression of asthma, with the important goals of both primary and secondary asthma prevention.

Acknowledgments

Financial support and sponsorship

Supported by NIH Grants PO1 HL70831

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Key Points

- Early life allergic sensitization and wheezing respiratory illnesses (both viral and bacterial) are independent and synergistic risk factors for asthma.
- Exposure to diverse microbial environments and antigens may instruct innate immune maturation and provide protection against allergic sensitization and subsequent wheeze.
- The period between birth and 6 years of age is a critical developmental window for the development of airflow limitation and thus an important time-frame to target for prevention strategies.

Figure 1.
Risk factors for inception and progression of asthma.