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Infections and Their Role in Childhood Asthma Inception

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Summary

The association of early onset wheezing with common viral and bacterial infections has raised significant interest in the role of infections in childhood asthma inception. This article serves to review these relationships among infections, host factors, and asthma inception in childhood.

Keywords

inception; asthma; infection; wheezing; virus; childhood; genetics

Introduction

Asthma is a common chronic respiratory disease, responsible for a significant amount of morbidity and mortality in the Western world. Understanding the origins of asthma inception and risk factors for severity of disease can potentially help elucidate modes of early intervention that could alter the disease course, with an aim at primary prevention. The majority of children with a history of asthma and impaired lung function at school age have a history of recurrent wheezing illnesses in early life(1-3). Additionally, throughout childhood and beyond, viral illnesses are the most common triggers of asthma exacerbations.(4) The timing of early onset wheezing with common viral infections has raised significant interest in the role of infections in childhood asthma inception. Furthermore, studies using molecular diagnostics suggest the airway microbiome may be involved in complex infectious relationships that may be altering the disease course of both chronic asthma and associated exacerbations. Host factors such as allergic sensitization, antiviral immune responses, and environmental exposures are additionally thought to modify these relationships(3, 5-8). In this article, we review these relationships among infections, host factors, and asthma inception in childhood (Figure 1).

Epidemiology of Wheezing and Asthma

Asthma, the most common chronic disease of childhood, often presents during the preschool years with wheezing viral respiratory infections. Viral wheezing illnesses during childhood are pervasive, with up to 50% of children having at least one episode of wheezing prior to school age.(1) Viral pathogens have been demonstrated in up to 90% of acute wheezing episodes within the first 3 years of life.(2) Improvements in molecular diagnostic techniques, through the advent of PCR, have enhanced our ability to recognize novel species

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and types of viruses previously undocumented or underestimated in the wheezing patient (Table 1). While respiratory syncytial virus (RSV) had long been recognized as a cause of lower respiratory tract infections in infants, particularly during the winter season, human rhinovirus (HRV) has been detected in more than 60% of asthma exacerbations, making it a common culprit throughout the year.(9) The previously difficult to culture HRV-C species has now been identified, with data indicating this particular virus may be intrinsically more virulent and likely to incite wheezing.(10) Parainfluenza, coronavirus, influenza, adenovirus, bocavirus, and human metapneumovirus (hMPV), have also been identified in wheezing children, along with bacteria including nontypeable haemophilus influenza, streptococcus pneumoniae, moraxella catarrhalis, mycoplasma pneumoniae and chlamydophila pneumoniae. (11-15)

Viral Infections: The Major Players

HRV and Asthma Inception

HRV is the most frequent cause of the common cold, and has been identified as a pathogen in both the upper and lower airways.(10, 16, 17) HRVs are non-enveloped, single stranded RNA viruses from the *Picornaviridae* family of viruses. Based upon sequence homology, 3 distinct species of HRV have been identified: HRV-A, HRV-B and HRV-C. HRV-A is composed of >70 types, and HRV-B with >25 types. More recently, a 3rd distinct group of HRV-C has been identified, with a rapidly expanding number of distinct serotypes. This particular species has proven difficult to grow in traditional culture, making their initial detection elusive. HRV-C has been identified frequently from patients hospitalized for fever, respiratory illness, and asthma exacerbations.(10) Children hospitalized with HRV infection tend to be older with a prior history of wheezing, as well as a personal history of atopy.(18) The omnipresent nature of HRV infections throughout the year can be further categorized via species analysis. Data has shown peak incidence of HRV-C types in the fall, timing that correlates with increased asthma exacerbations and hospitalization rates, and with increased HRV-A detection during the spring.(10, 19) There is a relatively low level of HRV-B burden throughout the year.(10) The broad spectrum of illness generated by HRV infections, from asymptomatic to severe respiratory compromise necessitating hospitalization, strongly suggests that host factors modify the impact of infection. As such, allergic sensitization and innate immune response patterns to infection are thought to play a vital role.(5, 6, 20)

Recent evidence has pointed to illnesses caused by HRV infection as a strong predictor of asthma development. In a prospective analysis of outcome in relation to asthma, Kotaniemi and colleagues investigated 100 children hospitalized for wheezing during the first 2 years of life, performing viral RT-PCR from frozen nasal aspirates obtained from the index episode of wheezing.(21) They found that while prior to 6 months of age, RSV was the most commonly isolated viral pathogen, from 6 months onward, HRV was most prevalent in wheezing children. The risk for asthma development by school age was 4x greater in the HRV infected group than for children hospitalized with other respiratory viral illnesses.(21) Kusel et al demonstrated, in a high-risk birth cohort, an association between outpatient wheezing with HRV in infancy and persistent wheezing at 5 years of age, particularly for children with early allergic sensitization.(3) The Childhood Origins of ASThma study (COAST), also a high-risk birth cohort, identified HRV-induced wheezing during infancy as the most significant predictor of persistent wheezing at 3 years of life, and a diagnosis of asthma at age 6 years.(2, 6, 12) These associations were strongest for those with a history of early aeroallergen sensitization(2).

RSV and Asthma

Respiratory Syncytial Virus (RSV), a negative stranded, enveloped, RNA virus of the *Paramyxoviridae* family, has long been recognized as an important viral pathogen during the winter months, frequently leading to early life wheezing. While RSV is not a predominant cause of asthma exacerbations in the older child or adult, debate has continued on the causal relationship to the subsequent development of asthma.(22-27) Several studies have demonstrated that RSV related severe lower respiratory tract infections (LRTI), particularly those requiring hospitalization, are associated with an increased risk of asthma diagnosis at school age.(28, 29) A prospective cohort study conducted in Sweden by Sigurs and associates (28, 30) used a case-control design to compare 47 hospitalized infants with documented RSV infection in infancy to 97 healthy controls, measuring rates of asthma and allergic sensitization over time. By the 18-year follow up, they found a higher percentage of both current asthma diagnosis (39% vs. 9%, $p<0.001$) as well as allergic sensitization (41% vs. 14%, $p=0.005$) in the RSV group than in the control.(30) Using a multivariate analysis approach, RSV infection was found to be the major risk factor in subsequent asthma development (OR 7.2). They concluded that severe early RSV bronchiolitis was associated with increased prevalence and persistence of allergic asthma into early adulthood. The Tucson Children's Respiratory Study (TCRS) reported persisting respiratory symptoms (wheeze) through early adolescence in subjects who experienced outpatient RSV LRTI during the first 3 years of life. Interestingly, the association to wheeze diminished with age, and lost significance by 13 years of age.(29) The Tennessee Asthma Bronchiolitis Study (TABS), a large unselected population based retrospective study of children identified through a Medicaid database, investigated the relationship between winter virus infection and asthma.(31, 32) They found that the risk of asthma by age 5 increased with the timing of infant birth in relation to the peak of the winter virus season, with subjects born 120 days prior to winter virus peak having the highest risk.(31)

These findings led to speculation that prevention of RSV infection could potentially reduce asthma outcomes. Simoes and colleagues compared a group of premature infants treated with palivizumab, an anti-RSV monoclonal antibody, and compared them to an untreated aged-matched cohort. They found on prospective follow up that the incidence of recurrent wheezing was significantly lower in the palivizumab treated group than for the untreated controls, suggesting that preventing LRTI with RSV could reduce the development of persistent wheezing.(33) A recent randomized controlled trial by Blanken et al showed that otherwise healthy premature infants treated with palivizumab had a relative reduction of 61% (95% CI 56-65) in the number of wheezing days within the first year of life when compared to controls that received a placebo injection during the RSV season. Perhaps even more encouraging was the demonstration of the extended protective benefit from palivizumab, noting a persistent reduction in total wheezing days and respiratory related hospitalizations >2months out from the last palivizumab injection.(34) Whether these findings will translate to asthma prevention is not known and of interest moving forward.

Conversely, there are several studies that argue against the causality of RSV in asthma inception. Poorisrisak and colleagues looked at 37 pairs of monozygotic twins, differing with respect to hospitalization for RSV-bronchiolitis during infancy, and found no difference with regard to subsequent development of asthma or allergic sensitization by 7 years of age within the twin pairs.(35) While definitive conclusions are limited due to the small sample size of the study, the results argued against the role of severe RSV infection in the development of asthma, as earlier studies had implied. Similarly, a larger twin based study, conducted in Denmark by Thomsen and associates, identified an association between severe RSV illness and asthma, but not a causal relationship.(36)

Other Viruses

Influenza, an RNA virus in the *Orthomyxoviridae* family, is responsible for a significant amount of respiratory related illness in both children and adults; however, its effect specifically within the asthma population has been debated(37). Studies have demonstrated significant morbidity associated with influenza infection for patients with underlying chronic conditions (such as asthma) when compared to healthy controls.(38) A large prospective study of children 6 months to 59 months of age looked at rates of influenza attributable outpatient visits and hospitalizations for children with asthma, and compared this to otherwise healthy children over a 5 year period of time.(39) They found that the average influenza associated hospitalization rate was 4x greater, with a 2 fold increase in outpatient visits, for the asthma group, than for the nonasthmatic children.(39) However, prospective studies looking to distinguish influenza's role in the setting of acute asthma exacerbations have failed to show a strong association.(27)

Human Bocavirus (HBoV), a member of the *Parvoviridae* family, is a relatively newly identified virus, first recognized in 2005 with the aid of molecular sequencing(40). It primarily infects the respiratory tract, and while the virulence in causing symptomatic respiratory symptoms has been debated, data have shown a high degree of co-infection with other viral pathogens, namely HRV, RSV, and adenovirus, particularly in children under age 2 years.(41, 42) These data suggest that its role in early life LRTI may be underappreciated; however, further investigation is needed.

Human metapneumovirus (hMPV), a *Paramyxovirus* closely related to RSV, has been linked to both asthma inception as well as exacerbations within the pediatric and adult populations.(24, 43-47) A study conducted by Garcia-Garcia and associates investigated the relationship between hMPV bronchiolitis and the subsequent development of wheezing. They compared this outcome, at ages 3 and 5 years, for 55 children who were hospitalized for either hMPV- related bronchiolitis or RSV-bronchiolitis during the first 2 years of life. They found, in a multivariate analysis, that hMPV was the most important risk factor for the development of asthma by the preschool years (OR=15.9). (43) Additionally, data published by Williams et al found a significant association between hMPV and wheezing among children less than 3 years of age; however, the relationship lost significance in children 3 years and older, indicating that hMPV may play an important role during early life, a critical period of lung growth and development.(47)

Bacteria and the Airway Microbiome

Advances in molecular diagnostics have expanded our knowledge of the diversity of the human microbiome and its relation to human diseases. With improved ability to recognize and identify a growing number of bacteria within the airway, the natural progression to investigate their potential role in chronic pulmonary diseases has come to the forefront of focus. Bisgaard et al published data from a large birth cohort study of high risk subjects identified at birth by maternal history of asthma, that noted positive associations between bacterial colonization with streptococcus pneumoniae, haemophilus influenzae, and moraxella catarrhalis (or a combination of these organisms) in the hypopharynx of asymptomatic neonates, and the subsequent development of asthma (prevalence in colonized 33%, not colonized 10%, OR 4.57) within the first 5 years of life. (48) The association was found to be "time specific", that is, present only for the infants colonized by 1 month but not at 12 months of age. (48) A second study, performed on the same high-risk population, looked at the frequency of bacteria and virus present in airway aspirates during acute wheezing illness.(49) They found that wheezing was significantly associated with bacterial infections (OR 2.9, $p<0.001$), primarily streptococcus pneumoniae, haemophilus influenzae, and moraxella catarrhalis, and this relationship was similar but distinct from the association

with viral infections (OR 2.8, p<0.001)(49). Similar findings were noted by De Shutter et al, who retrospectively analyzed a population of recurrent wheezing children between the ages of 4 and 48 months, who underwent bronchoscopy and BAL after failing to respond to inhaled corticosteroids.(50) 48% of subjects had significant bacterial BAL cultures, with non-typeable haemophilus influenz most common, followed by streptococcus pneumoniae and moraxella *catarrhalis*, respectively.(50)

Progression from Early Life Wheezing to Asthma

Inflammation in Preschool Children

Krawiec and colleagues performed bronchoscopy and bronchoalveolar lavage on 20 wheezing children (median age 15 months) with recurrent/persistent wheezing. When compared to normal controls, they found that the wheezing children had 3 times the total BAL cells. The cellular increase was nonspecific, unlike the eosinophilic predominance seen in many older children and adults with asthma(51, 52). They additionally found increased levels of inflammatory mediators PGE2, LTE4 and LTB4, suggesting that ongoing inflammation is present in the airways of young wheezers.(52) Saglani and colleagues performed endobronchial biopsies on both wheezing subjects (aged 3 months to 5 years) and aged matched controls(53). Unlike the pathogenic hallmarks of asthma established for older children and adults, they found no evidence of eosinophillic inflammation nor reticular basement membrane thickening in the infant wheezers (median age 12 months), even in the presence of atopy(54, 55). However, these pathologic markers were noted in slightly older wheezing children (median age 29 months), suggesting that the time between 1 and 3 years of age is a critical period for asthmatic airway remodeling, and that changes are not a congenital phenomenon, but more likely a consequence of environmental exposures and disease development over time (53).

Symptoms & Lung Function Changes in Early Life

Guilbert and colleagues followed a cohort of preschool aged children at high risk of asthma, and found that for children who did not outgrow their wheezing, their symptom burden progressively increased through their preschool years.(56) Those early wheezers with persistent disease have additionally been shown to have diminished lung function by school age. Within the TCRS cohort, children with persistent wheezing beginning prior to age 3, had reductions in lung function at age 6 years that persisted over time.(57) Similarly, the COAST study demonstrated an association between recurrent severe exacerbations in early life that required OCS and reduced lung function at school age.(58) The persistent and progressive nature of disease course noted in these studies suggests that early life remodeling of the airway may be occurring.

Host Factors and Asthma Development

Immunologic Factors

Whether infection leads to asthma versus the counter argument of an underlying predisposition to asthma and early life wheezing illnesses has long been debated, with the search for explanatory mechanisms a goal for many research groups. Multiple cohort studies have identified impaired IFN-γ responses at birth or infancy with recurrent wheezing in early life, but these relationships have not generally persisted to childhood asthma risk (5, 7, 59). Sensitization to aeroallergens is a clear risk factor for asthma development, with recent data suggesting that children who develop sensitization to multiple allergens in early life are at particularly high-risk of asthma inception and severe exacerbations. (60, 61), In fact, a sequential developmental relationship with allergic sensitization leading to HRV-induced wheezing, and subsequent asthma, has recently been identified.(6) This leads one to

question: what mechanisms link allergic sensitization to HRV-induced wheezing and asthma?

One potential mechanism involves impairment of antiviral immunity by allergic sensitization and exposure. Children and adults with allergic asthma have been reported to have reductions in peripheral blood mononuclear cell production of types I and III interferons in response to influenza and HRV infection. (62, 63) These abnormalities are associated with expression of the high-affinity IgE receptor (FcεRI) on plasmacytoid dendritic cells (pDCs) and are accentuated by FcεRI crosslinking. Additionally, epithelial cell antiviral responses have been reported to be abnormal in patients with allergic asthma (8, 64), although not all groups have been able to replicate these findings(65)

Other potential pathways that may enhance HRV susceptibility in allergic individuals involve the effects of allergic inflammation on the airway leading to enhanced airway responsiveness, impaired barrier function, and increased mucous secretion (66). It has also been recently proposed that allergic asthmatics may have an impaired ability to “shut-off” HRV-induced inflammation. (67) Finally, HRV can directly lead to a number of airway changes critical to asthma development. Leigh and colleagues looked at the response of airway epithelial cells following infection with HRV, and noted an overall up-regulation of several growth factors important in airway remodeling including amphiregulin, activin A, and VEGF (68). Zhu and associates found HRV infection triggered mucin production via toll like receptor 3, and also caused up-regulation of epidermal growth factor receptor, providing mechanisms for mucus plugging and epithelial remodeling.(69)

Genetic Susceptibility to HRV Infections

Genetic mutations in a variety of single nucleotide polymorphisms (SNPs) related to innate signaling responses have been linked to asthma, leading to further interest in the complex relationship between a gene-by-environment interaction in asthma inception. Variation at the 17q21 locus is the most replicated asthma susceptibility region of the genome, but is not associated with the development of allergic sensitization.(70-72) Caliskan and colleagues recently reported that the increased risk of asthma in the at-risk “TT” genotype at SNP rs7216389 was seen only in children who wheezed with HRV infections in early life.(70) The mechanisms underlying these observations are unknown and of clear interest for further investigation.

Conclusions and Future Directions

Both viral and bacterial infections in early life cause a significant amount of morbidity, with potentially life-long implications. Their identification during wheezing illnesses and their subsequent presence during exacerbations once disease has been established suggest an import role in airway inflammatory responses, which may lead to the development of various asthma phenotypes. The implications for proving a causal relationship could open new doors for asthma treatment and prevention through the use of vaccination and direct antimicrobials, or indirect means of enhancing the immune response in high-risk individuals. Studies focusing on early prevention, such as the case with palivizumab and RSV, are encouraging in demonstrating that early intervention may modify subsequent risk and morbidity from recurrent wheezing illnesses. These findings foreshadow the potential therapeutic and preventative role for strategies against other respiratory pathogens, notably HRV. The relationships among infections, host responses, and asthma inception remain complex and an important area for future study.

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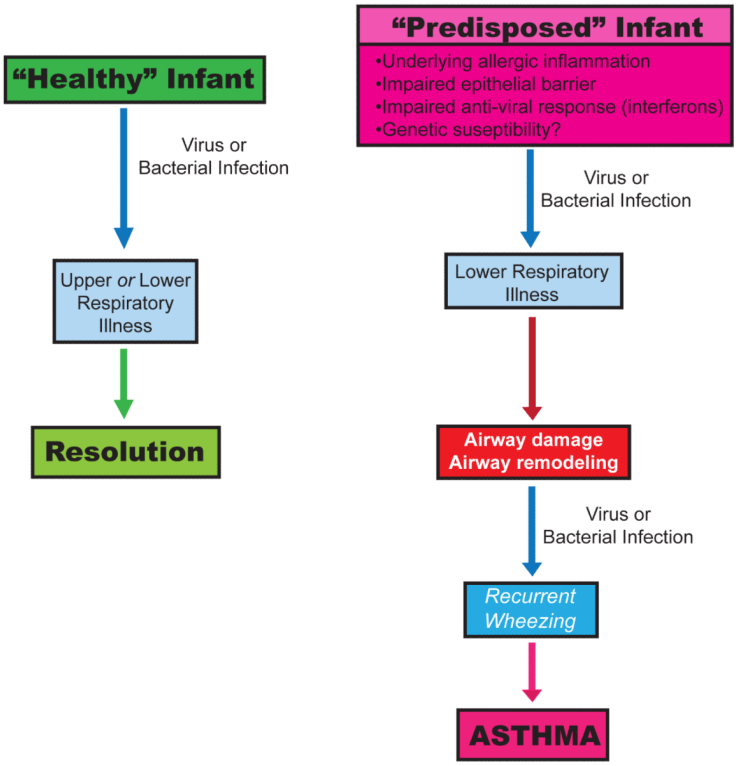

Figure 1. Pathogenesis of Asthma Inception

Adapted from Jackson et al, 2010 **(**73**)** This figure highlights relationships among infections, environmental and host factors in the inception of asthma.

Table 1

Etiology of infection with various outcomes. (Citations in parenthesis)

	Outpatient early life wheezing illnesses	Illnesses associated with hospitalization	Illnesses associated with increased asthma risk
Viruses	• HRV (2,3,21) • RSV (29) • Influenza (40) • HBoV (43) • hMPV (47)	• HRV (10,17,18) • RSV (22,23,28,29,30) • Influenza (40) • hMPV (44,45,46)	• HRV (2,3,6,12,21) • RSV (22,28,29,30,31,32) • hMPV (44,48)
Bacteria	• S. pneumonia • H. influenza • Moraxella catarrhalis(50,51)	• Mycoplasma (13,15)	• S. pneumonia • H. influenza • Moraxella catarrhalis(49)