

Infection-Related Asthma

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The role of infection in asthma is varied in that it may exacerbate established asthma or contribute to the initial development of the clinical onset of asthma. Mounting evidence implicates both roles with particular viral pathogens, namely human rhinovirus and respiratory syncytial virus, among the most likely culprits in asthma inception. Once asthma is present, infection, particularly viral infection, is a common precipitant of asthma exacerbations. Bacterial infections and colonization also have been associated with exacerbation and recurrent wheeze, an effect that may be independent or a cofactor with viruses. Atypical bacterial infections such as *Mycoplasma pneumoniae* and *Chlamydia pneumoniae* and fungi in the case of allergic bronchopulmonary aspergillosis, also play a potential role in inducing and exacerbating this disease. In addition, certain individuals may have a genetic predisposition toward viral-induced wheezing and the development of asthma. This article will discuss host and environmental factors, common pathogens, clinical characteristic, and genetic influences associated with infection-related asthma. © 2014 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2014;2:658-63)

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The role of infection in asthma is varied in that it may exacerbate established asthma or be a contributing factor to the initial development of the clinical onset of asthma. Mounting evidence implicates both roles, with particular viral pathogens, namely human rhinovirus (HRV)^{1,2} and respiratory syncytial virus (RSV),³ among the most likely culprits in asthma inception.^{1,2} Once asthma is present, infection, particularly viral infection, is a common precipitant of asthma exacerbations.⁴ Bacterial infections and colonization also have been associated with exacerbation and recurrent wheeze, an effect that may be independent^{5,6} or a cofactor with viruses.⁷ Atypical bacterial

infections such as *Mycoplasma pneumoniae*⁸ and *Chlamydia pneumoniae*,⁹ and fungi in the case of allergic bronchopulmonary aspergillosis,¹⁰ also play a potential role in inducing and exacerbating this disease. In addition, certain individuals may have a genetic predisposition toward viral-induced wheezing and the development of asthma.¹¹

DEMOGRAPHICS AND PATHOGENESIS

Host and environmental factors

Upper respiratory infections (URI) are the most common cause of acute illnesses in both children and adults. Such viral infections result in increased health care cost and in work and school absenteeism.¹² The demographics of exposure to these agents is of significance in that the seasonal pattern of asthma exacerbations often mirrors the occurrence of viral infections in the community.¹² Infection-related asthma is more common during preschool and early childhood. Although the prevalence of asthma is more common in boys before adolescence, there is no evidence that the incidence or prevalence of infection-related asthma differs based on sex. For viral-induced exacerbations, increases in prevalence during both fall and spring are reported.¹³ The administration of omalizumab virtually eliminated spring and fall exacerbations, which were primarily caused by viral URIs.¹⁴ These observations indicate that interactions between allergic sensitization (antigen-specific IgE antibody formation) and viral respiratory illnesses play an important role in asthma control. Genetic variation at a number of different loci also contributes to the frequency and severity of the host response to viral infection.¹⁵⁻¹⁸ Finally, the socioeconomic environment also may contribute. Results of a 2012 study by Gern et al¹⁹ that showed comparisons of the viral etiology during infancy in children who live in the inner cities of the United States compared with a more suburban environment revealed some interesting differences. Overall, inner-city infants had lower rates of viral detection. When considering specific viruses, urban

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Abbreviations used
HRV- Human rhinovirus
RSV- Respiratory syncytial virus
URI- Upper respiratory infection

infants who were ill had lower rates of detectable HRV or RSV infection and higher rates of adenovirus infection.¹⁹

Pathogen-related factors

Viral and bacterial pathogens most commonly associated with infectious asthma are listed in Table I.

Viruses. Both RSV and HRV are capable of producing significant lower respiratory tract illnesses that require hospitalization (bronchiolitis) during infancy, with individuals with HRV infection tending to be older and presenting with atopic dermatitis and peripheral eosinophilia.²⁰ In addition, outpatient wheezing illnesses caused by RSV and HRV early in life may increase the risk for subsequent wheezing episodes and the development of asthma.^{21,22} Evidence tends to favor a stronger propensity for these developments with HRV than with RSV.^{21,23-26} However, there are significant differences observed even among HRV species A, B, and C. HRV-C and HRV-A are more likely than HRV-B to produce moderate-to-severe lower respiratory illnesses,²⁷ whereas HRV-C is more frequently associated with clinically significant exacerbations.²³

Furthermore, there is evidence that HRV-C may be more likely to cause viremia than HRV-A or HRV-B.²⁸ These collective findings led many researchers to believe that HRV-C may be more virulent.²⁹ One of the notable differences between HRV-C and HRV-A or HRV-B is the receptor used to permit cell entry and viral replication. Species A and B use primarily intercellular adhesion molecule 1 and low-density lipoprotein receptor, whereas HRV-C is thought to use a unique yet, thus far, unidentified receptor.²⁹ Through attempts at culturing the virus *in vivo*, it is thought that this receptor is expressed on epithelial cells in differentiated tissues.²⁹ RSV has 1 serotype that is divided into antigenic subgroups A and B, with further division of each into genetic variants.^{30,31} Among hospitalized infants, group A RSV infection is associated with greater severity of disease.³² There also are data that indicate that infection with RSV promotes T-helper 2-type cytokine production and that this may be involved in the subsequent development of asthma.³³

Bacterial pathogens. In addition to viral causes, there have been investigations into the host microbiome as it relates to asthma inception and exacerbations. Bacteria such as *Lactobacillus* and *Helicobacter pylori* are reported to be protective against asthma, whereas other bacteria are associated with an increased risk of asthma.³⁴ One study demonstrates associations between neonatal hypopharyngeal colonization of *Haemophilus influenzae*, *Streptococcus pneumoniae*, and *Moraxella catarrhalis*, with the subsequent increased risk of developing recurrent wheezing and childhood asthma.^{6,35} It is unclear from these findings whether early colonization with these organisms in some way influences the development of asthma or if the presence of these organisms is a reflection of an altered immune system that predisposes to altered host airway responses to respiratory pathogens. Acute wheezing episodes of preschool children are associated with these bacterial pathogens, with a frequency similar to that seen with viruses.⁵

TABLE I. Viral and bacterial pathogens most commonly involved in infectious asthma

Viruses	Rhinoviral species
RSV	
Bacteria	<i>H influenza</i>
	<i>S pneumoniae</i>
	<i>M catarrhalis</i>
	<i>M pneumoniae</i>
	<i>C pneumoniae</i>

Mycoplasma and Chlamydia. Atypical bacterial infections, for example, *M pneumoniae* and *C pneumoniae*, play a potential role in inducing and exacerbating asthma.³⁶ Results of early studies that involve *C pneumoniae* suggest a link to infection and the onset of asthma.³⁷ Kraft et al³⁸ published an analysis of data that showed that subjects with stable asthma who had positive results by PCR for *M pneumoniae* or *C pneumoniae* improved their lung function when treated with clarithromycin. However, although a later trial that investigated the addition of clarithromycin to fluticasone showed improvement in airway hyperresponsiveness, it failed to show improvement in lung function, asthma control, or other secondary outcomes.³⁹ In a 15-year longitudinal study, subjects who were serologically diagnosed with acute or chronic *C pneumoniae* infection had no greater chance of developing asthma than those who did not. However, subjects who did develop asthma had a more progressive decline of lung function compared with those who tested negative.⁴⁰ A 2013 study by Wood et al⁸ that involved children with and without asthma found *M pneumoniae* in 61% of all the subjects, with no significant difference between subjects with asthma and subjects without asthma. Children with asthma have lower antibody levels to *M pneumoniae* compared with healthy controls, which suggests a poor humoral response. Among patients with asthma, those who tested positive for *M pneumoniae* had significantly lower scores on asthma control and quality-of-life questionnaires.⁸

CLINICAL CHARACTERISTICS

Clinically, HRV and RSV infections are indistinguishable and may not be symptomatic.⁴¹ If symptomatic, infections in adults typically present with nasal discharge, nasal obstruction, cough, and sore throat. Fever is not typical with adult illness.⁴² Children present with fever, cough, nasal discharge, and obstruction. The duration of symptoms is longer than with adults, which often lasts more than 10 days.⁴³ Indications of bacterial infection in children include high fever that persists for ≥ 4 days, accompanied by purulent nasal discharge and ill appearance.^{44,45} Production of purulent sputum does not distinguish a viral from a bacterial infection.⁴⁶ Virally induced asthma exacerbations typically begin 1 to 2 days after symptoms of infection begin and are characterized by brief episodes of wheezing and decreased pulmonary function. Symptoms are most significant during the first 48 hours of exacerbation and return to baseline within 5 to 10 days.⁴⁷

Approximately 80% of asthma exacerbations with children and 50% with adults are attributed to respiratory viral infections, with HRV accounting for nearly two-thirds of them. Such exacerbations may be followed by asymptomatic periods and normal pulmonary function. This pattern of asthma differs from other forms of asthma in both adults and children, which are

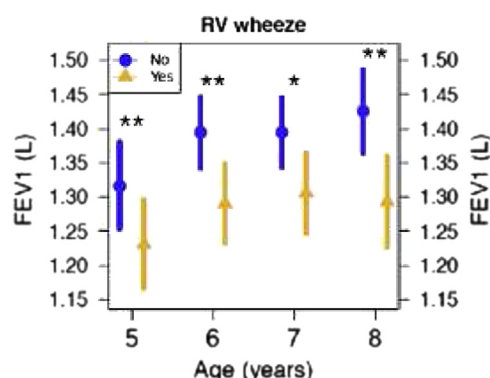


FIGURE 1. Children with preschool HRV wheezing illnesses had significantly lower FEV₁ at ages 5–8 years. Circles and triangles represent means, and bars represent 95% CI. Significant differences between treatment groups denoted by * $P < .05$ and ** $P < .01$. With permission Ref 54.

characterized by more chronic and persistent symptoms as well as alterations in pulmonary function that are present between infectious episodes. More chronic asthma may have superimposed increases in symptoms and reductions in pulmonary function that occur intermittently during respiratory tract illnesses. Importantly, the number of corticosteroid-requiring exacerbations most commonly related to respiratory tract illnesses, both in children⁴⁸ and adults⁴⁹ is associated with reductions in lung function over time. The mechanism(s) that underlies these changes are unknown but may be due to altered immune responses to repeated viral infections, increased and prolonged airway inflammation, and the potential for long-term structural changes. A 2007 study by Saglani et al⁵⁰ that involved endobronchial biopsy specimens obtained from children ages 3 months to 5 years and with a history of wheezing (which is most likely related to respiratory pathogens) showed that pathologic changes may develop as early as 1 to 3 years of age.

The progression of asthma disease as it relates to infection evolves throughout life, along with the microbiome. The infant gut microbiome has decreased diversity. Children up to 5 years of age are prone to episodic wheezing caused by viral pathogens, and viral wheezing within the first 3 years is the most important risk factor for asthma at age 6 years.³⁴ As children grow into adulthood, there is an increased burden and diversity of bacteria. Those with asthma are more vulnerable to virally induced exacerbations, likely due to defects in the respiratory epithelial barrier.³⁴ In elderly individuals concomitant diseases often contribute to decreasing lung function, which makes them particularly vulnerable to viral infections.³⁴

Physiological changes also occur in the airways of individuals with asthma in response to infection. More than 5 decades ago, it was noted that significant changes in lung function occur in patients with asthma during infection, with decreases in FEV₁ and forced vital capacity as well as evidence of increased air trapping.⁵¹ Animal models show that viral airway injury at an early age may induce small airway lesions that are associated with small airway physiological dysfunction, which may persist into maturity.⁵² However, such experiments are difficult to perform in human models. In 2013, Konstantinou et al⁴⁷ demonstrated that, during viral infections, children have enhanced airway

inflammation, reversible airflow limitation, and elevated fraction of exhaled nitric oxide. Experimental infections with HRV show more pronounced airway narrowing in response to methacholine up to 15 days after infection compared with uninfected controls.⁵³ Children with a history of preschool HRV wheezing illness have significantly lower FEV₁ in later childhood (Figure 1),⁵⁴ and analysis of additional data shows that more-frequent severe exacerbations (which require corticosteroid intervention) with children induce more persistent and pronounced losses in lung function (Figure 2).⁴⁸

COMORBID CONDITIONS

Allergic sensitization

A history of atopic disease is a common comorbid finding of individuals with asthma and is present in up to 80% of individuals.⁵⁵ In children, sensitization to aeroallergens is a clear risk factor to develop asthma and for asthma exacerbations. Results of studies also showed an increased risk of asthma development in children with food allergy⁵⁶ and eczema,⁵⁷ but it is not established whether these conditions influence the response to URIs. Indeed, analysis of data demonstrated that asthma development is influenced by both the developmental stage⁵⁸ and the pattern⁵⁹ of allergic sensitization. As mentioned above, trials with omalizumab raise the possibility that IgE-dependent processes are risk factors for viral respiratory infections to provoke an asthma exacerbation.¹⁴ This altered host response to viral infections in the presence of allergic sensitization may be related, at least in part, to reductions in innate immune responses in the form of reduced elaboration of interferons from antigen-processing cells.⁶⁰

Other respiratory-tract diseases

Both RSV and HRV infections can induce more-severe lower airway involvement, termed “bronchiolitis,” during infancy. The clinical presentation of these illnesses can include coughing and wheezing, and may be associated with the subsequent development of asthma.^{61,62} Croup and recurrent croup also have been reported to be associated with the development of asthma.⁶³ Other conditions, for example, cystic fibrosis, of patients with concomitant asthma may predispose them to infections that lead to exacerbations. Allergic bronchopulmonary aspergillosis, although not a true fungal infection, is an allergic response to a fungal organism and is closely tied to asthma, cystic fibrosis, and atopic disease.¹⁰

Rhinosinusitis

Symptoms of acute rhinosinusitis often accompany acute viral URIs; however, chronic rhinosinusitis is not an uncommon finding among patients with infection-induced asthma.⁶⁴ Subjects with chronic sinus disease may have nasal polyps⁶⁵ or humoral immunodeficiencies.⁶⁶ The increased frequency of sinus infections associated with these conditions may increase the frequency of infection-related asthma exacerbations and their severity and duration.⁶⁵ As noted above, bacteria also may play a role in asthma exacerbations. Further investigation regarding the interaction between the upper and lower airways in these conditions is warranted.

Gastroesophageal reflux

Gastroesophageal reflux disease is highly prevalent in children with asthma, and nearly half are asymptomatic.⁶⁷ The majority

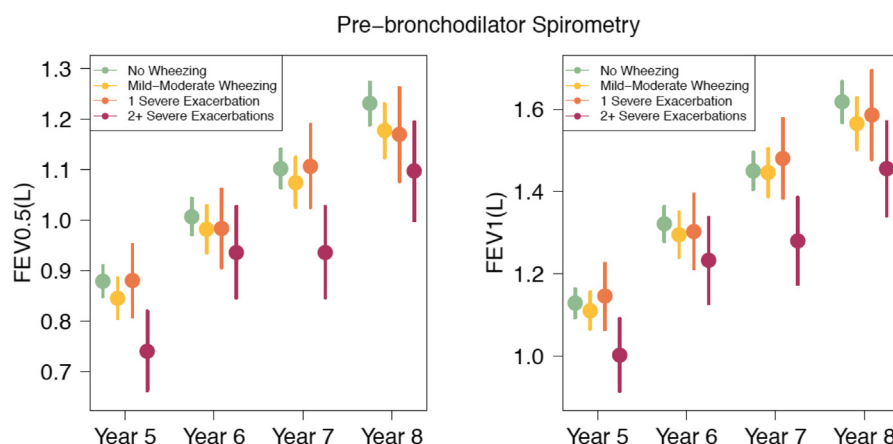


FIGURE 2. Prebronchodilator FEV_{0.5} and FEV₁ values assessed longitudinally between 5 and 8 years of age and demonstrate significant reductions in children with a history of recurrent (≥ 2) wheezing exacerbations treated with oral corticosteroids (OCS) compared with those seen in children with no wheezing, mild-to-moderate wheezing, or 1 severe wheezing exacerbation that required OCS. With permission Ref 48.

of studies thus far show that treatment for gastroesophageal reflux disease does not consistently provide significant improvements on most asthma end points.⁶⁷⁻⁶⁹ In fact, results of some studies demonstrated an increased risk of URIs and pneumonia with treatment of gastroesophageal reflux disease.^{68,70} In addition, a meta-analysis of 31 trials confirmed an association of proton pump inhibitor use and pneumonia.⁷¹

BIOMARKERS

Genetic

Analysis of genetic data from 2007 indicates that individuals who possess certain genotypes may be at increased asthma risk during childhood.⁷² This genetically determined risk may be related to respiratory tract infections during early childhood. Specifically, Caliskan et al¹⁶ demonstrated that associations between a variation in the 17q21 genetic region and asthma risk is in fact limited only to children who had HRV wheezing illnesses in early life. The 17q21 locus contains the genes gasdermin B (*GSDMB*) and orosomucoid 1-like 3 (*ORMDL3*), which code for relevant proteins in white cells, lymphoblastoid cell lines, and CD4⁺ T cells. Importantly, this genetically attributable increased risk was not seen with RSV wheezing illnesses and was totally independent of the presence of allergic sensitization. Thus, it appears that HRV wheezing illnesses may be associated with increased asthma risk from at least 2 pathways: 1 that involves the presence of allergic sensitization, and 1 totally independent of it.^{16,73} A number of research groups are investigating mechanisms that may underlie these associations.⁷⁴⁻⁷⁶ For RSV infections, single nucleotide polymorphisms in IL-1RL1 are associated with increased severity of bronchiolitis; however, subsequent development of asthma was not investigated.¹⁸ Polymorphisms in IL-10, chemokine receptor 5, transforming growth factor β , *TLR4*, *IL-13*, *IL-4*, and *IL-4RA* genes also are associated with RSV induced bronchiolitis severity.¹⁵

Recent genome-wide association studies demonstrate a susceptibility locus that is associated with early childhood asthma with severe exacerbations.¹⁷ CDHR3 is a gene-encoding transmembrane protein that belongs to the cadherin family and is

highly expressed in bronchial epithelial cells, although its exact function is unknown. Single nucleotide polymorphisms in this gene are associated with increased risk of severe asthma exacerbations and asthma-related hospitalization.¹⁷ It is hypothesized that single nucleotide polymorphisms in CDHR3 lead to impaired epithelial integrity and/or repair, which predisposes such individuals to infection. Also, in a family-based association study of 134 children with bronchiolitis, a variation in the promoter region of the IL-8 gene was transmitted significantly more often than expected in children who subsequently developed persistent wheezing.⁷⁷

Laboratory

Other than standard laboratory tests, for example, a complete blood cell count, or a chest radiograph, there are no well-established biomarkers to indicate acute infectious asthma. Possible biomarkers of infectious asthma are the presence of peripheral blood and sputum eosinophilia. These biomarkers have been linked to seasonal asthma exacerbations, often triggered by URIs.¹⁴ If infection is present, in association with an exacerbation, as suggested by clinical evaluation, then there are techniques that can be used to determine the causal organism. Nasopharyngeal aspiration and lavage have been used to obtain specimens for viral identification by using culture or PCR technology.^{6,73} Sputum culture results can help to direct antimicrobial therapy for bacterial infections. Analysis of available data indicates that macrolide antibiotics induce antiviral responses in airway epithelial cells⁷⁸; however, research is ongoing to determine if this is a clinically relevant finding.

DEFINITION

Infection-related asthma is defined as a respiratory tract infection that influences asthma in one of the following ways:

1. Associated with new onset of disease (in both children and adults).
2. Associated with exacerbation of disease in which infection is
 - a. The only mechanism of exacerbation.

- b. One mechanism of exacerbation in multitriggered asthma, which may be more severe in nature compared with other exacerbation triggers.

RECOMMENDED INFORMATION TO BE OBTAINED TO SUPPORT THE DIAGNOSIS OF INFECTIOUS ASTHMA

1. For association with onset of disease:
 - a. Asthma first appeared after URI or lower respiratory tract infection.
1. Associated with exacerbation of disease in which infection
 - a. Is the only mechanism of exacerbation.
 - b. Is one of a number of exacerbating factors.
 - c. Induces severe exacerbations.

RESEARCH QUESTIONS AND FUTURE DIRECTION

1. What are the mechanisms through which infections lead to new-onset asthma?
2. What host factors determine the susceptibility of an individual to infection-induced asthma or to an infection-induced exacerbation of asthma?
3. How do certain comorbidities or underlying allergic diseases influence response to infection and the resultant clinical characteristics of asthma exacerbations?
4. What biomarkers are most reliable to establish the susceptibility of individuals to develop infection-induced asthma or to experience asthma exacerbations or worsening of disease severity secondary to infectious agents?
5. Are certain strains of viruses (eg, RSV and HRV) more pathogenic for inducing or causing asthma exacerbations?
6. How does the host's respiratory microbiome contribute to the protection or risk for exacerbations due to infection?
7. Is targeting the host's immune response to infection more important than targeting the infectious organism?
8. How will the use of the new biologic agents for asthma affect infection-induced exacerbations?
9. Can the genetic profile of an individual help to predict asthma inception (17q21 region) or the severity of exacerbations once asthma is established in the host (eg, CDHR3)?

CONCLUSION

URIs are a common cause of acute illness in both adults and children, and are a common cause of asthma exacerbations. Several pathogens are implicated in asthma inception and exacerbations. Host factors such as allergic sensitization, genetic polymorphisms, and other comorbid conditions are associated with susceptibility to infection-related asthma.

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