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# Virus/Allergen Interactions and Exacerbations of Asthma

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**KEYWORDS**

• Asthma • Viral-induced wheezing • Allergic sensitization

Viral infections and allergen exposure are 2 of the most common causes of acute wheezing and exacerbations of asthma in both children and adults. Clinical research findings indicate that there are synergistic interactions between allergy and viral infection that cause increased severity of asthma exacerbations. This article summarizes the current literature linking these 2 risk factors for asthma exacerbation, and reviews experimental data suggesting potential mechanisms for interactions between viral infection and allergy that cause asthma exacerbations. Finally, the authors discuss clinical evidence that treatment of allergic inflammation could help to reduce the frequency and severity of virus-induced exacerbations of asthma.

## ROLE OF VIRAL INFECTIONS IN WHEEZING ILLNESSES

Overall, 25% to 30% of infants experience at least one episode of wheezing during their first year of life. This incidence increases to 40% of children by age 3 and almost half of all children by age 6 years.[1] Two major pathogens, respiratory syncytial virus (RSV) and human rhinovirus (HRV), cause most of these illnesses. RSV is the major pathogen associated with wheezing illnesses in children younger than 2 years.[2–4] Of other viruses causing wheezing illnesses in infancy, HRV is next most common, and a variety of viruses (coronaviruses, metapneumoviruses, parainfluenza viruses, influenza viruses, bocavirus) also cause significant numbers of illnesses.

In children with established asthma, from 80% to 85% of asthma exacerbations are related to viral illness and up to two-thirds of those illnesses are caused by HRVs.[5]

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Asthma exacerbations in adults are also commonly caused by viral infections, usually HRV or influenza viruses. The etiology of virus-induced wheezing illnesses varies with the season: RSV, metapneumoviruses, and influenza viruses (with the notable exception of 2009 H1N1) are usually limited to the winter and early spring. HRV infections are most common in the spring and fall, but can occur throughout the year. Of note, asthma exacerbations are also quite seasonal, and seasonal peaks in children occur regularly in the fall and spring. In Canada, the peaks in pediatric asthma exacerbations occur approximately 17 days after Labor Day every year, and it is assumed that viral infections that are spread within schools are a major contributor to the fall peaks, and perhaps also in the spring after the children return from spring break.[6,7] It is important to bear in mind that other environmental exposures, including allergens and pollutants, also vary by season, and it seems likely that a combination of environmental factors contributes to the seasonal peaks in exacerbation rates.

## ALLERGIC SENSITIZATION AS A RISK FACTOR FOR DEVELOPING VIRUS-INDUCED WHEEZE AND ASTHMA

Sensitization to aeroallergens is a risk factor for the development of asthma, particularly when it occurs in the first few years of life.[8] In addition, the prevalence of asthma is strongly related to serum IgE level.[8,9] In a recent prospective cohort study, the risk for persistent wheeze was strongly linked to early sensitization and early infection.[8] Mite-specific IgE titers of greater than 0.20 kU/L by age 2 years was associated with a 12.7% risk of persistent wheeze, increasing progressively to an 87.2% risk with increasing numbers of severe lower respiratory tract illnesses experienced.

In addition, in a longitudinal cohort, subjects with airway hyperresponsiveness (AHR) in early adulthood had higher IgE levels than subjects with past AHR or with life-long normal responsiveness.[8,10] Recent wheeze, AHR, and allergic sensitization all had a positive relation to serum IgE. The finding that young adults who are sensitized to common allergens are highly likely to have AHR even in the absence of symptoms is further evidence of the fundamental role of IgE-mediated responses in the natural history of AHR throughout childhood and into adulthood.

In a German birth cohort study, 90% of children with wheeze but no atopy lost their symptoms at school age and retained normal lung function at puberty.[11] In contrast, sensitization to perennial allergens (eg, house dust mite, cat and dog hair) developing in the first 3 years of life was associated with a loss of lung function at school age. Allergen exposure also enhanced the development of airway hyperresponsiveness in sensitized children with wheeze. Of note, sensitization and exposure later in life had much weaker relationships to airway physiology, and sensitization to seasonal allergens was not an important influence.

An Australian birth cohort study involving babies with at least one parent with allergy or asthma provides strong evidence of an interaction between allergy and viral wheeze in early life. In this study, allergic sensitization before the age of 2 years was associated with viral-induced wheezing and asthma at age 5.[12] Furthermore, there was a significant association between HRV- and RSV-induced wheezing and lower respiratory illness in the first year of life and the subsequent development of persistent wheeze at 5 years. These findings were found to be attributable only to those children who were sensitized to allergens in early life.

The Childhood Origins of Asthma (COAST) study is a high-risk birth cohort study in which families with at least one parent with allergies or asthma were enrolled prenatally, and both immune development and respiratory illnesses were prospectively evaluated.[13] Children with aeroallergen sensitization and HRV-induced wheezing during

the first year of life had a high likelihood of developing asthma compared with patients with HRV wheezing within the first year of life without aeroallergen sensitization (86% vs 39%). At age 3 years, HRV wheezing status was the principal indicator of asthma risk, independent of sensitization status. Viral recovery at routine study visits was similar for children with and without asthma, suggesting that asthma is associated with greater severity of illness rather than an increased number of infections.

## ALLERGY AND VIRUS-INDUCED EXACERBATIONS OF ASTHMA

There is strong clinical evidence that allergic sensitization and viral illnesses increase the risk of asthma exacerbation and hospitalization. In a cross-sectional study performed at a tertiary pediatric emergency department, allergy and viral infection (most commonly HRV) were both identified as risk factors for wheezing. Children who had HRV infection detected in combination with either eosinophilia or a positive radioallergosorbent test to common aeroallergens had the strongest odds of wheezing.[14] A second study from the same group supported these findings, and also provided evidence that many children with isolated HRV infection do not wheeze in the absence of allergic cofactors.[15] When considered together, these findings indicate that a large majority of emergent wheezing illnesses during childhood can be linked to infection with HRV, and that these wheezing attacks are most likely to occur in those who have HRV together with evidence of atopy or eosinophilic airway inflammation.

Other studies have gone one step further and have considered interactions between allergy, allergen exposure, and viral respiratory infection in causing wheezing illnesses. In a case-control study of 84 asthmatics admitted for acute exacerbations versus stable asthmatics and patients hospitalized for nonrespiratory diagnoses, a significantly higher proportion of children hospitalized for an acute exacerbation were virus-infected (44%) as compared with the stable asthmatics (18%) and nonrespiratory hospital admissions (17%; both $P<.001$).[15,16] The combination of allergic sensitization and allergen exposure was also found more frequently in asthma hospitalization group (76%) than in the 2 control groups (48% and 28%, respectively, $P<.001$). In the multivariate analysis, the viral illness and allergic sensitization/exposure were no longer significant, but the combination of these risk factors dramatically increased the risk of hospital admission (odds ratio 19.4, $P<.001$), demonstrating the link between these factors in causing asthma exacerbations. Similar findings were reported in an earlier case-control study involving adults; the combination of sensitization, high exposure to one or more indoor allergens, and viral detection considerably increased the risk of being admitted to the hospital with asthma (odds ratio 8.4, 95% confidence interval 2.1–32.8; $P = .002$).[17] Finally, in the Inner City Asthma Study (ICAS), children who were sensitized and highly exposed to cockroach allergen were more likely to be admitted to hospital, have more unscheduled medical visits, and more time off school than either nonexposed or nonsensitized children.[18] Virology was not performed in ICAS, but it can be presumed that viral infections were important contributors to asthma morbidity in this population.

Many studies have assessed the impact of allergy and viral illness on asthma exacerbations in the community. In fact, most surveillance studies have focused on detection of HRV during periods of illness, but there are limited data available regarding true rates of infection in children with asthma. It is presumed that children frequently develop asymptomatic or mild infections that do not cause asthma exacerbations. If this is true, other factors must contribute to the risk of more severe illnesses and those with wheezing. To determine the contribution of viral infections and allergic sensitization to loss of asthma control, nasal secretions were obtained weekly in a group of 58 children with

asthma during peak HRV seasons (September and April).[2] As expected, virus-positive weeks were associated with greater severity of both cold and asthma symptoms. Clinically defined illnesses were then classified according to temporal association with detection of a respiratory virus. For virus-positive illnesses, the duration of cold and asthma symptoms was twice as long, and loss of asthma control occurred more frequently. Approximately two-thirds of the children were sensitized to common aeroallergens. When comparing sensitized with nonsensitized subjects, rates of infection were similar between the 2 groups; however, the sensitized group had 47% more virus-associated illnesses per season. Finally, nonsensitized subjects most commonly reported "none" or "mild" cold and asthma symptoms with their viral infections, whereas almost half of the viral infections in sensitized children resulted in moderate or severe cold or asthma symptoms (**Fig. 1**). These findings provide evidence that for children with asthma, atopy is an important risk factor for more severe cold and asthma symptoms.

## RESPONSE TO EXPERIMENTAL HRV INFECTIONS IN ALLERGIC ASTHMATICS

Despite the initial assumption that HRV affects only the upper airway, studies using experimental inoculation followed by bronchoscopy or sputum induction have demonstrated HRV protein and mRNA in the lower airways.[19–21] These studies indicate that HRV infections have the potential to modify and interact with allergic airway inflammation in the lower airways. Accordingly, subjects with allergic rhinitis who were inoculated with HRV had increased levels of histamine in bronchoalveolar lavage (BAL) samples immediately and 48 hours after antigen challenge during HRV infection.[22] These same changes were not observed in nonallergic subjects infected with HRV and challenged to antigen, suggesting that the combination of viral infection and allergic disease leads to greater airway inflammation. In addition, experimentally induced HRV infection caused an enhanced eosinophilic response to allergen challenge in the allergic but not nonallergic subjects. This effect persisted for as long as 1 month after the acute HRV infection.

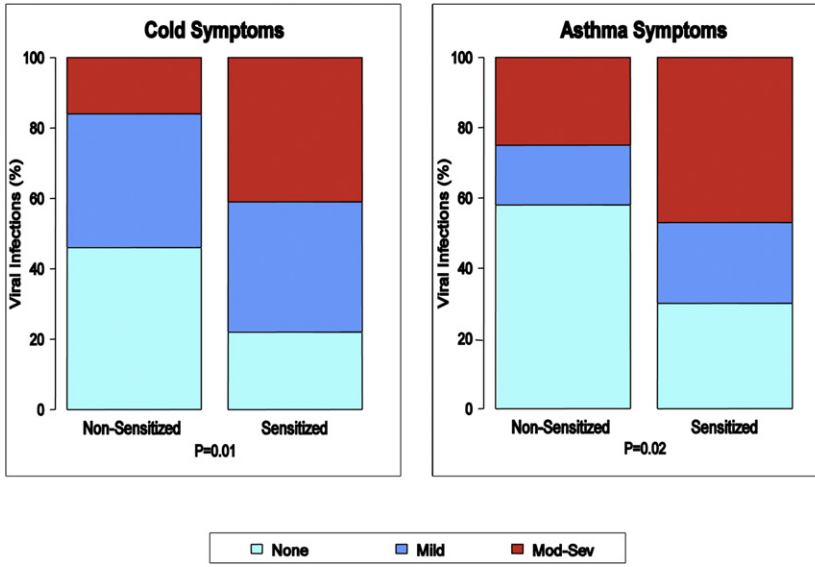


**Fig. 1.** Effect of sensitization on the severity of cold and asthma symptoms associated with viral infection. Mod-Sev, moderate to severe.

Two additional studies determined whether the induction of allergic inflammation would increase the severity of HRV-induced respiratory symptoms. Contrary to expectations, allergen exposure before HRV inoculation led to either no change or a slight reduction in the severity and duration of cold symptoms.[23,24] Of note is the difference in the sequence of administration of virus and allergen; this raises the question of which initiates the exacerbation, the virus or the allergic inflammation? Other factors to consider in thinking about the different outcomes of these studies are the nature of the allergen and pattern of exposure (dose and duration). It is possible that chronic low-dose allergen exposure before HRV infection amplifies the response to subsequent HRV inoculation.

Several studies have tested the theory that HRV infections cause distinct patterns of inflammation and changes in airway physiology in subjects with allergies or asthma. These studies have generally reported that the upper airway manifestations of HRV infections are similar in subjects with or without allergies or asthma, but that lower airway symptoms are increased in asthma. Two studies involving subjects with mild asthma have found similar cellular inflammation and proinflammatory cytokines in airway cells when compared with normal control subjects.[25,26] In contrast, Message and colleagues[27] found several asthma-related differences in the response to experimental HRV infection. In asthmatic subjects, HRV infection enhanced eosinophilic inflammation. In addition, virologic and clinical outcomes were related to deficient interferon (IFN)-$\gamma$ and interleukin (IL)-10 responses and to augmented IL-4, IL-5, and IL-13 responses from blood and airway mononuclear cells. In a study of similar design, DeMore and colleagues[25] found that numbers of airway eosinophils preinoculation were significantly related to cold scores induced by HRV infection. Collectively, these findings suggest that eosinophilic inflammation and T-helper 2 (Th2)-biased immune responses associated with allergic sensitization enhance the clinical severity of illness associated with HRV infection.

## MECHANISMS OF VIRUS-ALLERGEN INTERACTIONS

There are several potential mechanisms for allergy and viral infections to synergize in causing wheezing, airway obstruction, and exacerbations of asthma (**Box 1**). These

**Box 1**
**Potential interactions between allergy and viral infections**

*Common underlying predisposition*

- Interferon deficiency
- Th2-biased immunity
- Defect in anti-inflammatory responses

*Effects of allergen-induced inflammation*

- Airway hyperresponsiveness
- Mucus production
- Secondary depression of interferon synthesis

*Epithelial abnormality*

- Reduced barrier function
- Abnormal repair mechanisms
- Airway remodeling

mechanisms, which are not mutually exclusive, include the possibility that there are common predisposing factors, interactions related to allergic inflammation, or deficiencies in the epithelium that predispose to allergy/asthma and increased severity of viral infections.

### *Common Underlying Predisposition to Allergy and Viral Illnesses*

Likely risk factors that would predispose to both allergy/asthma and increased severity of viral infections include genetic or acquired abnormalities that lead to either underproduction of interferons or overproduction of Th2 cytokines, leading to a Th2 bias in the immune system. Clinical studies[28,29] and experimental evidence from animal models[30] suggest that either weak T-helper 1 (Th1) responses or Th2 bias can lead to more severe viral infections, and both of these abnormalities have also been implicated as a risk factor for allergies and asthma.[31–33] In addition, children with recurrent respiratory infections were reported to have low IFN-$\alpha$ responses.[34] Interferons have also been related to outcomes of HRV illnesses in studies of volunteers inoculated with a safety-tested strain of HRV-16. Virus-induced IFN-$\gamma$ responses in blood mononuclear cells were inversely associated with viral shedding after inoculation,[35] and stronger Th1-like responses in sputum cells (higher IFN-$\gamma$/IL-5 mRNA ratio) during induced colds were associated with milder cold symptoms and more rapid clearance of the virus.[36]

In addition to findings in the experimental inoculation model, there is evidence from clinical studies that asthma is associated with impaired virus-induced blood cell production of IFN-$\alpha$ and IFN-$\gamma$.[37–39] Furthermore, some studies have reported that HRV-induced epithelial cell production of IFN-$\beta$ and IFN-$\lambda$ is also impaired in asthma, suggesting that interferon responses in asthma are generally depressed.[40,41] On the other hand, these findings were not replicated in 2 recent studies examining cytokine responses in cultured airway epithelial cells,[42,43] and so far studies of experimentally inoculated volunteers with asthma have not found evidence of increased HRV shedding in either the upper or lower airways. Additional studies of naturally acquired colds in patients with asthma are needed to resolve these differences.

Asthma is often associated with other inflammatory diseases such as atopic dermatitis and allergic rhinitis. Together with the propensity to develop more severe illnesses with respiratory infections, these findings suggest that T-regulatory cells or other anti-inflammatory mechanisms could be impaired in asthma. To date, studies of asthma and atopic dermatitis indicate that T-regulatory cell numbers may be increased in the blood and tissues, and this paradoxic finding could represent evidence of a compensatory response to inflammation.[44,45] Important questions remain as to whether T-regulatory cell function or other anti-inflammatory regulatory mechanisms are impaired in asthma.

Finally, results obtained using animal models of respiratory viral infection suggest that biased innate immune responses to respiratory viruses in early life may establish overproduction of key cytokines such as IL-13, leading to suboptimal antiviral responses, increased risk for respiratory allergies, and changes in airway structure to promote asthma.[46] These findings suggest that early innate immune responses to viral infection could promote the development of Th2 bias, leading to allergic diseases and asthma. This concept is further supported by a recent study of gene expression patterns from peripheral blood cells of children presenting for emergency treatment of acute asthma exacerbations, mostly associated with viral respiratory infections.[47] Monocyte-dendritic cell populations had an up-regulated expression of Fc$\epsilon$RI$\alpha$ with a concomitant gene expression signature that is representative of the IL-4/IL-13-dependent “alternatively activated” phenotype. Together, these studies

suggest an important link between early innate antiviral responses and the subsequent development of atopic diseases. This concept is also supported by evidence that asthma and allergy are associated with reductions in some innate antiviral responses, such as IFN-$\alpha$ secretion in response to Toll-like receptor (TLR)-7 and TLR-9.[48,49]

### *Effects of Allergen-Induced Inflammation on Antiviral Immunity*

It is well established that Th1- and Th2-like responses are counterregulated, and there is recent evidence to suggest that allergic inflammation can inhibit innate immune IFN responses under some conditions. For example, engagement of IgE receptors on plasmacytoid dendritic cells leads to reduced IFN-$\alpha$ production in response to either TLR-9 stimulation or incubation with influenza virus.[50,51] This counterregulation between IgE-mediated and antiviral responses suggests a mechanism linking allergy, allergen exposure, and more severe viral illnesses.

There have been recent advances in understanding how environmental influences can modify dendritic cell and, subsequently, T-cell polarization through effects on the epithelium. Thymic stromal lymphopoietin (TSLP) is an epithelially derived cytokine that is induced by both viral infections and allergic inflammation. Cytokines such as IL-4 that are overproduced in asthma synergistically enhance TSLP secretion,[52] which in turn acts on dendritic cells to promote the differentiation of naïve T cells into Th2 cells. This mechanism also provides a potential mechanism for synergy between viral respiratory infections and allergic airway inflammation.

### *Defective Epithelial Barrier and Virus-Allergen Interactions*

Viral infections damage the barrier function of the airway epithelium, and one of the consequences of this effect may be to enhance absorption of allergens and/or irritants across the airway wall, leading to an increased inflammatory response.[53] Furthermore, healthy, intact epithelial layers are difficult to infect with HRV in vitro. Viral replication is enhanced by mechanical or chemical damage to the epithelium, including removal of the apical layer of cultured epithelial cells.[54,55] These findings suggest that eosinophilic inflammation and pollutants that damage the barrier function of airway epithelium could increase susceptibility to infection and/or lead to more severe infections. This effect could be compounded in asthma because of the association between asthma and defective epithelial repair processes.[56] Finally, asthma is associated with remodeling of the airways, which includes increase in the numbers of mucus-secreting goblet cells. Experiments using epithelial cells differentiated at an air-liquid interface indicate that HRV replication is enhanced in goblet cells.[57]

## DOES TREATMENT OF ALLERGIC ASTHMA DECREASE EXACERBATIONS?

Given that viral infections contribute to most exacerbations of asthma, it seems likely that effective treatment against exacerbations of asthma might also reduce the number of virus-induced exacerbations of asthma. Surprisingly, there is little or no information about the effects of asthma controllers or relievers on defined virus-induced exacerbations.

Eosinophils tend to increase during the convalescence phase following an acute upper respiratory infection in patients with allergic airway disease, and presence of eosinophils in the airways has been identified as a risk factor for more severe colds.[15,25] Furthermore, experimental HRV infection can enhance antigen-induced eosinophil influx in BAL and persistent eosinophil infiltration in bronchial mucosa and submucosa.[22,58] These findings suggest that medications that reduce eosinophil recruitment or activation might be of clinical benefit in reducing the risk of exacerbations.

Both inhaled corticosteroids and montelukast can inhibit eosinophilic airway inflammation, and reduce the risk of exacerbations (inhaled corticosteroids more so than montelukast). To date there is only indirect evidence that these treatments can specifically prevent virus-induced exacerbations.[59] A recent study showed a significant decrease in eosinophil-derived neurotoxin (EDN) levels in patients started on montelukast after an RSV infection. Furthermore, montelukast-induced reductions in EDN levels were associated with a significant decrease in wheezing episodes in follow-up.[60] Finally, omalizumab reduces the risk of exacerbations in patients with allergic asthma,[61] and provides an ideal tool to determine whether inhibiting allergic inflammation will reduce the risk for virus-induced exacerbations. Additional studies are needed to more fully explore the effects of asthma controllers on viral exacerbations.

## SUMMARY

There is strong clinical evidence to support the interaction between allergy and viral infection with respect to the risk of developing asthma, and in the causation of asthma exacerbations. There is also growing evidence that asthma is associated with a defective immune response to both viruses and allergens. As we learn more about this interaction, the goal is to identify those patients who are at risk for viral-induced wheezing, treat the underlying problem, and prevent exacerbations of asthma. Understanding the mechanisms behind virus-induced asthma will help us design and use more effective treatment strategies.

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