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VIRUS-INDUCED WHEEZING IN CHILDREN

Respiratory Syncytial Virus (RSV) and Rhinovirus

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The strong association between infantile wheezing and respiratory tract infections caused by the respiratory syncytial virus (RSV) has been well established. In studies of older children, rhinovirus becomes the major virus associated with asthma. These relationships are outlined in the box on page 36. In the past, this relationship was more difficult to appreciate, because rhinovirus does not always grow well in culture. In addition, the linkage between asthma and atopy during childhood has raised the question whether viral infections alone can precipitate exacerbations of asthma. Use of the polymerase chain reaction (PCR) to measure viral nucleic acid material has provided the opportunity to study virus-induced wheezing among children in greater detail, and investigations of experimental rhinovirus infections in adults have demonstrated how this virus can augment both the early and late phase manifestations of airway hyperreactivity. This article reviews recent advances that have enhanced our understanding of virus-induced wheezing, along with new information indicating that interactions between viral infections and allergic inflammation may be critical to the pathogenesis of acute symptoms.

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### Relationship Between Early Childhood Wheezing and Asthma*

**A. Early Childhood Wheezing (1st 2 years of life):**
1. **Predisposing risk factors:** Prematurity; lower lung function at birth; maternal smoking during and following pregnancy; frequent exposure to viral infections at day care.
2. **Major risk factors for acute attacks:** Viral infections, especially RSV; tobacco smoke exposure.

**B. Development of Asthma:**
1. **Predisposing risk factors:** Genetic predisposition (maternal asthma and atopy is a stronger influence than asthma and atopy in the father); atopic dermatitis and/or food hypersensitivity; increased exposure to aeroallergens early in life.
2. **Major risk factors for acute attacks:** Viral infections, especially rhinovirus; exposure to aeroallergens (dust, pollen, weed, mold allergens); tobacco smoke exposure. The interaction between rhinovirus infections and allergic inflammation becomes significantly associated with wheezing after the age of 2 years.

*Data from information and literature cited in References 11, 17, 23, 35, and 48.

### VIRUSES AND WHEEZING DURING INFANCY

A vast majority of children become infected with RSV during their first 2 years of life, and approximately 90% of children have a serologic response to this virus by the age of 2. In keeping with this, RSV is the most common viral respiratory tract pathogen isolated from infants who wheeze. Many of the attacks that lead to emergency room visits and hospitalizations occur within the first 6 months of life, when infants are more likely to experience their initial infection. Current information indicates that RSV infections during infancy are not, by themselves, responsible for the development of asthma. It has become clear, for example, that most infants who wheeze (approximately 60% to 70%) become symptom-free as they grow older. Nevertheless, up to one third of the children who wheeze with RSV are at risk for recurrent and persistent wheezing, and there is considerable interest in research that will improve our ability to identify those children early in life. It has become apparent, for example, that infants whose parents have allergic symptoms or asthma, especially the mother, have a greater risk for developing asthma and that predisposing events that may influence this process may even begin in utero. Infants with atopic dermatitis or those who become sensitized to food allergens early in life also have an increased risk for developing allergic respiratory tract symptoms, including asthma, as they grow older.

Among infants who die from serious RSV disease, a vigorous perivascular lymphocyte response has been observed in the lungs at autopsy. However, a different pathogenic process also has been observed during clinical trials of a formalin-inactivated RSV vaccine; this process led to serious pulmonary disease as well as peripheral blood eosinophilia in over half of the vaccine recipients when they acquired a subsequent RSV infection. Pulmonary eosinophilia, characteristic of lung inflammation in asthma, also was noted in autopsy specimens from some of the recipients who died. Mechanisms for the development of this
eosinophilic response in infants are not clear. In previous studies, an IgE mechanism for wheezing was proposed for some infants based on the detection of IgE antibody specific for RSV antigen in their nasopharyngeal secretions. Increased levels of histamine in secretions from the same patients also were reported. In addition, elevations in nasal eosinophil cationic protein (ECP) were observed by the same investigators in a separate study of RSV infected infants. At present, however, it is not clear that IgE to RSV has a positive predictive value for the development of asthma, and high levels of nasal ECP and IgE to RSV have not yet been measured in the same patients. Thus, the functionality of IgE to RSV in the pathogenesis of infantile wheezing and its relevance to the development of asthma is uncertain.

Under certain circumstances, there is evidence that RSV infections may be capable of inducing a Th2 lymphocyte response leading to the development of eosinophil inflammation. In mice, Th2 responses to the capsular RSV-attachment antigen (G protein) have been demonstrated, leading to the production of IL-5 when lymphocytes from sensitized mice are stimulated in vitro with RSV-G. These mice also developed pulmonary eosinophilia following subsequent intranasal infection with RSV. The quantities of IL-4 or IgE antibody produced by these animals is not significant, and the eosinophil response in lungs also has been produced in B-cell-deficient mice, suggesting a mechanism independent of IgE antibody. This eosinophilic process, however, requires prior immunization (sensitization) and may not explain the pathogenesis of RSV-induced wheezing in humans when they experience initial infections during early infancy. Other studies have examined the elaboration of cytokines (e.g., IL-11) that may be important in the pathogenesis of airway inflammation caused by RSV, as well as parainfluenza virus. Taken together, our understanding of infantile wheezing induced by RSV has increased substantially. However, research leading to new treatments (vaccines and pharmacologic agents) to counter the adverse effects of RSV and the identification of wheezing infants who are predisposed to developing asthma remain important problems.

**VIRUSES AND ASThma EXACERBATIONS IN OLDER CHILDREN**

In studies of school-age children with asthma, common cold viruses were associated with 80% to 85% of wheezing exacerbations in a community-based study of asthmatic children aged 9 to 11 years. Using PCR analysis, rhinovirus accounted for two thirds of the viruses isolated. Inspection of symptom score charts revealed sudden falls in peak flow values within 2 days of the onset of cold symptoms, followed by recovery to baseline during the subsequent 2 to 3 weeks. In another study, a strong relationship between rhinovirus infection and asthma was observed in children treated in a pediatric emergency department for acute wheezing. Rhinovirus was the dominant virus cultured in nasal aspirates from wheezing children after the age of 2 years. From this age on, RSV was not significantly associated with wheezing, whereas the combination of allergen-specific IgE antibody and a positive culture for rhinovirus was particularly striking (odds ratio for wheezing = 10.8). When nasal washes from another study of children seen in the emergency room were tested using PCR techniques, rhinovirus was again the most common virus associated with wheezing after the age of 2. Once again, the combination of allergen-specific IgE antibody and viral infection increased the risk for wheezing (odds ratio = 16.4). Even more striking among the wheezing children was a strong relationship between a positive PCR test for rhinovirus and the presence of eosinophils or ECP in nasal
secretions. Although school-age children experience approximately six to eight colds per year as compared with two to three colds per year for adults, recent PCR data also indicate that rhinovirus infections were associated with 38% of asthma exacerbations in adult individuals 19 to 46 years old.39

Other respiratory tract pathogens have been isolated from children and adults during asthma exacerbations. Coronavirus, which has been identified as a causative agent in 10% to 20% of common colds, also has been implicated in attacks of asthma.41 Less frequently, influenza and adenovirus have been detected. Although *Mycoplasma pneumoniae* has been observed in up to 20% of community-acquired episodes of pneumonia, this organism probably is an infrequent cause of asthma exacerbations.36 Thus, evidence from several studies indicate that rhinovirus is the major viral pathogen linked to attacks of asthma in children and adults. This information has stimulated additional studies, primarily experimental infections in adults, to explore how rhinovirus alters lower airways function.

**RHINOVIRUS STRUCTURE AND INTERACTIONS WITH ICAM-1**

Because of the importance of rhinovirus as a cause of common cold symptoms, there is considerable information characterizing the structure of rhinovirus and its interactions with the intercellular adhesion molecule-1 (ICAM-1) receptor. The human rhinoviruses represent a large genus within the class of picornaviruses (small RNA viruses). The genus contains up to 100 distinct serotypes showing antigenic diversity.44 The molecular structure of rhinovirus (type 14) has been characterized in great detail. This virus is a small (30 nm) nonenveloped particle within an icosahedral protein capsule composed of 60 protomeric units with four capsid proteins (VP 1, VP 2, VP 3, and VP 4). X-ray diffraction studies have shown canyons on the capsid surface that contain recognition binding sites for ICAM-1.44 The receptor ICAM-1 belongs to the immunoglobulin super-group of proteins and is expressed on the luminal surface of epithelial and endothelial cells. Its natural ligand is LFA-1 (lymphocyte function associated antigen), which is widely expressed on leukocytes including eosinophils. Its up-regulation can be induced by a number of cytokines (i.e., IFN-γ) and is associated with the recruitment of leukocytes to the sites of inflammation. ICAM-1 is also the host receptor used by the vast majority (90%) of rhinovirus serotypes for cell attachment and entry.50 It has been suggested that its up-regulation in allergic inflammation may predispose allergic individuals to higher rates of rhinovirus infection, leading to further increases in ICAM-1 expression and inflammatory cell infiltrations.5 It proposed up-regulation in asthma also may increase the probability of a rhinovirus infection and the capacity of this virus to provoke an asthma attack.

Standard methods for detecting rhinovirus have included viral culture, serology, and immunofluorescent techniques. Many epidemiologic studies of the common cold and initial studies of experimental rhinovirus infections relied on cultures for detection. Recovery rates of rhinovirus in nasal secretions from children experiencing natural colds have varied from 10% to 30%.44 However, rhinovirus does not grow optimally in culture, and positive results in population based studies may underestimate the prevalence of rhinovirus infections. More recently, PCR methods that detect rhinovirus RNA have been compared with cultures in children with common cold symptoms. The results demonstrated a detection rate up to threefold greater using PCR analysis.28 However, during experimental colds, rhinovirus can be recovered in culture in up to 90% of nasal
washes obtained from patients at the height of symptoms (2 to 3 days following inoculation).\(^{18}\) This raises the possibility that the lower detection rates for rhinovirus using cultures from individuals during natural colds may result from the delay in obtaining samples and abatement of viral shedding once the infection is in progress.

**RHINOVIRUS INFECTIONS IN NONALLERGIC INDIVIDUALS**

Several investigations have examined rhinovirus infections and the pathogenesis of common cold symptoms in nonallergic individuals as outlined in the box below. These studies have explored the effects of rhinovirus on the upper and lower respiratory tract and have established a framework for more recent studies of rhinovirus infections in allergic individuals. The timing of viral shedding in relation to cold symptoms has been carefully examined following experimental rhinovirus inoculation of adult volunteers.\(^ {18}\) Viral replication in the nasopharynx was noted to increase 1 day after inoculation and peaked at 48 hours. Cold symptoms including rhinitis, pharyngitis, and bronchitis began within 24 to 48 hours and then peaked by day 3 or 4. In a study of CT scans from adults, sinus involvement with membrane thickening and mucous hypersecretion was evident in 87% of patients within 2 to 4 days after experimental rhinovirus inoculation.\(^ {19}\) This indicates that rhinovirus colds are likely to encompass a viral rhinosinusitis, not just rhinitis.

| Pathogenic Events During the Course of Rhinovirus Infection in Nonallergic Adults* |
|---|
| 1. Viral exposure and inoculation in the upper airway (and eyes) with mucociliary transport to the nasopharynx. |
| 2. Viral replication. |
| a. Peaks at 48 hrs. Abates but can persist up to 3 weeks. |
| b. Occurs in a small percentage of epithelial cells in the nasopharynx and adenoid M (membrane) cells. No significant cytopathic changes have been observed. |
| 3. Cold symptoms (rhinitis, pharyngitis, bronchitis) begin at 24 to 48 hrs and peak by day 3 or 4. |
| 4. Sinus involvement frequently develops within 2 to 4 days. |
| 5. Cellular response. |
| a. Neutrophils in the epithelium by day 2; influx into nasal secretions by days 4 to 5. |
| b. Lymphocytes: mild infiltration (submucosa) by 2 to 4 days. |
| c. Eosinophils: Increase in the epithelium during the acute infection. In allergic subjects this response persists into convalescence. |
| 6. Mediators and cytokines. |
| a. Histamine: no significant change in plasma or nasal secretions during the acute infection. |
| b. Kinins: increased in nasal secretions during the infection. |
| c. Increased production of IL-8, INF-γ, TNF-α, IL-11, GM-CSF, and other proinflammatory cytokines has been reported. |

*Adapted from Gwaltney JM: Rhinovirus infection of the normal human airway. Am J Respir Crit Care Med 152:536–39, 1995; with permission.
RHINOVIRUS IN THE UPPER RESPIRATORY TRACT

During experimental infections, no significant cytopathic changes have been found in either ciliated or nonciliated nasal epithelial cells. In addition, no destruction of the nasal mucosa or the inferior turbinate was observed by scanning electron microscopy. Implications of these findings are that the production of cold symptoms with rhinovirus are caused by mechanisms other than tissue destruction. These findings are in marked contrast to epithelial cell damage caused by adenovirus and influenza A and B virus in cell cultures. In situ hybridization has been used to localize sites and determine the extent of rhinovirus replication. In experimentally infected volunteers, rhinovirus replicated in a small proportion (patchy involvement) of epithelial cells distributed in the nasal epithelium and in nonciliated cells in the nasopharynx.

Following the onset of cold symptoms, the number of neutrophils in the epithelium and subepithelial cell layer were noted to increase by day 2 during an experimental infection. This was followed by an influx of neutrophils into nasal secretions leading to a purulent discharge in experimentally infected volunteers 4 to 5 days after the onset of symptoms. This change was not accompanied by associated changes in bacterial pathogens, suggesting that rhinovirus itself may be involved in initiating this neutrophil response. Although the number of lymphocytes observed in the nasal mucosa did not change significantly, a mild lymphocyte infiltration was noted after a period of 2 to 4 days.

Even though the local immunopathologic and pathophysiologic processes of colds induced by rhinovirus are not fully understood, recent information about mediators and cytokines is likely to contribute to knowledge of the pathogenesis of events leading to symptoms. Generally, levels of histamine in nasal secretions do not change significantly during acute experimental rhinovirus infections in nonallergic individuals. However, increased concentrations of kinins, which act as potent vasoactive substances, have been detected in nasal secretions of adults given rhinovirus experimentally; and such symptoms as sore throat, nasal congestion, and rhinorrhea have been observed in healthy volunteers after administering bradykinin intranasally. Increased levels of IL-8, a potent leukocyte chemoattractant, have been measured in nasal secretions from subjects with wild-type rhinovirus infections.

RHINOVIRUS AND THE LOWER RESPIRATORY TRACT

The capacity of rhinovirus to cause infection and replicate in the lower respiratory tract has been difficult to confirm. In part, this derives from difficulty in obtaining specimens that are free of contamination. In studies of adults with allergic rhinitis who were infected experimentally with rhinovirus (type 16), virus was not isolated either from fluid or cells obtained by bronchoalveolar lavage (BAL). By comparison, virus always was found in high titers in nasal washes. Explanations for the preferential replication of rhinovirus in the upper airways has been attributed to its temperature sensitivity in culture, which may tend to favor its replication in the upper airways. More specifically, reducing the temperature of incubation of rhinovirus in culture from 37°C to 33°C greatly enhances the efficacy of virus isolation. While studies continue to document rhinovirus replication and infection in the lower airways, investigations focused on inflammatory pathways involving mediators and cytokines will continue to
be important in defining the immune response stimulated by this virus. In contrast, there is less doubt that other respiratory viruses (adenovirus, influenza virus, RSV, and parainfluenza virus) can infect the lower airways.

**RHINOVIRUS INFECTIONS: ATOPY AND ASTHMA**

Several studies have compared the severity of upper respiratory tract symptoms and lower airway responsiveness in allergic and nonallergic adults following experimental rhinovirus inoculation. In studies of experimental viral rhinitis by Bardin and colleagues, no difference between atopic patients and controls was observed with respect to shedding of rhinovirus or symptom scores. A particularly interesting finding was that the severity of colds experienced by nonallergic individuals was increased in those who lacked preinoculation neutralizing antibodies in their sera to the rhinovirus serotype used for inoculation. This was not observed in atopic individuals, who developed severe colds and had a significant increase in nasal wash albumin in spite of the presence of neutralizing antibody.

Doyle and colleagues found little evidence to support an increased susceptibility of atopic subjects to rhinovirus. However, atopic patients did experience an earlier onset of sneezing and nasal congestion. These investigators examined peripheral blood lymphocyte responses during experimental infection. A consistent feature was the persistence of T-cell activation to rhinovirus in atopic subjects up to 3 weeks after infection. Skoner and others from this group noted that experimental rhinovirus (type 39) infection induced significant increases in total serum IgE, leukocyte histamine release, and platelet aggregation during the acute phase of infection in adults with allergic rhinitis. However, the acute phase rise in total serum IgE could not be correlated to a rise in specific IgE antibody to allergens tested, and there was no correlation between the rise in serum IgE and enhanced release of histamine from leukocytes stimulated with anti-IgE antibody. Similarly, total IgE levels in atopics given a rhinovirus infection did not correlate with the severity of rhinitis in studies by others. Thus, the functional significance of the rise in total IgE during infection is unclear. No changes in plasma histamine or in histamine in nasal secretions have been observed in nonatopic individuals during rhinovirus infections. However, increased histamine secretion was seen more frequently during the initial days of rhinitis in nasal washes from allergic adults following rhinovirus inoculation.

In studies of bronchial reactivity, increased airway hyperresponsiveness demonstrated by spirometry and methacholine challenges were observed in some but not all asthmatic subjects during experimental infection with rhinovirus (type 39). These changes were not observed in nonallergic subjects. In a more recent study, ragweed-allergic patients with rhinitis developed increased lower airway responsiveness to inhaled histamine and ragweed allergen during an acute infection with rhinovirus (type 16). Of interest in this study by Lemanske and colleagues was that their patients also had an increased likelihood of developing late phase bronchoconstrictor responses following allergen challenge. These changes remained persistent up to 4 weeks after the experimental infection. Overall, these observations suggest an important relationship between rhinovirus infection and the potentiation of allergic inflammation in the airways.

The effects of bronchoprovocation with ragweed allergen during rhinovirus infection were examined in individuals with allergic rhinitis by Calhoun and colleagues. Using a segmental allergen bronchoprovocation method, the investigators detected increased levels of histamine in BAL samples, both immediately
and 48 hours after antigen challenge. During the infection, tryptase from mast cells was initially detected in BAL samples; however, a significant increase in histamine, but not tryptase, during the late phase response suggested that basophils rather than mast cells may be the cell source of histamine at 48 hours. The most striking observation during the acute infection was an augmented recruitment of eosinophils into the airways 48 hours after allergen challenge. Moreover, these effects persisted and were apparent up to 1 month after rhinovirus inoculation. These data indicate that rhinovirus infection in the upper respiratory tract can significantly augment both immediate and late phase cell and mediator responses in the lower airways of allergic individuals.

In another study of adult volunteers, including six allergic asthmatics, an increase in lower airways responsiveness to histamine was noted during the acute phase of rhinovirus infection. This was accompanied by increases in submucosal lymphocytes followed by a fall in lymphocyte numbers in the epithelium and submucosa detected in bronchial biopsy specimens during the convalescent period. An increase in epithelial eosinophils also was noted during the cold, and the rise in eosinophil numbers persisted into convalescence in the asthmatic, but not in the normal subjects. Increased sensitivity to histamine in the asthmatics also persisted in the convalescent period.

Taken together, these studies have demonstrated a relationship between rhinovirus upper respiratory tract infections and augmented late phase bronchial responsiveness associated with eosinophil recruitment into the lungs. More detailed studies directly linking infections to the development of this eosinophil response and studies to define the mechanisms leading to this reaction are of great interest. Recent studies provide evidence for rhinovirus activation of T cells through a monocyte-dependent mechanism that also promoted eosinophil survival in vitro. A link between virus infections and allergic eosinophil inflammation has also been implicated in a mouse model, demonstrating that a bystander CD4+ Th2 cellular response to ovalbumin can switch virus peptide-specific CD8+ T cells in the lung to produce IL-5, leading to eosinophil infiltration following virus peptide challenge.

THERAPEUTIC AND RESEARCH IMPLICATIONS

Epidemiologic studies have shown a correlation between the seasonality of viral upper respiratory tract infections—particularly RSV and rhinovirus—and asthma exacerbations. In the northern hemisphere, RSV infections are most common during the midwinter months (December through February). These are months when infants are more likely to be seen in clinics, emergency rooms, and the hospital for acute attacks of wheezing (Fig. 1). In a time/trend analysis, the seasonal patterns of respiratory tract infections and hospital admissions were evaluated for older children and adults. A particularly strong correlation was found between the seasonal pattern of upper respiratory tract infections, particularly rhinovirus, and hospital admissions for asthma among children. Upper respiratory tract infections and admissions for asthma also are more frequent during periods of school attendance and less frequent during school holidays. Consistent with this, peak admissions to the pediatric emergency room for wheezing at the University of Virginia are observed annually in the fall and spring months when rhinovirus infections are most common combined with increased exposure to tree and grass pollens in the spring and ragweed, Alternaria, and higher levels of household dust mite allergen during the fall (Fig. 2). This visiting pattern already becomes apparent for wheezing
Figure 1. Emergency room visits for infants and children treated for wheezing at the University of Virginia Medical Center (1991 through 1994). Children less than 2 years of age (black bars) were seen more frequently in December, January, and February at the height of the RSV season. Older children, ages 2 through 16 years (hatched bars) were seen more often in the spring (March through May), and fall (September through December) when allergen exposure and viral infections (rhinovirus) are more common.

Exacerbations in young children, aged 2 and 3, when the diagnosis of asthma often is considered (Figure 2). An awareness of the combined seasonal influences of allergen exposures and viral infection can be very helpful in designing treatment plans for individual patients. These treatment plans should include allergen avoidance and emphasize seasonal requirements for daily antiinflammatory medications. Physicians also should be aware that these seasonal influences are likely to vary geographically.

Evidence that infections with rhinovirus may augment the late phase eosinophil response in asthmatic individuals provides a rationale for using steroids to minimize the severity and persistence of airway inflammation and decrease the reliance of patients on inhaled bronchodilators during colds. When children with asthma develop a cold, peak flow tests can be useful to monitor changes in lower airway function. Morning peak flow tests should be checked with the onset of cold symptoms and for the duration of the infection, with particular attention focused on changes that may occur during the first 2 to 4 days. Recent studies indicate that inhaled steroids may benefit asthmatic children during colds. Those who are already using inhaled steroids daily may benefit from an increased dose for 2 to 3 weeks. Should symptoms worsen, the need for systemic steroids should be considered with the patient’s physician.

Important questions remain about the capacity of viral respiratory tract pathogens to augment inflammatory pathways in the lungs of asthmatic children. More research is needed to learn whether the examples of pulmonary eosinophilia stimulated by RSV antigens (i.e., the attachment G protein) in animals and humans represent an immune response similar to parasite induced eosinophilia or whether this is a process characteristic of allergic inflammation.
Figure 2. Emergency room visits for children ages 2 and 3, treated at the University of Virginia for wheezing (1991 through 1994). Rhinovirus, rather than RSV, is the dominant virus associated with wheezing in this age group. A Similar to older children with asthma, about 50% of children treated for acute wheezing in this age group are also sensitized to inhaled allergens and/or have an elevated total IgE level. (Data from Duff AL, Pomeranz ES, Gelber LE, et al: Risk factors for acute wheezing in infants and children: Viruses, passive smoke, and IgE antibodies to inhalant allergens. Pediatrics 92:535–540, 1993; Heymann PW: Allergy: Early childhood asthma: What are the questions? Am J Respir Crit Care Med 151:S22–S23, 1995; and Johnston SL, Pattemore PK, Sanderson G, et al: The relationship between upper respiratory infections and hospital admissions for asthma: A time-trend analysis. Am J Respir Crit Care Med 154:654–660, 1996.)

in an individual who is genetically predisposed to develop allergic respiratory symptoms and asthma. The absence of cytopathic changes in the respiratory tract epithelium during rhinovirus colds, the patchy involvement of infected epithelial cells, and the lack of direct evidence for virus replication and infection in the lower airways suggest mechanisms involving the enhanced production of proinflammatory cytokines in the pathogenesis of inflammation induced by this virus. Candidate cytokines such as TNF-α, IFN-γ, IL-5, IL-8, IL-11, and GM-CSF currently are being investigated with respect to their cell sources and production during rhinovirus infections in allergic and nonallergic patients. In addition, efforts to develop reagents to block the binding of rhinovirus to ICAM-1, the major receptor used by rhinovirus to infect cells, also represent a therapeutic approach for preventing episodes of asthma induced by this virus. Overall, our understanding for the capacity of viral infections to precipitate wheezing attacks in infants and children has improved significantly during the last decade. The need for new information and strategies to treat virus-induced asthma exacerbations is now becoming more important as the prevalence of asthma continues to increase.

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