

Rhinovirus-induced asthma exacerbations during childhood: The importance of understanding the atopic status of the host

Peter W. Heymann, MD,^{a,b} and Joshua L. Kennedy, MD^b Charlottesville, Va

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Rhinovirus is the most frequent infectious agent associated with exacerbations of wheezing during childhood and among young adults. Areas of investigation that have been improving our understanding for the strong association between rhinovirus infections and attacks of asthma include studies that have (1) examined the role of rhinovirus infections during infancy in promoting the development of asthma¹⁻³; (2) demonstrated the striking association between rhinovirus infections, allergic sensitization, and exposure to environmental allergens among children who wheeze during the preschool and school-age years^{4,5}; and (3) examined the mechanisms of rhinovirus-induced exacerbations that will hopefully lead to new treatments.

From birth through the school-age years, children are frequently exposed to a variety of respiratory tract pathogens, and controversies persist as to why rhinovirus stands out as the dominant pathogen linked to wheezing. Surprisingly, mechanisms to explain how rhinovirus provokes an attack of asthma remain poorly understood. However, an abundance of data from pediatric population-based studies indicate that rhinovirus-induced wheezing exacerbations after 3 years of age are most likely to occur among children who are atopic.⁴⁻⁶ More recently, data from adults with asthma indicate that innate antiviral responses (eg, the production of type I and type III interferons) might be deficient in the asthmatic airway and could be instrumental in explaining the susceptibility of the asthmatic population to wheezing attacks caused by rhinovirus and possibly other viral pathogens.^{7,8}

Because asthma attacks provoked by rhinovirus are more common among children than adults,⁹ the study in this issue of the *Journal* by Baraldo et al,¹⁰ which examines whether innate antiviral responses to rhinovirus may be deficient in the airways of asthmatic children as previously reported in adults, is important. In addition, most pediatric data to date have been derived from

studies using nasal washes to test for the presence of virus along with biomarkers of airway inflammation. Thus the study by Baraldo et al¹⁰ is unique because of their evaluation of samples obtained by means of bronchoscopy from 4 groups of children (mean age, 5 years). These children included 2 groups with physician-diagnosed asthma (both atopic and nonatopic subjects), one group of atopic children without asthma, and nonatopic children without asthma who were enrolled as control subjects (12 in each group). The atopic status of these children was evaluated by using tests for total IgE and allergen-specific IgE antibodies in sera. Bronchoscopies were obtained when the children were asymptomatic, and samples sufficient for the analyses were available from 8 to 9 subjects in each group. During the bronchoscopies, bronchial brushings were obtained to grow epithelial cells in culture along with biopsy specimens for immunohistochemical analyses. The 2 asthmatic groups were well matched for previous hospitalizations, emergency department visits, and medication requirements. Only 6 of the children were being treated with low-dose inhaled corticosteroids, 3 in each group, and their results did not differ significantly from the results of those who were not using inhaled steroids. Before inoculation of the bronchoepithelial cells with virus, rhinovirus (strain 16) RNA was undetectable in all of the primary cell cultures. After inoculation, the expression of IFN- λ_1 and IFN- β mRNA was evaluated at 8 hours, and the production of protein (ie, the quantities of IFN- β detected were sufficient for analysis) was evaluated at 48 hours.

Similar to the data previously reported in adults, the authors found that the expression of mRNA for IFN- λ_1 and IFN- β and the production of IFN- β protein from epithelial cells after infection with rhinovirus 16 was also decreased in cells from the atopic asthmatic children and also from the cells obtained from the nonatopic asthmatic children and the atopic children without asthma compared with samples from the control subjects. In addition, the production of these innate cytokines *in vitro* correlated inversely with rhinovirus replication, as judged by using quantitative PCR in supernatants from these cells at 8 hours. The authors conclude that the decreased expression of these cytokines observed within hours after viral inoculation might impart susceptibility to infections with rhinovirus in the asthmatic host.

Whether this innate cytokine deficiency and the increased viral load observed by the authors reflect how bronchoepithelial cells would respond to a rhinovirus infection in the intact airway and whether this deficiency and increased viral load would persist throughout the course of the infection are important questions. In this regard significantly higher IFN- λ_1 levels were recently reported in nasal washes from asthmatic children who had positive test results for rhinovirus during an episode of acute wheezing compared with those seen in nonwheezing asthmatic children with rhinovirus-induced rhinitis.¹¹ Thus, although the expression of IFN- λ_1 in response to rhinovirus might be reduced when

From ^athe Department of Pediatrics and ^bthe Asthma and Allergic Diseases Center, University of Virginia School of Medicine.

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Corresponding author: Peter W. Heymann, MD, Pediatric Respiratory Medicine, University of Virginia School of Medicine, PO Box 800386, Charlottesville, VA 22908-0386.

E-mail: PWH5A@virginia.edu.

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bronchoepithelial cells from asthmatic patients are infected *in vitro*, the production of this cytokine during an attack of rhinovirus-induced asthma appears to be enhanced, at least in the upper airway where this virus replicates vigorously.

The beauty of the biopsy results reported by Baraldo et al¹⁰ is the discovery of increased tissue eosinophilia and IL-4-expressing cells, along with epithelial cell damage, not only in samples from the atopic asthmatic patients but also in biopsy specimens from nonatopic asthmatic children and atopic children without asthma. These results were also inversely related to the expression of IFN- λ_1 and IFN- β mRNA in the bronchoepithelial cells infected *in vitro*. The results from the children with asthma who were not atopic are of interest because there is little information about this phenotypic group in the literature and because the presence of T_H2-driven immunopathology in their lower airways might, as the authors note, also impart a greater risk for acute asthma symptoms provoked by rhinovirus, even in the absence of allergic sensitization. Of interest, however, is that compared with the atopic asthmatic children in this study, the nonatopic asthmatic children had significantly lower levels of blood eosinophilia and a trend toward lower tissue eosinophilia in their biopsy specimens. This might suggest a better prognosis for these children; however, a larger longitudinally based study is needed, which might be difficult because nonatopic asthmatic children at this age represent a minority (<20%) of those who need hospitalization or treatment in the emergency department for acute wheezing.^{4,6,12}

Among the atopic children without physician-diagnosed asthma, the authors also discovered T_H2-associated immunopathology in their biopsy samples along with reduced IFN- λ_1 and IFN- β expression in their bronchoepithelial cells after rhinovirus 16 inoculation. However, like other children in this study, the 8 children in this group had clinical indications for their bronchoscopies, including 5 who were being evaluated for recurrent pneumonias, 2 for chronic cough, and 1 for middle-lobe syndrome. Therefore these children differ from the majority of children with allergic rhinitis who do not require bronchoscopic evaluations for reasons that might be consistent with asthmatic changes in their lower airways.

More directly related to the relevance of atopy, the authors found a positive correlation between total IgE levels in sera from the children in the study and an increased viral load detected in their epithelial cell supernatants at 8 hours and an inverse correlation between total IgE levels and the expression of

IFN- λ_1 . These results are in keeping with a recent study of school-age asthmatic children demonstrating that increasing serum titers of allergen-specific IgE antibody (eg, to dust mite allergen) substantially increase the probability of wheeze provoked by rhinovirus.¹² Taken together, the data from the study by Baraldo et al¹⁰ provide important information relevant to the pediatric population and help to highlight the importance of defining the atopic status of asthmatic patients in studies to decipher the mechanisms of wheezing induced by rhinovirus.

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