Published in final edited form as:

J Allergy Clin Immunol. 2012 December ; 130(6): 1315–1316. doi:10.1016/j.jaci.2012.10.024.

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

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Rhinovirus (RV) is the most frequent infectious agent associated with exacerbations of wheezing during childhood and among young adults. Areas of investigation which have been improving our understanding for the strong association between RV infections and attacks of asthma include studies that have 1) examined the role of RV infections during infancy in promoting the development of asthma (1-3); 2) demonstrated the striking association between RV infections, allergic sensitization and exposure to environmental allergens among children who wheeze during the pre-school and school-age years (4,5); and 3) examined the mechanisms of RV-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 RV provokes an attack of asthma remain poorly understood. However, an abundance of data from pediatric population based studies indicate that RV-induced wheezing exacerbations leading to urgent care visits and hospitalizations 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 anti-viral responses (e.g., the production of type I and type III interferons) may be deficient in the asthmatic airway and may be instrumental in explaining the susceptibility of the asthmatic population to wheezing attacks caused by RV and possibly other viral pathogens (7,8).

Because asthma attacks associated with RV are more common among children than adults (9), the study in this issue of the Journal by Baraldo and colleagues is important and examines whether innate anti-viral responses to RV might also be deficient in the airway of asthmatic children is important. In addition, most pediatric data to date has been derived

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from studies using nasal washes to test for the presence of virus and associated biomarkers of airway inflammation. Thus, the study by Baraldo et al is unique because of their evaluation of samples obtained via bronchoscopy from four groups of children (mean age 5 years old). These children included two groups with physician-diagnosed asthma (both atopic and non-atopic individuals), one group of atopic children without asthma, and non-atopic children without asthma who were enrolled as controls (12 in each group). The atopic status of these children was evaluated 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 biopsies for immunohistochemical analyses. The two asthmatic groups were well matched for previous hospitalizations, ER 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 those who were not using inhaled steroids. Prior to inoculation of the broncho-epithelial cells with virus, RV (strain 16) RNA was undetectable in all of the primary cell cultures. Following inoculation, the expression of mRNA IFN- λ_1 and β was evaluated at 8 hours and the production of protein (i.e., the quantities of IFN- β detected were sufficient for analysis) at 48 hours.

Similar to the data previously reported in adults, the authors found that the expression of mRNA for IFN- λ_1 and β and the production of IFN- β protein from epithelial cells after infection with RV-16 was also decreased in cells from the atopic asthmatic children, and also from the cells obtained from the non-atopic asthmatics and the atopic children without asthma, compared to samples from the controls. In addition, the production of these innate cytokines *in vitro* correlated inversely with RV replication as judged by qPCR in supernatants from these cells at 8 hours. The authors conclude that the decreased expression of these cytokines observed within hours after virus inoculation may impart susceptibility to infections with RV in the asthmatic host. Whether this deficiency and the increased viral load observed by the authors (and others in previous studies from adults) reflects how broncho-epithelial cells would respond to a RV 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 levels of IFN- λ_1 were recently reported in nasal washes from asthmatic children who tested positive for RV during an episode of acute wheezing compared to non-wheezing asthmatic children with RV-induced rhinitis (10). Thus, although the expression of IFN- λ_1 in response to RV may be reduced after broncho-epithelial cells from asthmatics are infected *in vitro*, the production of this cytokine during an attack of RV-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 the authors is the discovery of increased tissue eosinophils and IL-4 expressing cells along with epithelial cell damage not only in samples from the atopic asthmatics, but also in biopsies from non-atopic asthmatics and the atopic children without asthma. These results were also inversely related to the expression of IFN- λ_1 and β mRNA in the broncho-epithelial cells infected *in vitro*. The results from the children with asthma who were not atopic is of interest, because there is little information

about this group in the literature, and because the presence of Th2-driven immunopathology in their lower airway may, as noted by the authors, also impart a greater risk for acute asthma symptoms provoked by RV, even in the absence of allergic sensitization. Of note, however, is that compared to the atopic asthmatic children in this study, the non-atopic asthmatics had significantly lower levels of blood eosinophilia and a trend toward lower tissue eosinophilia in their biopsies. This might suggest a better prognosis for these children; however, a larger longitudinal-based study is needed which may be difficult because non-atopic asthmatic children at this age represent a minority (< 20%) of those who need hospitalization or treatment in the ER for acute wheezing (4,6,11).

Among the atopic children without physician-diagnosed asthma, the authors also discovered Th2-associated immunopathology in their biopsy samples along with reduced IFN- λ_1 and β expression in their broncho-epithelial cells after RV-16 inoculation. However, like the 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 one for middle-lobe syndrome. So these children differ from the majority of children with allergic rhinitis who do not require bronchoscopic evaluations with reasons that might be consistent with asthmatic changes in their lower airway. More directly related to the relevance of atopy, the authors found a positive correlation between levels of total IgE in sera from the entire study population and the increased viral load detected in their epithelial cell supernatants at 8 hours and an inverse correlation between total IgE and the expression of IFN- λ_1 . These results are in keeping with a recent study of school-aged asthmatic children demonstrating that increasing serum titers of allergen specific IgE antibody (e.g., to dust mite allergen) substantially increases the probability of wheeze provoked by RV (11). Taken together, the data from the study by Baraldo and co-authors provide important information relevant to the pediatric population and help to highlight the importance of defining the atopic status of asthmatic subjects in studies to decipher the mechanisms of wheezing induced by rhinovirus.

Acknowledgments

Funding source: U01 AI 100799 and the University of Virginia Children's Hospital

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