

September epidemic of asthma exacerbations in children: A manifestation of persistent or episodic disease?

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Johnston et al,¹ in the January issue of the Journal, addressed the "September Epidemic of Asthma Exacerbations in Children." This well-designed case controlled study demonstrated a higher frequency of recovering viruses from children seen in the emergency department (ED) for acute asthma and a lower rate of anti-inflammatory medication use compared with a group of controls with asthma with similar or greater disease severity. In addition, this study presented important demographic information on these children with an acute ED event. The article also has raised several important questions that deserve further discussion. First, are children with asthma at greater risk for being infected with common viral respiratory agents? Second, does viral-induced asthma occur as a manifestation of an episodic disease, or is it a characteristic of persistent childhood asthma? Finally, are anti-inflammatory medications effective treatments for the prevention of viral-induced asthma?

The association of asthma exacerbations and acute viral illness has been well documented for the past 4 decades both in clinical and laboratory settings.²⁻⁴ The current study¹ reports viral detection in 62% of the cases seen in the ED and 41% of the asthma control cohort ($P = .011$). The authors¹ state that the significance of these differences may be limited by the fact that the cases were seen during acute illnesses and that the controls were sampled at random times during the 3-week study.

The literature is divided on whether children who wheeze with viral infections have a greater number of these infections compared with control groups of patients with asthma. Thumerelle et al⁵ reported that viral infections were a common association in children with acute

Abbreviation used

ED: Emergency department

asthma and that viral identification was less frequent in asymptomatic children with asthma of similar severity. Rakes et al⁶ demonstrated that although the detection of rhinovirus by RT-PCR was higher in acute asthma than controls, viral isolation was similar. This latter finding illustrates the ubiquitous nature of these infections and suggests that both exposure and infection rates may be comparable in cases and controls. In addition, the host response to the infection may be the determinant of whether an acute ED visit or exacerbation occurs. These 2 studies^{5,6} support the association of viral infections as the etiology of acute asthma. Because of their study designs these articles do not completely describe the rate of infection in the control subjects.

The current study by Johnston et al¹ notes that 40% of the controls had evidence of rhinovirus infection. Although a statistically lower rate than the cases, this confirms the pervasiveness of rhinovirus in school-age children, even in those without acute illnesses. These results may support the hypothesis that it is the host response, potentially modified by controller medication, that determines the clinical expression of disease.

Two earlier studies have demonstrated differences in the rates of viral infections in patients with asthma and their family controls. Minor et al⁷ showed a greater frequency of viral identification in children with asthma compared with their siblings without asthma. This contrasts with the findings of Tarlo et al,⁸ who reported more symptomatic colds in patients with asthma but higher viral isolation rates and increased serological changes in their spouses without asthma. The literature is still not definitive about whether there is an increased risk of viral infections in children with asthma. What is well documented is that these infections are common in the school-age population, are triggers of acute severe exacerbations, and occur in epidemics.

The children in the study by Johnston et al¹ are predominantly males and atopic, as expected in this age

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group. There is a high rate of exercise-induced asthma both in the cases, 65%, and in the controls, 78%. Nighttime awakening is reported in 60% of cases and 71% of controls. Although 44% of cases had 1 to 3 previous ED events and 47% had more than 3 previous ED episodes in the previous year, 2/3 of these children reported that their asthma was well controlled. As in other studies, there was a mismatch in perceived asthma control and reporting of symptoms and acute exacerbations.⁹

The majority of children in this study with epidemic viral asthma had symptoms of persistent asthma and recurrent severe exacerbations. The low rate of controller therapy in the cases despite a high rate of multiple ED events and the fact that nearly 50% missed school because of asthma illustrates the underreporting and/or underrecognition of disease morbidity. In addition, it may suggest the limitation of classifying viral-induced asthma as an episodic disease.

Another important observation in this study was the finding that patients seen in the ED, when compared with controls, reported a significantly lower rate of prescriptions for anti-inflammatory medications, especially inhaled corticosteroids (49.1% compared with 84.7%, respectively). The literature is divided about whether inhaled corticosteroids can prevent the occurrence of acute asthma caused by viral respiratory infections. Viral infections are reported as the cause of 80% to 85% of exacerbations in children.¹⁰ Inhaled corticosteroids are identified in several large studies as reducing severe exacerbations including ED visits, hospitalizations, and use of oral corticosteroids.^{11,12} However, clinical trials that have attempted to show the effect of inhaled corticosteroids on preventing viral-induced asthma have not demonstrated an effect. Does the current article¹ offer any explanations of these contradictory statements?

The Childhood Asthma Management Program¹¹ demonstrated a 40% to 45% reduction in severe exacerbations with the use of inhaled budesonide. The inhaled Steroid Treatment as Regular Therapy in Early Asthma study¹² also reported a 44% reduction in severe exacerbations in patients treated with inhaled budesonide. Although these 2 important studies did not document the etiology of acute episodes of asthma, the literature, including the current study,¹ supports the correlation of acute severe asthma with viral infections and suggests that treatment with inhaled corticosteroid may be preventative.

The Cochrane database¹³ searched the literature to address the issue of the inhaled corticosteroid therapy as preventive treatment for viral-induced asthma. It reported only 2 studies on this topic. The report by Wilson et al¹⁴ investigated infants and toddlers, and the article by Doull et al¹⁵ studied school-age children. Both looked at children with mild viral disease. In the study by Doull,¹⁵ the need for oral corticosteroids was uncommon in both treated and untreated populations. A review by Doull¹⁶ discusses some of the discrepancies between the clinical and observational studies. A limitation of the research may be in the populations selected. The longitudinal studies from both Tucson¹⁷ and Melbourne¹⁸ describe multiple

asthma phenotypes. The children in the study by Wilson et al¹⁴ may fit better into the transient asthma or wheezy bronchitis classifications. The children in the study by Doull et al¹⁵ were entered on the basis of the history of respiratory symptoms and not an asthma diagnosis. Further, this study was designed “to have an 80% power of detecting a difference of one peak expiratory flow episode...” and was not powered on asthma exacerbations. Both studies reported in the Cochrane analysis¹³ would need more subjects with a defined asthma phenotype to assess more specifically the effect of inhaled corticosteroids on severe exacerbations. The current article by Johnston et al¹ suggests that the clinical expression of viral-induced asthma may be favorably downregulated with inhaled corticosteroids.

Johnson et al¹ have drawn attention to the importance of the September epidemic of asthma. This article addresses this topic well and also suggests areas that deserve further study. First is the need to describe and diagnose better the pediatric asthma phenotype that requires controller therapy to reduce these acute viral-induced exacerbations of asthma. Epidemic viral-induced asthma appears in this study to be persistent disease rather than episodic. Treating these children at risk for acute asthma as having an intermittent disease may unnecessarily restrict the use of appropriate therapy, including inhaled corticosteroids. The majority of the children seen in the ED reported that their asthma was not in control before the acute episode, and 91% had a previous ED visit in the previous year. Further, there is the need to understand better the effect of controller medications, especially inhaled corticosteroids, and their effect on viral-induced asthma. The current article¹ suggests that appropriate identification and treatment with anti-inflammatory medications may modify the September epidemic of asthma exacerbations in children.

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Correction

With regard to the October 2004 article entitled "Corticotropin-releasing hormone deficiency increases allergen-induced airway inflammation in a mouse model of asthma" (2004;114:747-54): It should have been noted in the footnotes on the article's first page that Drs Silverman and Breault contributed equally to the final manuscript.