Editorial

Asthma exacerbations: Putting a lid on the volcano

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Key words: *Asthma, asthma control, asthma impairment, asthma risk, asthma exacerbations*

The recently revised National Asthma Education and Prevention Program asthma guidelines now emphasize the importance of asthma control, a stepwise approach to asthma management, and the importance of early diagnosis and intervention.[1] The National Asthma Education and Prevention Program introduced several new terms to consider in following the course of asthma management. A full resource document and Executive Summary is available.[1,2]

Several key terms were introduced with the new guidelines, including *severity*, *control*, *responsiveness*, *impairment*, and *risk*.[3] *Severity* is defined as the intrinsic intensity of the disease process and can be measured most readily and directly in patients who are not receiving long-term controller therapy. *Control* is the degree to which the manifestations of asthma (symptoms, functional impairment, and risks of untoward events) are minimized and the goals of therapy are achieved. *Responsiveness* is the ease with which control is achieved by therapy.

Asthma severity and asthma control are both divided into 2 domains: impairment and risk. *Impairment* is the assessment of the frequency and intensity of symptoms, as well as the functional limitations that the patient is experiencing now or has experienced in the past because of asthma. *Risk* is the estimate of the likelihood of an asthma exacerbation, progressive loss of pulmonary function over time caused by asthma, or an adverse event from medication or even death. The assessment of severity and control provide guidance on the direction to take in stepping up or stepping down medications. In the updated asthma guidelines, there is increased attention paid to the assessment of risk in the form of previous asthma exacerbations, loss of lung function, and potential risk for adverse effects to medications.

Inhaled corticosteroids are recognized as the preferred long-term controller in children 5 years of age and older on the basis of strong evidence from comparison studies. A carefully implemented guidelines approach works well to get most asthma well controlled; however, there is still significant variability in response that is identified when patients are closely monitored.[4] This theme issue carefully examines current knowledge regarding asthma exacerbations, including epidemiology, etiology, and mechanisms of rhinovirus-induced exacerbations. This issue also contains several original publications related to this topic that provide new insights for future considerations in management.

EPIDEMIOLOGY

Dr Malcolm Sears[5] provides an overview of current information related to the epidemiology of asthma exacerbations, especially the "September epidemic." He makes the point that several definitions have been used for documenting exacerbations of asthma in clinical practice and in research studies. A practical working definition of an exacerbation that is useful clinically and has also been applied in several recent trials of pharmacologic therapies has been a worsening of asthma of sufficient severity to require intervention from a medical professional or self-administration of oral corticosteroids.

Exacerbations of asthma sufficient to require urgent medical intervention are often, but not always, associated with viral infection, follow seasonal patterns especially in children, and are aggravated by lack of adequate maintenance anti-inflammatory drug treatment. In addition, frequent exacerbations may be an indication of greater severity of disease, significant comorbidities, or poor compliance with therapy. It is important to recognize risk factors for exacerbations and implement an appropriate long-term management strategy to reduce morbidity and mortality related to asthma exacerbations. This will help us control the volcano of inflammatory mechanisms associated with an asthma exacerbation (Fig 1).

ETIOLOGY

Drs Sykes and Johnston[6] review information related to causes of asthma exacerbations. Exacerbations are associated with environmental factors such as ozone, nitrogen dioxide, living close to roads, and allergy; however, the majority of exacerbations are related to viral infection, particularly rhinoviruses. Approximately 80% of exacerbations are associated with respiratory viral infections, and rhinovirus infection is responsible for approximately 2/3 of these viral infections. In addition, patients with asthma have more severe lower respiratory tract illness with rhinovirus than normal controls.

It is important to keep in mind that an asthma exacerbation can occur as a result of a single etiology but more often results from a combination of etiologies triggering inflammatory pathways and

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Supported in part by Public Health Services Research Grants HR-16048, HL64288, HL 51834, AI-25496, HL081335, and HL075416; General Clinical Research Center Grant 5 MO1 RR00051; and the Colorado Cancer, Cardiovascular and Pulmonary Disease Program.

Disclosure of potential conflict of interest: S. J. Szefler has served as a consultant for AstraZeneca, GlaxoSmithKline, Aventis, Genentech, and Merck and has received research support from the National Institutes of Health (NIH)/National Heart, Lung, and Blood Institute (NHLBI) Childhood Asthma Management Program, NHLBI Childhood Asthma Research and Education, the NIH/NHLBI Asthma Clinical Research Network, the NIH/National Institute of Allergy and Infectious Diseases Inner-City Asthma Consortium, and Ross Pharmaceuticals.

Received for publication August 18, 2008; accepted for publication August 27, 2008.

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J Allergy Clin Immunol 2008;122:697-9.
0091-6749/$34.00

doi:10.1016/j.jaci.2008.08.022

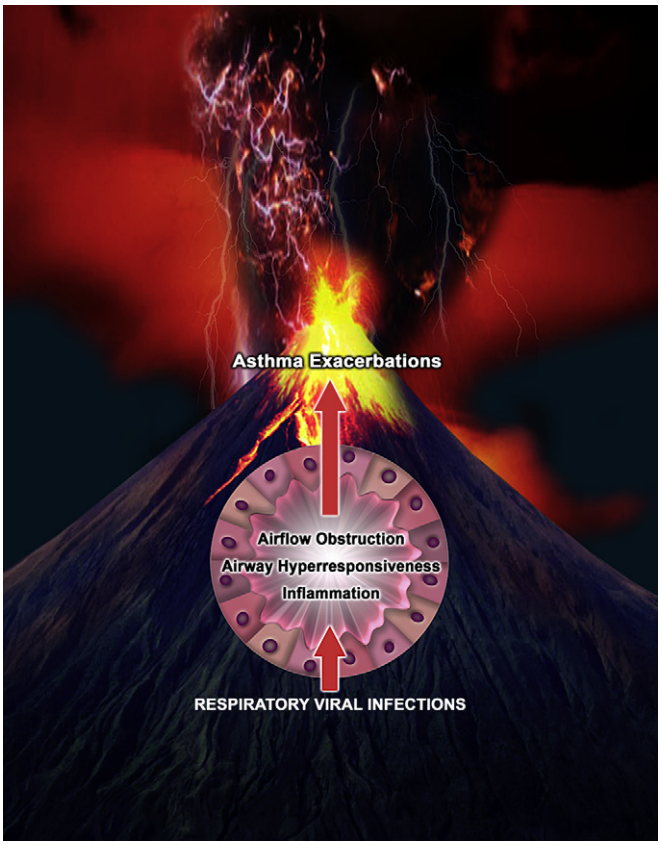

FIG 1. Underlying features of an erupting asthma exacerbation. Underlying mechanisms, in this case related to a rhinovirus infection, lead to increasing inflammation, airflow obstruction, and airway hyperresponsiveness on top of existing airway inflammation. Controlling the underlying inflammation enhanced by a viral infection will in effect put a lid on this volcano. This image is also featured on the cover of this issue of the Journal.

associated airway obstruction. Virus infections are the major precipitant of asthma exacerbations, and identification of the relevant mechanisms should result in treatments that are directed to the etiology. To reduce health care costs related to exacerbations, it is important to develop innovative prevention and management strategies.

IMMUNE RESPONSE TO RHINOVIRUS

Drs John Kelly and William Busse[7] summarize what is known about the immune response to rhinovirus with *in vitro* models and observations from *in vivo* studies, and then discuss how these findings may relate to asthma exacerbations and possibly disease pathogenesis. In addition, they explore the possibilities that some patients with asthma may have abnormal antiviral responses to rhinovirus and consider how such deficiencies may play a role in the ability of this virus to exacerbate asthma. Finally, they discuss current treatment in terms of further understanding the immune response to virus and then speculate on the potential for novel interventions to regulate the immune response specifically to rhinovirus and maintain asthma control.

The discovery of an increased susceptibility of patients with asthma to the adverse effects of a respiratory infection has helped to define better the immune response to viruses, and to rhinovirus in particular. We now have a better understanding of the inflammatory cytokine response to rhinovirus infection as well as the profile of cellular infiltrates involved, including neutrophils, eosinophils, and lymphocytes. Investigation into specific cellular responses as potential targets for therapy will be important in attenuating, and perhaps even preventing, one of the most common causes of asthma exacerbations. Of further interest is the observation of persistent rhinovirus antigen within the lower airway during periods of asthma stability that must be studied in the framework of chronic airway inflammation.

NEW INSIGHTS

Several original reports in this issue could be relevant for future management of asthma. Dr Ronald Sorkness et al[8] sought to develop a measure of objective and subjective features of asthma control for the purpose of defining an asthma exacerbation and for describing the time course of changes associated with specific triggers. In addition to providing a criterion for defining qualitatively the occurrence of an exacerbation, the Asthma Index is a continuous variable that can be used for a comparison of magnitudes of changes among groups, and for tracking the time course of changes associated with an event such as a viral illness.

A report on the features of asthma exacerbations from a 1-year clinical trial from the National Heart, Lung, and Blood Institute Childhood Asthma Research and Education Network is summarized by Dr Ronina Covar et al.[9] A regression model was used to identify historical, phenotypic, treatment, and time-dependent factors associated with the occurrence of exacerbations, defined by a need for oral corticosteroids or emergency or hospital care in the 48-week Pediatric Asthma Controller Trial study that was previously summarized.[10] As a result of this additional analysis, the investigators concluded that children with mild-to-moderate asthma with previous exacerbations are more likely to have a repeat exacerbation even during a course of long-term controller therapy, such as an inhaled corticosteroid or leukotriene receptor antagonist. Although it was recognized that the risk of exacerbations was lower in those receiving inhaled corticosteroid therapy compared with a leukotriene receptor antagonist, the baseline physiologic measures and biomarkers and diary card tracking are not reliable predictors of asthma exacerbations. Therefore, there is a need for a more reliable indicator of an immanent exacerbation, especially one that could lead to a need for urgent care.

Another interesting report in this issue is an evaluation of inflammatory mediators in exhaled breath condensates after an allergen-induced bronchoconstriction by Ono et al.[11] They report that in patients with an early asthmatic response to allergen, an increase in cysteinyl leukotrienes and prostaglandin D_2 could be measured. They suggest that it may be possible to use this measure in monitoring acute asthmatic airway inflammation.

WHERE DO WE GO FROM HERE?

Based on these current reports, several important questions are raised. Can we continue to improve asthma control by reducing impairment and risk domains? Can we identify more reliable early indicators of an asthma exacerbation? Once recognized, can we take steps to attenuate an impending asthma exacerbation? One method would be to provide more effective long-term control therapy that would further minimize the frequency of unstable asthma. For example, omalizumab is not approved for use in children less than 12 years of age, and asthma exacerbations occur most frequently in young children. Perhaps omalizumab would be

even more effective in reducing asthma exacerbations if used at an earlier age in certain patient populations at risk for significant asthma exacerbations caused or exaggerated by allergic airway inflammation. Another strategy may be measuring biomarkers that are present early in the course of an asthma exacerbation—for example, exhaled nitric oxide. This would require a device that is easy to use and has a reasonable cost. Yet another strategy would be to identify populations of patients at risk for asthma exacerbations, perhaps by genetics,[12,13] and provide a comprehensive management plan to minimize the frequency and severity of breakdowns in asthma control. Last year, an interesting report in the Journal suggested that a course of prednisolone could reduce the risk of recurrent wheezing after a first wheezing episode associated with rhinovirus infection.[14] Needless to say, a number of strategies are worth considering in future asthma management to reduce the impact of asthma exacerbations on the course of asthma.

I thank Gretchen Hugen for assistance with manuscript preparation.

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