Asthma Exacerbations: Pathogenesis, Prevention, and Treatment

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Guideline-based management of asthma focuses on disease severity and choosing the appropriate medical therapy to control symptoms and reduce the risk of exacerbations. However, irrespective of asthma severity and often despite optimal medical therapy, patients may experience acute exacerbations of symptoms and a loss of disease control. Asthma exacerbations are most commonly triggered by viral respiratory infections, particularly with human rhinovirus. Given the importance of these events to asthma morbidity and health care costs, we will review common inciting factors for asthma exacerbations and approaches to prevent and treat these events. © 2017 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2017;5:918-27)

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Despite optimal guideline-directed treatment, and irrespective of underlying disease severity, patients with asthma experience exacerbations, which are caused by an accentuation of existing inflammatory processes and a loss of disease control.

Asthma exacerbations are a major cause of disease morbidity, increases in health care costs, and, in some patients, a greater progressive loss of lung function.[1] The frequency of exacerbations can be reduced, but not always fully prevented, with adequate inhaled corticosteroid (ICS) treatment or combination ICS/long-acting β-agonists (LABA).[2] Because asthma exacerbations can break through standard treatment regimens, identifying at-risk patients and having a plan of management can improve disease control and patient well-being.

Asthma exacerbations remain a major reason for health care utilization and a significant financial burden to patients and society. Patients with asthma exacerbations have significantly higher total health care costs, $9223 versus $5011 (2007 dollars) per person per year, and asthma-specific costs, $1740 versus $847 per person per year, compared with matched patients without exacerbations.[3] In 2007, total expenditures for asthma were estimated to be $56 billion per year with productivity losses due to morbidity and mortality of $3.8 and $2.1 billion, respectively.[4] Moreover, patients requiring an emergency department (ED) visit or hospitalization for asthma are at significantly increased risk for future exacerbations independent of demographic and clinical factors, asthma severity, and asthma control,[5] collectively reflecting an ongoing need to develop better strategies to prevent and treat these events.

PATHOGENESIS

Viral respiratory infections

The most common triggers for an exacerbation are viral respiratory infections with human rhinovirus (RV), particularly subtypes A and C,[6,7] most frequent. In school-age children, hospital admission rates for asthma exacerbations correlate with the seasonal increase of RV infections in September through December and again in the spring.[8] Similar asthma hospitalization peaks are observed in adults.[9]

Other respiratory viruses also may cause exacerbations. During the 2009 H1N1 influenza A pandemic, mortality and admissions to the intensive care unit with H1N1 infections were frequently associated with asthma.[10-12] Respiratory syncytial virus, a frequent cause of wheezing in infants and young children, may also trigger acute asthma in adults, particularly, patients older than 65 years.[13] Coronaviruses, human metapneumoviruses, parainfluenza viruses, adenoviruses, and bocaviruses have all been detected in asthma exacerbations, but in low frequencies.[14]

Patient risk factors

There are a number of susceptibility, or risk, factors that help to determine whether a viral respiratory infection causes an exacerbation (Figure 1).

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Abbreviations used
ED- Emergency department
FEV_1- Forced expiratory volume in 1 second
ICS- Inhaled corticosteroids
LABA- Long-acting β-agonist
RV- Rhinovirus
SABA- Short-acting β_2-agonist

Allergy and defective anti-viral immunity

Allergic sensitization is a risk factor for wheezing with RV infection, particularly in children. Whether allergic inflammation often found with sensitization increases the susceptibility for viral infections or enhances their ability to provoke further inflammation is not entirely clear.[16] Type I interferons are important innate antiviral responses to respiratory viruses.[14,17] There is evidence that virus-induced interferon generation from peripheral blood mononuclear cells,[18-20] plasmacytoid dendritic cells,[21] and bronchial epithelial cells[22,23] is reduced in some patients with allergic asthma (Figure 2). It has been show that IgE occupancy of their membrane receptors inhibits antiviral generation of IFN-α from plasmacytoid dendritic cells and may increase susceptibility to RV-induced wheezing and asthma exacerbations (Figure 3). Deficient immune responses to viral infections may be present in type 2 inflammatory conditions with interferon production being inversely correlated with increasing airway eosinophilia, IL-4 levels, and total serum IgE.[23] Finally, the use of inhaled IFN-β at the time of an upper respiratory infection reduces the airway viral load and improves clinical symptoms in patients with asthma.[24]

Bacterial infections

Bacterial infections may impair mucociliary clearance and increase mucus production in the lung and may cause chronic lower airway inflammation. Evidence linking bacterial infections to acute asthma exacerbations has been limited.[25,26] However, respiratory viruses may impair the antibacterial defenses by human alveolar macrophages and thereby facilitate emergence of bacterial infections or change in the microbiome.[27] How these interrelationships contribute to exacerbations is not established, but they may be of potential therapeutic importance[28] to prevent acute asthma.

Allergen exposure

Environmental allergens can provoke asthma.[29] Furthermore, more than 80% of children with asthma are sensitized to environmental allergens, with indoor allergens being especially important to underlying asthma.[30,31] Mast cell activation by allergens releases[32,33] histamine, prostaglandin D2, and cysteinyl leukotriene generation to cause airway smooth muscle constriction, increased microvascular permeability, mucus secretion, and enhanced inflammation. Allergic sensitization is also associated with diminished innate immune responses and may be a susceptibility factor to viral-induced wheezing. This allergen associated inflammation also increases airway responsiveness to RV[34] to further enhance a loss of asthma control.

Mold sensitization and their seasonal increase parallel greater asthma severity and seasonal exacerbations. Patients sensitized to *Alternaria alternata* were approximately 5 times more likely to have asthma[35] and increased airway responsiveness, wheeze, and bronchodilator use.[36] Emergency visits for asthma exacerbations correlate with high airborne concentrations of mold.[37] Finally,

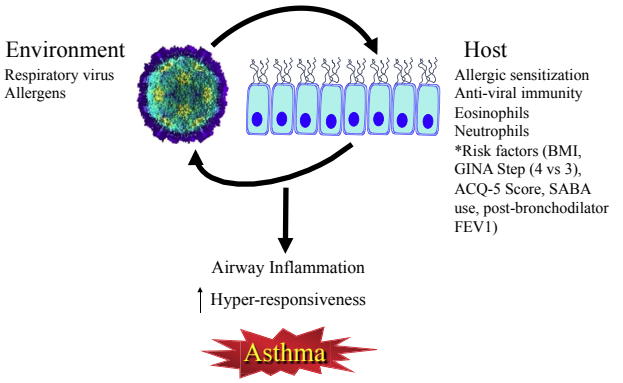

FIGURE 1. The interplay of the environment and host susceptibility factors in the pathogenesis of asthma exacerbations. Risk factors from Bateman et al.[15] *ACQ*, Asthma Control Questionnaire; *BMI*, body mass index; *FEV1*, forced expiratory volume in 1 second; *GINA*, Global Initiative for Asthma; *SABA*, short-acting β_2-agonist.

Alternaria sensitization was found to be associated with an approximate 200-fold increase in the risk of respiratory arrest in children and adults.[28,38]

Other contributing causes

Pollutants such as tobacco smoke, ozone, and particulate matter, along with occupational exposures, provoke asthma exacerbations. Tobacco smoke has also been implicated in the development of persistent wheezing[39] and greater asthma severity.[40] Hospitalizations and ED visits for asthma occur more frequently among cigarette smokers.[41]

Particulate matter, ozone, nitrogen dioxide, sulfur dioxide, and diesel exhaust can increase airway inflammation and airway responsiveness.[32,33,42] Airway pollutants, together with a viral infection, may act synergistically to cause asthma exacerbations. The severity of lower respiratory tract symptoms increased and peak expiratory flow measurements fell with rising exposure to nitrogen dioxide in the week before a respiratory infection.[33]

Prevention of exacerbations

Four essential components of asthma management include patient education, monitoring of symptoms and lung function, control of triggering factors and comorbid conditions, and pharmacologic therapy. Patient education on asthma decreases exacerbations and improves control.[43,44] However, because asthma severity varies and differs among individuals and age groups, it is essential to regularly monitor the effectiveness of asthma control to guide necessary treatment adjustments.

The Expert Panel Report 3 and Global Initiative for Asthma describe a stepwise treatment approach and strategy to reduce impairments and prevent future risks like asthma exacerbations.[45,46]

TREATMENTS

Inhaled corticosteroids

ICS improve disease control and reduce asthma exacerbations.[47-49] In new onset, untreated persistent, asthma, low-dose inhaled budesonide reduces asthma exacerbations by almost 50%.[50,51] In asthmatic patients already taking moderate doses of