

Mechanisms and Treatment of the Diverse Presentations of Acute Wheezing and Asthma



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For patients with asthma, and for the practitioners treating such patients with asthma, acute deteriorations of asthma represent a major concern. They interfere with routine activities, jobs, and education and may be life-threatening. Patients who present with acute wheezing are highly diverse in age, sex, ethnicity, and socioeconomic status. Just as the patients represent a diverse population, the underlying predisposing factors (genetics, environment, lifestyle) and pathogenic mechanisms (infection, allergic, eosinophilic, non-type 2) are broad-ranging and can vary by season and, more importantly, by respiratory and asthma phenotype (Figure 1). In any given week, urgent consultations, emergency department visits, or hospitalizations may be required for infants with infectious wheeze who may or may not have asthma, children with acute asthma exacerbations after returning to school, adults with environmental or occupational exposures, and both children and adults presenting with exacerbations without clear cause, many of which may be due to viral infections. Adverse social conditions and poor connections to the health care system increase the risk of recurrent exacerbations. There are multiple phenotypes of adult asthma with different triggers, inflammatory mechanisms, and responses to asthma control medications. Finally, children and adults with severe

uncontrolled asthma are at the most significant risk for exacerbations.

For all of these patients, asthma exacerbations and acute wheezing illnesses are major causes of morbidity. They represent the primary cause of lost days from school and work in asthma and may result in an inability to maintain full-time employment. They are also associated with a more rapid decline in lung function.¹ Using systemic corticosteroids, as infrequently as once per year, can accelerate osteoporosis and promote the development of diabetes.² Moreover, exacerbations may be a characteristic of a particular subcategory of patients who are exacerbators.

Treating this diverse group of wheezing patients is challenging. Once acute respiratory distress is controlled, the treatment goal shifts to preventing future wheezing episodes. Success is likely to depend on understanding both the asthma phenotype and the triggers of acute symptoms related to personal, environmental, and social conditions. We need further insights into these diverse mechanisms of exacerbations to precisely and effectively control asthma. In this issue of the *Journal of Allergy and Clinical Immunology: In Practice*, an invited group of experts consider management of acute wheezing and asthma exacerbations in the emergency department, preventing exacerbations in adults and children, and whether exacerbators are a biological phenomenon or a social construct.

First, Hasegawa and colleagues³ provide a comprehensive review of the treatment of asthma in the emergency department. Following the aphorism that “all that wheezes may not be asthma,” they provide a comprehensive differential diagnosis for children and adults presenting to the emergency department. They provide a handy chart of assessments and interventions in the emergency department, including considerations for hospitalization and referral to intensive care. In addition, they stress the importance of a discharge action plan to help prevent returns to the emergency department and provide a model action plan form. Of importance to clinicians, they note that pregnant women are frequently undertreated in the emergency department (22% not receiving corticosteroids in the emergency department and a concerning 37% not being discharged with a corticosteroid prescription).

Preschool children have the highest rate of acute-care visits and hospitalization for acute wheezing illnesses.⁴ They also present particular diagnostic challenges because the clinical presentation of a child with acute viral wheeze is quite similar to that of asthma exacerbation. Furthermore, response to asthma-directed therapies is uneven in this age group. Bacharier and colleagues⁵ review criteria for the diagnosis of asthma in this age group and discuss the utility and limitations of current asthma risk indices. Biomarkers such as eosinophil count and allergic sensitization can be helpful in making therapeutic decisions about selection of asthma control medications. Finally, they

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FIGURE 1. The diversity of acute wheeze and asthma exacerbation. Respiratory and asthma phenotypes are written in blue and selected risk factors for exacerbation are shown in red.

review data suggesting that pinpointing the etiology of the acute wheezing episodes (eg, rhinovirus, respiratory syncytial virus, bacterial pathogens) could help to guide selection of treatment strategies.

Once asthma is established in children, environmental exposures such as viral infections, allergens, and pollutants are common causes of acute exacerbations. Murray et al⁶ discuss building a personalized treatment and prevention plan. Components of the evaluation include identifying modifiable and fixed risk factors for exacerbations, considering the frequency and severity of exacerbations, and response to previous therapies. This information can be used to formulate a comprehensive plan that includes mitigation of triggers and personalized prescription of asthma control medications. Teaching children and families to recognize the early signs of exacerbations can enable prompt initiation of treatment for emerging exacerbations in the outpatient setting.

A subset of children experience severe exacerbations. Identifying these children is the key to preventing asthma-related morbidity while not exposing lower-risk children to unnecessary medications and side effects, and this is the subject of a review by Navanandan and colleagues.⁷ Despite an expanding

evidence base related to potential biomarkers, a history of an exacerbation in the past year is currently the best indicator of future risk. More information is needed about the contributions of stress, genetic factors, and personal exposures to indoor and outdoor pollutants. Currently available biomarkers (eg, fractional excretion of nitric oxide, blood eosinophilia) have limited value in predicting exacerbations. New advances in measuring gene expression, proteins, and metabolites coupled with advanced analysis techniques such as machine learning could improve the prediction of exacerbation risk and, in turn, enable better-informed preventive strategies.

In the paper entitled Prevention and Treatment of Asthma Exacerbations in Adults, Menzies-Gow and colleagues⁸ highlight the interaction between viral infections (primarily rhinovirus) and allergic and type 2 inflammation. They point out a reciprocal relationship between the two. Viral infections can promote type 2 inflammation with eosinophils, which play a major role in exacerbations, as evidenced by the effectiveness of anti-interleukin 5 (IL-5) therapies in preventing exacerbations. In turn, allergic sensitization can reduce the production of antiviral, interferons suggesting a possible additional mechanism of action explaining the particular effectiveness of

anti-immunoglobulin E in preventing exacerbations when children return to school during the virus season. The authors review the effectiveness of anti-immunoglobulin E, anti-IL5, and anti-type 2 cytokine (anti-IL4–IL-13) strategies. They note that antiviral strategies have not been effective. Still, the significant reduction in exacerbations reported with sheltering in place during the coronavirus disease 2019 (COVID-19) pandemic suggests that antiviral prevention measures may deserve another look.

The reviews cited previously noted that the major progress in treating exacerbations has related to interventions targeting type 2 inflammation. In another article in this series, Murphy et al⁹ address non-type 2 asthma and strategies to reduce exacerbations in such patients. Their review stresses that non-type 2 asthma can encompass any and all of multiple immune pathways, including (1) type 1 inflammation (characterized by tumor necrosis factor alpha and interferon-gamma); (2) type 3 inflammation—related to T helper 17 and CXC chemokines; (3) innate inflammatory responses involving both phagocytes and resident cells; and (4) paucigranulocytic asthma with airway hyperresponsiveness with alterations in the epithelium, airway smooth muscle, and nerves. The authors speculate that several factors, including viral infections, airway microbiome dysbiosis, smoking, and air pollution, can play a role in non-type 2 asthma. In addition to smoking cessation and reducing pollutant exposure, they review the recent studies suggesting the effectiveness of azithromycin. Interestingly, although azithromycin has both antibacterial and anti-inflammatory effects, efficacy was greatest in patients with the highest *Haemophilus influenzae* abundance. The authors note the promising preliminary data with anti-TSLP and review possible approaches targeting IL-6, mast cells, and obesity.

In the final paper of this series, Federico and colleagues¹⁰ discuss whether exacerbation-prone asthma is a biological phenotype or a social construct. The reviews and commentaries in this issue provide ample evidence that specific biological mechanisms contribute to asthma exacerbations. Conversely, societal factors such as air pollution and climate change contribute to adverse respiratory outcomes, including increased asthma exacerbations. Furthermore, there are multiple social determinants of health, such as inadequate housing, neighborhood violence and stress, and poor access to health care, that correlate with the risk of exacerbations. These data suggest that efforts to reduce asthma exacerbations should address both social and biological determinants of respiratory health.

Collectively, these 7 scholarly reviews and commentaries summarize the state-of-the-art information about acute management of wheezing illnesses and exacerbations of asthma,

mechanisms of these episodes, and preventive strategies. The papers also discuss gaps in the evidence base and highlight areas in need of further study. Some of the main outstanding questions relate to the optimal treatment of viral wheeze in children and management of non-type 2 asthma in children and adults. Intriguingly, the COVID-19 pandemic has opened up a new window to understand factors that cause exacerbations. The near halving of exacerbations during the pandemic shutdown as reported by Saliccioli et al,¹¹ even for outcomes not affected by avoidance of care, suggest that viral and/or work-related exposures are a major factor in exacerbations in adults. New biomarkers to identify patients at risk for exacerbations are needed, and advances in biospecimen and data analytic technologies provide hope for further discovery. Finally, it is abundantly clear that social determinants of health significantly contribute to exacerbation risk and outcomes disparities. We need to redouble efforts to identify practical and effective solutions to improve environmental conditions for urban minorities and other populations with high rates of asthma morbidity.

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