Clinical Management Review

Severe Asthma in Children

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Overall Purpose/Goal: To provide excellent reviews on key aspects of allergic disease to those who research, treat, or manage allergic disease.

Target Audience: Physicians and researchers within the field of allergic disease.

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List of Design Committee Members: Sima K. Ramratnam, MD, MPH, Leonard B. Bacharier, MD, and Theresa W. Guilbert, MD, MS

Learning objectives:

1. To understand all the components involved in the evaluation of a child with severe asthma.

2. To appreciate how various cluster analyses have helped to explain clinical phenotypes and heterogeneity of severe asthma in children.

3. To identify specific phenotypic-directed therapies for severe asthma in children.

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Severe asthma in children is associated with significant morbidity and is a highly heterogeneous disorder with multiple clinical phenotypes. Cluster analyses have been performed in several groups to explain some of the heterogeneity of pediatric severe asthma, which is reviewed in this article. The evaluation of a child with severe asthma includes a detailed diagnostic

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Abbreviations used
EPA- Environmental Protection Agency
ETS- Environmental tobacco smoke
FDA- Food and Drug Administration
ICS- Inhaled corticosteroid
LABA- Long-acting beta-agonist
PEF- Peak expiratory flow
SARP- Severe Asthma Research Program

assessment and excluding other possible diagnoses and addressing poor control due to comorbidities, lack of adherence to asthma controller medications, poor technique, and other psychological and environmental factors. Children with severe asthma require significant resources including regular follow-up appointments with asthma education, written asthma action plan, and care by a multidisciplinary team. Management of pediatric severe asthma now includes emerging phenotypic-directed therapies; however, continued research is still needed to further study the long-term outcomes of pediatric severe asthma and its treatment. **(J Allergy Clin Immunol Pract 2017;5:889-98)**

Key words: *Childhood severe asthma; Difficult to treat asthma; Severe asthma phenotypes; Severe asthma treatment; Review*

Asthma currently affects 8.6% of all children younger than 18 years in the United States.[1] Most children achieve symptom control with low to medium doses of inhaled corticosteroids (ICSs); however, there is a small but significant subset of children with severe asthma who require higher intensity therapy to maintain symptom control[2,3] or who may remain uncontrolled despite such therapy. Children with severe asthma are at increased risk for adverse outcomes including medication-related side effects, life-threatening exacerbations, and impaired quality of life.[4] The economic impact of asthma in the United States is quite significant. In 2007, asthma cost the United States $56 billion,[5] with severe asthma accounting for 50% of these costs due to direct and indirect costs such as physician visits, hospitalizations, medications, and missed days from school and work.[3] Greater asthma impairment among children has been associated with greater total cost burden, with mean annual total asthma costs more than twice as high in a very poorly controlled asthma group compared with not well-controlled and well-controlled asthma groups.[6] Among children aged 5 to 17 years, asthma is one of the most common causes of missed school days and can affect a child's academic performance and participation in school- related activities.[7,8] Poorer childhood asthma control has been associated with lower caregiver quality of life.[9] In a review of 300 school-aged children (ages 6-17 years) from the National Heart, Lung and Blood Institute's Severe Asthma Research Program (SARP) between 2001 and 2011, Fitzpatrick[3] found that, similar to adults with severe asthma, children with severe asthma have a high burden of asthma symptoms, but were more likely to seek medical care for acute exacerbations. In addition, nearly 30% of children with severe asthma in SARP reported a lifetime history of intubation for near-fatal respiratory failure, suggesting that the children enrolled were at high risk for future asthma morbidity.[3]

DEFINITION OF SEVERE ASTHMA

Before 2000, there was not a clear consensus definition of severe asthma. In 2014, a task force supported by the European Respiratory Society and the American Thoracic Society updated the definition of severe asthma in pediatric patients 6 years and older.[10] This definition of severe asthma requires treatment with high-dose ICSs and either a long-acting beta-agonist or a leukotriene antagonist for the previous year OR systemic corticosteroids for at least 50% of the previous year to prevent asthma from becoming uncontrolled or asthma that remains uncontrolled despite this therapy. The definition by the European Respiratory Society/American Thoracic Society Task Force differentiates patients with asthma that is difficult to treat because of comorbid conditions, improper inhaler technique, and other environmental factors from patients with severe, refractory asthma that remains uncontrolled despite treatment with high-dose ICSs. See Table I for high-dose ICS thresholds for children aged 12 to 17 years and 6 to 11 years.

EVALUATING THE CHILD WITH SEVERE ASTHMA

The first step in the evaluation of a child with severe asthma should be a detailed diagnostic assessment to exclude alternative diagnoses.[11] Several diseases can mimic asthma (Table II) and should be considered in the differential diagnosis of asthma.

CONFIRMING THE DIAGNOSIS

The first step in the confirmation of asthma diagnosis consists of a detailed history, including the pattern of respiratory symptoms and triggers for cough, wheeze, shortness of breath, and chest tightness, previous treatment and response to treatment, and family history. The evaluation also includes spirometry using standardized ATS criteria.[12] Spirometry should be repeated following the administration of a short-acting bronchodilator, such as albuterol sulfate, to determine the presence of bronchodilator reversibility. It is essential to recognize that children with severe asthma often have normal lung function or may exhibit only mild airflow limitation in the absence of acute exacerbations,[13-15] and that the spirometric index most likely to be abnormal is the FEV_1/forced vital capacity (FVC) ratio.[16] Body plethysmography can assess lung volumes and identify hyperinflation, restrictive lung disease, and airtrapping using residual volume and total lung capacity measures. From the pediatric SARP cohort from Emory University of 77 children with severe asthma and 71 children with nonsevere asthma aged 6 to 17 years, Sorkness et al[17] demonstrated that subjects with nonsevere asthma did not have an increase in residual volume or total lung capacity, but boys with severe asthma had more hyperinflation and air trapping. Girls with severe asthma also exhibited some air trapping but to a lesser magnitude than seen with boys, and this finding was generally reversible with bronchodilation.[17] Further testing such as bronchoprovocation testing with methacholine challenge or exercise challenge may be warranted in difficult cases to assess for evidence of airway hyperresponsiveness to establish an asthma diagnosis,[10] with recognition of the effects of ongoing asthma therapy (particularly high-dose ICS) on the magnitude of airway hyperresponsiveness. Children with severe versus mild-to-moderate asthma have increased bronchial responsiveness to methacholine, higher concentrations of fractional exhaled nitric oxide, and serum IgE[15] and blood eosinophils.[18,19] High-resolution computed tomography scanning may be helpful in the differential diagnostic