Severe Asthma in Children: Lessons Learned and Future Directions

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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: Anne M. Fitzpatrick, PhD

Activity Objectives

Learning Objectives:

1. To define "severe asthma" in children.
2. To identify unique features of severe asthma in children that differ from those in children with nonsevere asthma.
3. To identify unique features of severe asthma in children that differ from those in adults with severe asthma.

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Severe asthma in children is a complicated and heterogeneous disorder that is extremely challenging to treat. Although most children with asthma derive clinical benefit from daily administration of low-to-medium-dose inhaled corticosteroid (ICS) therapy, a small subset of children with "severe" or "refractory" asthma require high doses of ICS and even systemic corticosteroids to maintain symptom control. These children with severe asthma are at increased risk for adverse outcomes including medication-related side effects and recurrent and life-threatening exacerbations that significantly impair quality of life. This review highlights findings on severe asthma in school-age children (age 6-17 years) from the National Heart, Lung and Blood Institute's Severe Asthma Research Program (SARP) over a 10-year period, between 2001 and 2011. Although SARP has advanced knowledge of the unique clinical, biological, and molecular attributes of severe asthma in children, considerable gaps remain for which additional studies are needed. © 2015 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2016;4:11-9)

Key words: *Severe asthma; Children; Lung function; Phenotype; Endotype; Inflammation*

Asthma currently affects nearly 6 million or 8.8% of all children less than 15 years of age in the United States.[1] Although most children with asthma (ie, up to 95%) derive clinical benefit from daily administration of low-to-medium-dose inhaled corticosteroid (ICS) therapy,[2] nearly half of these children experience at least 1 episode of poor asthma control despite the prescription of asthma controller therapy.[1] Moreover, there is a small subset of children with "severe" or "refractory" asthma who require high doses of ICS and even daily systemic corticosteroids to achieve or maintain symptom control.[3] Although the exact prevalence of severe asthma in children is unknown, it tends to be rare in the setting of good medication access and compliance[4] and likely affects less than 5% (or approximately 300,000) of all asthmatic children in the United States.[5]

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Abbreviations used
ATS- American Thoracic Society
FEV_1- Forced expiratory volume in one second
FVC- Forced vital capacity
ICS- Inhaled corticosteroid
IgE- Immunoglobulin E
RV- Residual volume
SARP- Severe Asthma Research Program
Th2- T-helper type 2
TLC- Total lung capacity

Severe asthma in children is a complicated and heterogeneous disorder that is extremely challenging to treat. As a result, the economic impact of severe asthma in children is quite significant. Total medical expenditures for childhood asthma are estimated at more than $10 billion annually,[6] with severe asthma accounting for up to 50% of these costs due to multiple physician and hospital visits, medications, and missed days from school and work.[7,8] Furthermore, whereas the incremental direct costs of asthma have been estimated at more than $3250 (in 2009 dollars) per person per year,[9] these costs are more than doubled for children with severe asthma and are highest in those children with the poorest asthma control.[8] Moreover, children with severe asthma are at increased risk for adverse outcomes including medication-related side effects and recurrent and life-threatening exacerbations that significantly impair quality of life.[10]

This review highlights findings on severe asthma in school-age children (age 6-17 years) from the National Heart, Lung and Blood Institute's Severe Asthma Research Program (SARP) over a 10-year period, between 2001 and 2011. Although SARP has advanced knowledge of the unique attributes of severe asthma in children, considerable gaps remain for which additional studies are needed. Future directions for SARP and personalized medicine for children with severe asthma are also discussed.

STRUCTURE OF SARP

SARP is a multicenter program focused on the clinical and biological attributes of severe asthma in adults and children that has been ongoing since 2001. At the beginning of the program, awards were made to 8 clinical centers. Each center had unique scientific aims, which could only be addressed through sharing of data and biological samples. For example, recruitment of children was primarily conducted at 3 sites. However, each of the SARP clinical sites utilized a standardized definition of severe asthma and uniform procedures for asthma characterization that were detailed in a manual of procedures. This collaborative approach to the study of severe asthma allowed for rigorous yet consistent characterization of participants with standardized medical history questionnaires, pulmonary function testing, methacholine challenge, exhaled nitric oxide determination, and biomarker collection. Detailed methods for the characterization procedures have been published previously.[11,12]

In the first two cycles of SARP (2001-2011), approximately 1600 participants with asthma across the severity spectrum were enrolled, including nearly 300 children aged 6 to 17 years. Although the majority of initial SARP participants were characterized at a single point in time, a small subset of adults and children across the network did complete abbreviated characterization visits over a period of 1 to 3 years. The excellent retention and interesting longitudinal features of these participants resulted in renewal of the SARP program in 2012. Whereas the first 2 cycles of SARP were primarily focused on asthma phenotypes (ie, observable clinical characteristics), SARP was renewed with the purpose of elucidating asthma endotypes (iie, biological mechanisms within phenotypes).[13] Awards were made to 7 clinical centers with the mandate that each center would enroll 25% children and that all SARP participants would complete up to 3 years of longitudinal study. The major efforts of the current SARP program are therefore to understand the disease at the molecular and cellular levels and to determine how severe asthma changes or progresses over time. The inclusion of children will also permit greater understanding of the natural history of severe asthma in the context of growth and development. The ultimate goal of these efforts is to improve mechanistic insight into severe asthma to promote the development of better pharmacological treatments for selected phenotypic subpopulations.

DEFINITION OF "SEVERE" ASTHMA IN CHILDREN

Before 2000, there were no consensus definitions of "severe" asthma and the use of the term varied widely across studies. The early SARP program therefore adopted a definition of severe asthma that was proposed in 2000 by an American Thoracic Society (ATS) Workshop on Refractory Asthma.[14] According to this definition, the diagnosis of severe asthma required (1) treatment with continuous high-dose ICS or continuous systemic corticosteroids to maintain asthma control, and (2) at least 2 minor criteria, including the use of additional asthma controller medications (ie, long-acting β-agonists), daily use of short-acting bronchodilators for symptoms, persistent airflow obstruction evidenced by a forced expiratory volume in 1 second (FEV_1) < 80% predicted at baseline, 1 or more urgent care visits for asthma in the previous year, 3 or more corticosteroid "bursts" in the previous year, a history of prompt deterioration in asthma symptoms with a reduction in the dose of ICS or systemic corticosteroid, or a near-fatal asthma event requiring intubation anytime in the past.[14]

Although the proposed definition of severe asthma advanced the concept that asthma severity is associated with intrinsic corticosteroid insensitivity, it did not easily distinguish between patients with severe refractory asthma and those in whom the asthma is difficult to treat because of comorbid conditions, poor medication delivery, or other factors.[15] Therefore, the third cycle of SARP (2012-2017) adopted the revised definition of severe asthma proposed by a joint European Respiratory Society/ATS Task Force in 2011.[16] This definition states that severe asthma requires treatment with either (1) high-dose ICS and a second controller medication for the previous year or (2) systemic corticosteroid for at least 50% of the previous year, to either prevent it from becoming uncontrolled or which remains uncontrolled despite this therapy attempt.[16] This revised definition emphasizes that asthma severity and control are related but not necessarily interchangeable concepts and further distinguishes between difficult-to-treat asthma and severe asthma that is refractory to intensive corticosteroid treatment. Thresholds of high-dose ICS proposed by these reports were reviewed by the SARP Steering Committee according to the relative potency of each drug as expressed by fluticasone equivalents. High-dose ICS thresholds for children 12 to 17 years of age were the same as