

Severe Asthma: An Expanding and Mounting Clinical Challenge

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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: Matthew C. Bell, MD, and William W. Busse, MD

Activity Objectives:

1. To recognize the clinical patterns of severe asthma.
2. To appreciate the rationale behind the development of asthma phenotypes and how this approach may lead to more specific and effective treatment.
3. To develop a treatment approach for severe asthma, which are based upon phenotypic features of disease.

Recognition of Commercial Support: This CME activity has not received external commercial support.

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Although all patients with asthma have variable airflow obstruction, airway inflammation, and bronchial hyperresponsiveness, some have disease that is severe in many aspects: persistent airflow obstruction, ongoing symptoms, increased frequency of exacerbations, and, most importantly, a diminished response to medications. A number of definitions have emerged to characterize the clinical features of severe

asthma, but a central feature of this phenotype is the need for high doses of medications, especially corticosteroids, in attempts to achieve disease control. The prevalence of severe asthma is also undergoing reevaluation from the usual estimate of 10% to larger numbers on the basis of medication needs and the lack of disease control achieved. At present, the underlying mechanisms of severe asthma are not established but likely reflect a heterogeneous pattern, rather than a single unifying process. Guideline-directed treatment for severe asthma has limits with usual approaches centered on high doses of inhaled corticosteroids, long-acting β -agonists, and trials with omalizumab, the monoclonal antibody to IgE. With the development of approaches to recognize asthma phenotypes with distinct pathogenesis and hence unique therapeutic targets, it is hoped that a personalized strategy in treatment directed toward disease-specific features will improve outcomes for this high-risk, severely affected population of patients. © 2013 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol: In Practice 2013;1:110-21)

Key words: Asthma; corticosteroids; bronchodilators; immunomodulators; anti-IgE

Asthma affects >18 million adults and 7 million children in the United States, making it one of the most common chronic diseases.¹ Moreover, the prevalence of asthma has continued to increase significantly, even over the past 10 years, with major

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Abbreviations used

- ABPA- Allergic bronchopulmonary aspergillosis*
- ATS- American Thoracic Society*
- EMTU- Epithelial mesangial trophic unit*
- ENFUMOSA- European Network For Understanding Mechanisms Of Severe Asthma*
- F_ENO- Fraction of exhaled nitric oxide*
- GINA- Global Initiative for Asthma*
- ICS- Inhaled corticosteroid*
- LABA- Long-acting β_2 -agonist*
- NHLBI- National Heart, Lung, and Blood Institute*
- SABA- Short-acting β_2 -agonist*
- SARP- Severe Asthma Research Program*
- WHO- World Health Organization*

expansions found in inner city populations. Fortunately, most patients with asthma can achieve good control of their disease with the use of anti-inflammatory medications or various combinations of inhaled corticosteroids (ICSs) and bronchodilators. However, a significant proportion of patients with asthma remains symptomatic despite treatment with high-dose ICSs, inhaled long-acting β_2 -agonists (LABAs), and, even in some cases, systemic corticosteroids. This group has been defined as having severe asthma, refractory asthma, or treatment-resistant asthma. Estimates vary as to what proportion of the asthma population falls into this most severely affected group. The Severe Asthma Research Program (SARP) from the National Heart, Lung, and Blood Institute (NHLBI) suggests that roughly 15% of asthmatic patients are in this group.² Information from other studies, however, including the Gaining Optimal Asthma Control study, suggests that this percentage may be an underestimate.³ Regardless of its overall prevalence in asthma, severe asthma remains a major challenge for the clinician because these patients require the greatest degree of health care and experience the most morbidity. Furthermore, patients with severe asthma likely represent a heterogeneous population of patients, complicating an already complex situation.

HOW MAY SEVERE ASTHMA BE DEFINED?

Asthma is defined by the World Health Organization (WHO) as a chronic disease that is characterized by recurrent attacks of breathlessness and wheezing, which varies in severity and frequency from person to person.⁴ It is this variance in severity and frequency that led the WHO to propose a more universal definition of severe asthma and one that is based on domains in the level of control, current treatment level given or required, responsiveness to treatment, and the associated risks of exacerbations.⁵ On the basis of this expanded perspective, a WHO panel proposed the inclusion of 3 groups of patients who would meet criteria for the diagnosis of severe asthma (Table I). One patient group would have underlying features of severe asthma but are untreated. This group would include patients for whom the diagnosis of asthma was not made, as well as those who, by choice or circumstance, have not appropriately accessed care and treatment. The undiagnosed patient with the potential for severe asthma or severe asthma exacerbations is important at a world health level because it helps to identify high-risk persons and, if resources are limited, to direct what treatment efforts are available to this group. The second group would include patients who are being treated for asthma but remain symptomatic because

TABLE I. Definitions of severe asthma by the WHO

1. Untreated severe asthma.
2. Difficult-to-treat severe asthma.
3. Treatment-resistant severe asthma. This group includes the following:
 - Asthma for which control is not achieved despite the highest level of recommended treatment: refractory asthma and corticosteroid-resistant asthma.
 - Asthma for which control can be maintained only with the highest level of recommended treatment.

Reprinted from Bousquet et al.⁵

TABLE II. Definition: ATS Workshop, requires diagnosis and drug treatment of comorbidities

- Major criteria (must have 1):
- Oral corticosteroids for >50% of past year
 - Continuous high-dose inhaled corticosteroids
 - ICS 1000 μ g fluticasone/BDP
- Two of 7 minor criteria:
- Concurrent use of at least 1 other controller medication
 - Daily symptoms requiring a SABA
 - FEV₁ <80% predicted
 - One or more urgent care visits in past year
 - ≥ 3 oral corticosteroid bursts in past year
 - Deterioration with decrease in corticosteroid dose of 25%
 - History of near-fatal event

Adapted from American Thoracic Society.⁷

of inadequate treatment plans by health care providers, poor adherence to medications, incorrect use of delivery devices, and/or adverse environmental conditions. A final group of severe asthma is patients whose disease either requires high-dose ICSs to achieve disease control or is not fully responsive, or resistant, to appropriate levels of treatments and, as a consequence, do not achieve asthma control.⁵ It is this final group that is proving to be the most challenging, even for the asthma specialist; given their underlying severity, it is no surprise that this group accounts for >50% of health care utilization related to this disease.⁶ A principal feature of the expanding definition of severe asthma is the required need and use of high doses of medications, primarily ICSs and/or systemic corticosteroids, to achieve control.

Other groups have approached the definition of severe asthma from a slightly different angle. The American Thoracic Society (ATS) defined refractory or severe asthma on the basis of the identification of 2 major and 7 minor criteria, of which at least 1 major and 2 minor requirements must be met for this diagnosis (Table II).⁷ This definition of severe asthma may include patients with good disease control and largely focuses on the need for high doses of corticosteroids. These criteria have become the working definition for the NHLBI SARP.²

In 1999, The European Respiratory Society task force defined what they termed “difficult/therapy-resistant asthma” as patients with poorly controlled asthma who require continued use of short-acting β_2 -agonists (SABAs) despite guideline-based therapy with reasonable doses of ICSs and regular follow-up with a respiratory specialist for 6 months.⁸

The Global Initiative for Asthma (GINA) had initially, like the NAEPP guidelines, classified asthma into 4 groups on the basis of markers of severity (intermittent plus mild, moderate, and severe persistent) in untreated subjects. Later revisions of the GINA guidelines have added to these levels of severity markers

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