Severe Asthma Phenotypes — How Should They Guide Evaluation and Treatment?

Anne M. Fitzpatrick, PhD[a], and Wendy C. Moore, MD[b] *Atlanta, Ga; and Winston-Salem, NC*

Although patients with "severe" asthma tend to be characterized by ongoing symptoms and airway inflammation despite treatment with high doses of inhaled and systemic corticosteroids, there is increasing recognition of marked phenotypic heterogeneity within affected patients. Although "precision medicine" approaches for patients with severe asthma are needed, there are many hurdles that must be overcome in daily practice. The National Heart, Lung and Blood Institute's Severe Asthma Research Program (SARP) has been at the forefront of phenotype discovery in severe asthma for the past decade. SARP, along with other international groups, has described clinical severe asthma phenotypes in both adults and children that can be evaluated in the clinical setting. Although these clinical phenotypes provide a good "starting point" for addressing disease heterogeneity in severe asthma in everyday practice, more efforts are needed to understand how these phenotypes relate to underlying disease mechanisms and pharmacological treatment responses. This review highlights the clinical asthma phenotypes identified to date, their associations with underlying endotypes and potential biomarkers, and remaining knowledge gaps that must be addressed before precision medicine can become a reality for patients with severe asthma. © 2017 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2017;5:901-8)

Key words: *Severe asthma phenotypes; SARP; Endotype; Precision medicine; Biomarker; Cluster analysis*

Although the majority of patients with asthma in the United States experience symptom improvement with the initiation of inhaled corticosteroid (ICS) therapy, asthma control remains suboptimal and nearly 50% of these patients experience at least one asthma exacerbation each year.[1] Although the reasons underlying poor asthma control are multifactorial and include medication access and compliance,[2] there is a relatively small subset of adults and children with "severe" or "refractory" asthma who have ongoing symptoms and airway inflammation despite daily receipt of high doses of ICS and even systemic corticosteroids.[3] These patients with severe asthma are at increased risk for medication-related side effects[4] and are also are more likely than patients with milder forms of asthma to experience recurrent and potentially life-threatening exacerbations that significantly impair quality of life.[5] Consequently, severe asthma may account for up to 50% of all asthma-related costs due to frequent health care encounters as well as numerous prescription medications and missed days from school and work.[6,7]

Although national asthma treatment guidelines have proven useful in standardizing care approaches and improving outcomes,[8,9] there is increasing recognition of phenotypic heterogeneity in patients with asthma that is particularly marked in those with severe disease. Given recent mandates for more personalized and more efficient medicine, "precision medicine" for patients with severe asthma is needed, particularly because the existing evidence base for severe asthma care is quite limited.[3] However, there are many hurdles that must be overcome. The first hurdle is to accurately and easily characterize a given individual's severe asthma and assign a "phenotype" for the application of personalized therapeutic approaches (ie, precision medicine). In this view, a "phenotype" is defined as observable characteristics that *may or may not be* associated with underlying disease mechanisms. An example of this is a patient with ongoing symptoms and severely obstructed patterns of lung function, which may be due to a variety of inflammatory factors including alterations in glucocorticoid receptor signaling and function, increased airway matrix deposition, or alternatively, progressive viral insults with impaired innate immune responses. The second hurdle is to ultimately refine these phenotyping efforts to measure or make inferences about basic pathophysiologic and biologic mechanisms (ie, "endotypes") that underlie the disease and ultimately guide therapy. The goal is to derive clinical phenotypes that clearly translate to biological endotypes, without excessive imaging and laboratory testing, for the purpose of time-efficient and resource-efficient precision pharmacological treatment. As more biological therapies become available, the final hurdle is to select the most appropriate first-line treatment.

The National Heart, Lung and Blood Institute's Severe Asthma Research Program (SARP) has been at the forefront of phenotype discovery in severe asthma for the past decade and has described clinical severe asthma phenotypes in both adults and children that can be evaluated in the clinical setting. These clinical phenotypes provide a good "starting point" for addressing disease heterogeneity in severe asthma in everyday practice. However, more efforts are needed to understand how these phenotypes relate to underlying disease treatment responses and underlying disease mechanisms. This review highlights the clinical asthma phenotypes identified in SARP, their associations

[a]Department of Pediatrics, Emory University, Atlanta, Ga
[b]Section on Pulmonary, Critical Care, Allergy and Immunologic Diseases, Department of Internal Medicine, Wake Forest School of Medicine, Winston-Salem, NC
This study received support from the National Heart, Lung, and Blood Institute (NHLBI) of the National Institutes of Health (NIH) grant number U10HL109164.
Conflicts of interest: The authors declare that they have no relevant conflicts of interest.
Received for publication April 26, 2017; revised May 15, 2017; accepted for publication May 17, 2017.
Corresponding author: Wendy C. Moore, MD, Section on Pulmonary, Critical Care, Allergy and Immunologic Diseases, Department of Internal Medicine, Wake Forest School of Medicine, Medical Center Blvd., Winston Salem, NC 27157. E-mail: wmoore@wakehealth.edu.
2213-2198

http://dx.doi.org/10.1016/j.jaip.2017.05.015

Abbreviations used
DREAM- Dose-Ranging Efficacy And safety with Mepolizumab
FeNO- Fractional excretion of nitric oxide
FEV1- Forced expiratory volume in 1 second
ICS- Inhaled corticosteroid
PrecISE- Precision Interventions for Severe and/or Exacerbation Prone Asthma
SARP- Severe Asthma Research Program

with underlying endotypes, and remaining knowledge gaps that must be addressed before precision medicine can be a reality for patients with severe asthma.

CLINICAL ASTHMA PHENOTYPES IN SARP

SARP is a multicenter network in the United States focused on the clinical, biological, and genetic attributes of severe versus nonsevere asthma in adults and children. Since the initiation of SARP in 2001, each participating clinical site utilized uniform procedures that permitted rigorous yet consistent characterization of participants, including standardized medical history questionnaires, pulmonary function testing, methacholine challenge, and biomarker collection.[10,11] Because consensus definitions of "severe" asthma were lacking before 2000, the early SARP program adopted the definition of severe asthma proposed by an American Thoracic Society Workshop,[12] which required: (1) treatment with continuous high-dose ICS or continuous systemic corticosteroids and (2) at least 2 minor criteria that demonstrated poor asthma control or life-threatening disease. This definition advanced the concept of severe asthma as a biological disease entity associated with corticosteroid insensitivity, and a number of resulting publications highlighted the unique clinical and intrinsic attributes of this group as compared with patients with milder disease.[13,14]

Despite global differences between "severe" and "nonsevere" asthma in SARP, significant heterogeneity was present in both groups, prompting further exploration of phenotypes irrespective of asthma severity definitions. Using unsupervised cluster analyses, subgroups of patients with asthma emerged.[15,16] In SARP adults, 5 phenotypic "clusters" emerged that were distinguished primarily by lung function and the age of asthma onset.[16] The most "severe" asthma subjects were assigned to clusters 3, 4, and 5 that were associated with frequent use of oral corticosteroids for asthma exacerbations, hospitalizations for severe near-fatal asthma, and increased medication requirements (Table I).[16] A similar cluster analysis in SARP children identified 4 phenotypic clusters that differed primarily according to asthma duration, the number of asthma controller medications, and lung function.[15] The most "severe" asthmatic children were assigned to clusters 3 and 4, which had the highest prevalence of comorbidity and symptom burden similar to the adults (Table I).[15] Pre-bronchodilator forced expiratory volume in 1 second (FEV1) % predicted and age of asthma onset were important in differentiating severe asthma clinical phenotypes in both the adult and pediatric analyses, emphasizing that onset of asthma before puberty is characteristic of the better understood "classic" allergic asthma phenotypes (Figure 1).

Pediatric severe asthma clinical phenotypes

Overall, children with severe asthma are characterized by ongoing symptoms and frequent exacerbations that impair daily

TABLE I. Adult and pediatric "severe" asthma clusters identified by the Severe Asthma Research Program (SARP)

	Early-onset allergic asthma			Later-onset adult asthma	
	Pediatric Severe asthma cluster 3	Pediatric Severe asthma cluster 4	Adult Severe asthma cluster 4	Adult Severe asthma cluster 5	Adult Severe asthma cluster 3
Cluster description	Comorbid, difficult-to-treat asthma	Refractory asthma with airflow obstruction	"Classic" early onset severe allergic asthma	Asthma with chronic airflow obstruction (COPD)	Obese asthma with high impairment, but normal lung function
Asthma onset	Infancy	Toddler to preschool years	Preschool or early school-age years, before puberty	Teenage years or adulthood, after puberty	Adulthood
Aeroallergen sensitization	Highly prevalent with multiple sensitization	Highly prevalent with multiple sensitization	Highly prevalent with multiple sensitization	Less prevalent	Less prevalent
Lung function	Reversible airflow obstruction	Partially reversible airflow obstruction	Partially reversible airflow obstruction	Severe, less reversible airflow obstruction	Borderline normal airflow obstruction
Asthma medications	Multiple controller medications, high-dose ICS, daily OCS	Multiple controller medications, high-dose ICS	Multiple controller medications, high-dose ICS, daily OCS	Multiple controller medications, high-dose ICS, daily OCS	Multiple controller medications, high-dose ICS
Health care utilization, past year	Multiple OCS bursts, acute visits, hospitalizations	Multiple OCS bursts, acute visits, hospitalizations	Multiple OCS bursts, acute visits	Multiple OCS bursts, acute visits, hospitalizations	Multiple OCS bursts, acute visits
Comorbid features	Sinus disease, gastroesophageal reflux, obesity	Less frequent comorbidity	Less frequent comorbidity	Pneumonia, hypertension, obesity	Sinus disease, hypertension, obesity

COPD, Chronic obstructive pulmonary disease; *ICS*, inhaled corticosteroid; *OCS*, chronic oral corticosteroid.
Adapted from references 15 (Pediatric Cluster Analysis) and 16 (Adult Cluster Analysis).