



Published in final edited form as:

J Allergy Clin Immunol Pract. 2017 ; 5(4): 901–908. doi:10.1016/j.jaip.2017.05.015.

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

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Abstract

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. While “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, have described clinical severe asthma phenotypes in both adults and children that can be evaluated in the clinical setting. While 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.

Keywords

Severe asthma phenotypes; SARP; endotype; precision medicine; biomarker; cluster analysis

Introduction

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

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exacerbation each year.¹ While 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 effects⁴ and are also 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 healthcare 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 since 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 (i.e., 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 (i.e., “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 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 multi-center network in the United States focused on the clinical, biological, and genetic attributes of severe versus non-severe 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 prior to 2000, the early SARP program adopted the definition of severe asthma proposed by an American Thoracic Society (ATS) Workshop,¹² which required: 1) treatment with continuous high-dose ICS or continuous systemic corticosteroids and 2) at least two minor criteria which 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 to patients with milder disease.^{13, 14}

Despite global differences between “severe” and “non-severe” 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 1).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 1).¹⁵ Pre-bronchodilator 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 prior to 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 functioning and quality of life.^{10, 17} Although not all children with severe asthma are atopic, the majority of children with severe asthma (>80%) have sensitization to aeroallergens, in contrast to adults.¹⁸ Airflow limitation and air trapping with incomplete reversal after bronchodilator administration are other prominent features¹⁹ that may worsen during adolescence²⁰ and increase the risk of chronic obstructive pulmonary disease in later adulthood.^{21, 22}

Yet despite these commonalities, the phenotypes identified in the SARP pediatric cluster analysis argue for differing risk factors for asthma severity (Table 1). Children in Cluster 3 (20% of children studied) had an early age of asthma onset, atopic features, the highest

prevalence of comorbidity, increased airway hyperresponsiveness to methacholine and airflow limitation. By contrast, children in Cluster 4 (18% of children studied) had the most advanced disease, with an early age of symptom onset accompanied by atopic features, less comorbidity, partially reversible and more advanced airflow obstruction and the greatest burden of symptoms and associated medication use.¹⁵ Although Clusters 3 and 4 did not completely conform to definitions of asthma severity proposed by current treatment guidelines, replication in a separate pediatric asthma population demonstrated that they were associated with differential and limited response to asthma therapies.²³ Whereas children in Cluster 4 had best response with fluticasone/salmeterol, children in cluster 3 had the least efficacy to available guideline-based asthma treatment.²³ However, that analysis was limited by relatively few children with highly symptomatic asthma and a focus on available asthma treatments, as opposed to novel biologics.

Adult Severe Asthma Clinical Phenotypes

The three severe asthma clusters in the adult SARP analysis represent the spectrum of severe early onset allergic asthma (Cluster 4), adolescent/early adult onset asthma with less reversible/chronic airflow obstruction (Cluster 5) and late onset, less allergic asthma, mostly obese individuals with high disease impairment but normal lung function (Cluster 3).¹⁶ Multiple other cluster analyses in different asthma cohorts have identified adult clinical phenotypes remarkably similar to those described in the SARP cluster analyses, suggesting that the phenotypes are fairly generalizable across different centers and internationally (Table 2).²⁴⁻³⁰ For example, Haldar et al. identified 4 clusters of severe, refractory asthma distinguished by age of onset, atopy, and obesity.²⁴ Schatz et al. also noted similar clusters in an adolescent and adult severe or difficult-to-treat asthma population that were not only distinguished by age of onset and atopic features, but also by race and aspirin sensitivity.²⁷

The four SARP phenotypes identified in the cluster analysis have also been replicated in “real life” clinics^{31, 32} and other cohorts^{33, 34} using a 3-variable algorithm that incorporates pre- and post-bronchodilator % predicted FEV1 and age of asthma onset to assign individual patients to these clusters (Figure 2). Reassuringly, from a practical sense, the described phenotypes resemble patients we actually see everyday in the clinic^{31, 32} and several studies have suggested that nearly half of patients demonstrate cluster stability over time, although the severe asthma cluster phenotypes (not surprisingly) appear to be slightly less stable temporally.^{28, 29, 34} As such, the challenge is how best to use these cross sectional clinical phenotypes to guide pharmacotherapy and effect clinical outcomes such as exacerbation rates and progressive lung function decline.

Pathobiology and Clinical Phenotypes

Ideally, distinct pathobiologic mechanisms (endotypes) would underpin clinical phenotypes and thus allow therapy to be targeted to the specific underlying biology, but this has not been so easily proven due to biologic heterogeneity. Sputum analysis in SARP adults had previously shown that subjects with concurrent elevations in sputum eosinophils and neutrophils had the most severe asthma,³⁵ but this pattern does not differentiate severe asthma subjects from clinical clusters 4 and 5 (Figure 3).¹⁸ A subsequent SARP cluster

analyses that aimed to reconcile the clinical phenotypes with biology by incorporating blood eosinophils and sputum granulocytes into a new cluster analysis also showed heterogeneity of inflammatory cell patterns within clusters with no clear distinction between the severe clusters.³⁶ A third SARP cluster analysis that incorporated bronchoalveolar lavage inflammatory variables identified clusters that clinically overlap with the previously published results, but showed increased exhaled nitric oxide and airway lavage eosinophil counts in patients with severe early onset atopic asthma supporting a strong role for Type-2 inflammatory mechanisms in this group.³⁷ This analysis confirmed an older age of onset and less atopic asthma phenotype, but again found that airway eosinophils and neutrophils did not clearly distinguish this group.³⁷

Similar analyses that have included biomarkers with clinical characteristics in other cohorts have likewise found heterogeneity within cluster groups.²⁹ A recent study involving sputum proteomics and transcriptomics noted differences in expression profiles between cluster groups, but elevations in sputum eosinophils were not isolated to one cluster but rather 3 of the 4 clusters identified.³⁰ Furthermore, the clusters in that report did not differ with regard to sputum neutrophil counts, exhaled nitric oxide or serum IgE levels.³⁰ These studies suggest that while clinical phenotypes do inform asthma heterogeneity and can be easily applied using algorithms, they are not yet refined endotypes and thus, not precise enough to guide targeted immunomodulator therapy without a “biologic” marker to reveal underlying biologic heterogeneity.

Biomarkers associated with Clinical Phenotypes

All of the current biomarkers available in clinical practice are focused on Type-2 “allergic” inflammation [blood eosinophils, exhaled nitric oxide (FeNO), sputum eosinophils]. Sputum eosinophils have been the “gold standard” Type-2 inflammatory biomarker,³⁸ but performing sputum analysis for inflammatory cellular profiles in clinic is challenging. Unfortunately, while blood eosinophils, serum total IgE and exhaled nitric oxide are easily obtained biomarkers, the correlation between these “noninvasive” measures and sputum eosinophils is suboptimal, making them poor surrogate measures of airway eosinophilia.^{39, 40} While several studies have used management approaches guided by these biomarkers and shown improved asthma outcomes,^{41, 42} these older studies contain very few patients with severe asthma making applicability of these approaches to severe asthma unclear.

In fact, these Type-2 inflammatory biomarkers in blood, sputum or exhaled gases are associated with subtypes of all clinical asthma phenotypes in SARP, not specifically with the severe asthma phenotypes (Figures 3, 4).^{15, 16, 18, 36} In the adult SARP severe asthma clusters (Figure 3), 20% of each cluster showed a bland inflammatory cell profile with few eosinophils and neutrophils, while 20-30% had a mixed granulocytic pattern with elevations of both eosinophils and neutrophils.^{16, 18, 36} Similarly, in the pediatric severe asthma clusters (Figure 4), 20-30% of subjects did not have elevated blood eosinophils or exhaled nitric oxide (FeNO) while 30-40% showed increased blood eosinophils and FeNO in the severe asthma clusters.^{15, 18} Again, neither the biomarkers nor the pattern of the biomarkers was specific for the severe asthma phenotypes. This variability in biomarkers within the SARP severe asthma clinical phenotypes is due to pathobiologic heterogeneity that underlies the

clinical phenotype. We instead propose that biomarkers be used to identify patients within a cluster who are most likely to be responders to a given immunomodulator as a disease modifier, not to define a specific clinical phenotype.⁴³

Using Clinical Phenotypes (+ biomarkers) in Clinical Trials

Most industry sponsored biologic clinical trials have effectively used the above approach by selecting study subjects that resemble the severe asthma clinical phenotypes of SARP (high intensity controller medication regimens, frequent exacerbations and low lung function), but then require an elevated biomarker (in blood, exhaled gas or sputum) that should identify patients most likely to be responders to a specific immunomodulator within those clinical phenotypes. The biologics in recently published clinical trials target Type-2 inflammatory pathways and restrict participation to subjects with elevated Type-2 biomarkers (blood or sputum eosinophils or FeNO). Post-hoc responder analyses to “group” biomarkers to better understand which patients have the greatest benefit from a biologic immunomodulator have led to an understanding that concurrent elevations in more than one Type-2 inflammatory biomarker may further identify “high responder” patients.⁴⁴

Perhaps more relevant to this review, however, is a post-hoc cluster analysis of the DREAM study (Dose-Ranging Efficacy And safety with Mepolizumab study) that showed that a combination of a biomarker (blood eosinophils), airway physiology (magnitude of bronchodilator reversibility) and a clinical characteristic (Body Mass Index) could accurately identify four patient clusters with different magnitudes of rate reductions in asthma exacerbations when treated with mepolizumab.⁴⁵ The cluster with a largest reduction in asthma exacerbations (67% reduction) was described as mostly obese women with reported age of onset in late adolescence or adulthood and less atopy by serum testing with poor baseline lung function. That clinical description is very similar indeed to SARP Cluster 5 (Table 1) in which 50% of patients had elevated sputum eosinophil counts (Figure 3). While it could be argued that the reduction in exacerbations in the multidimensional DREAM study group was not much greater than that observed when using sole biomarker directed anti-IL5 therapy without clinical input, these results provide some vision for how severe asthma management might be refined in the future.

A clinical cluster phenotype with limited biomarkers might identify the “best responder” for a pharmacologic therapy in the clinic while we await refinement of true endotypes needed for precision medicine. Figure 5 presents a possible approach for selection of a patient for a biologic therapy, using a combined approach of phenotyping by clinical characteristics together with a biomarker. Ultimately, this approach requires testing and prospective evaluation. The National Heart, Lung and Blood Institute's soon to be funded multicenter PrecISE network (Precision Interventions for Severe and/or Exacerbation Prone Asthma) will use patient phenotypes, endotypes and biomarkers to conduct adaptive clinical trials with sequential therapies to determine the most effective pathway to precision medicine in severe asthma.

Conclusions

Ideally, severe asthma phenotypes should be easy to identify in the clinic and be indicative of pathobiologic mechanisms (endotypes) that can guide precision medicine. Although the clinical severe asthma phenotypes identified by SARP and others provide a good “starting point” for addressing disease heterogeneity in severe asthma in everyday practice, the association between clinical phenotype and endotype today is imprecise. Some biomarkers can be measured in clinic as potential surrogate measures of underlying pathobiologic mechanisms, but they are too simplistic and nonspecific for a given clinical phenotype to guide therapy in isolation of clinical characteristics. Current clinical trials of immunomodulators are essentially utilizing SARP-like clinical severe asthma cluster phenotypes with selected biomarkers to identify “responder” phenotypes, not just a biomarker alone. The continued replication of similar severe asthma phenotypes around the world and ongoing –omic approaches to pinpoint the pathobiologic mechanisms that underlie these phenotypes is “real-time” refining the endotypes that are needed before precision medicine and targeted pharmacological treatment of severe asthma can become a reality in the clinic. The goal of the upcoming PreCISE network is to guide precision medicine for severe asthma patients in the future. Clinical asthma phenotypes such as those described by the Severe Asthma Research Program, however can be a good “starting” tool for clinicians in practice today.

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Abbreviations used

ATS American Thoracic Society

FeNO	Fractional Excretion of nitric oxide
ICS	Inhaled corticosteroid
OCS	Oral corticosteroid
SARP	Severe Asthma Research Program

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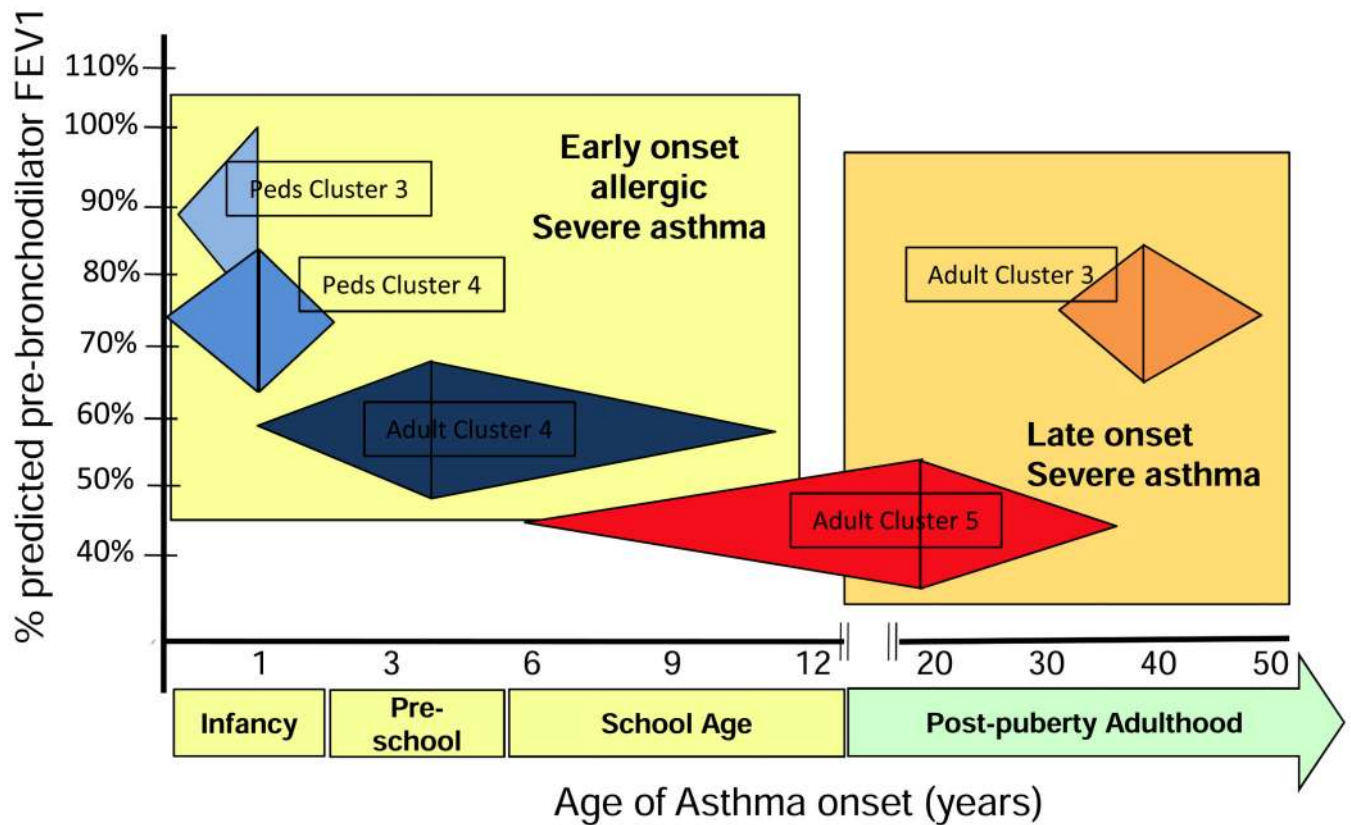


Figure 1.

A schematic of the adult and pediatric **severe** asthma phenotypes identified in the SARP cluster analyses.^{15,16} Heterogeneity within each phenotype is indicated by the shape of the diamond; the “width” represents heterogeneity in the age of asthma onset (median line, IQR), the “height” symbolizes heterogeneity of lung function within each group (IQR). Note that the majority of severe asthma subjects had abnormal baseline lung function when bronchodilators were appropriately withheld prior to spirometry, reinforcing the importance of extended lung function testing in the clinic.

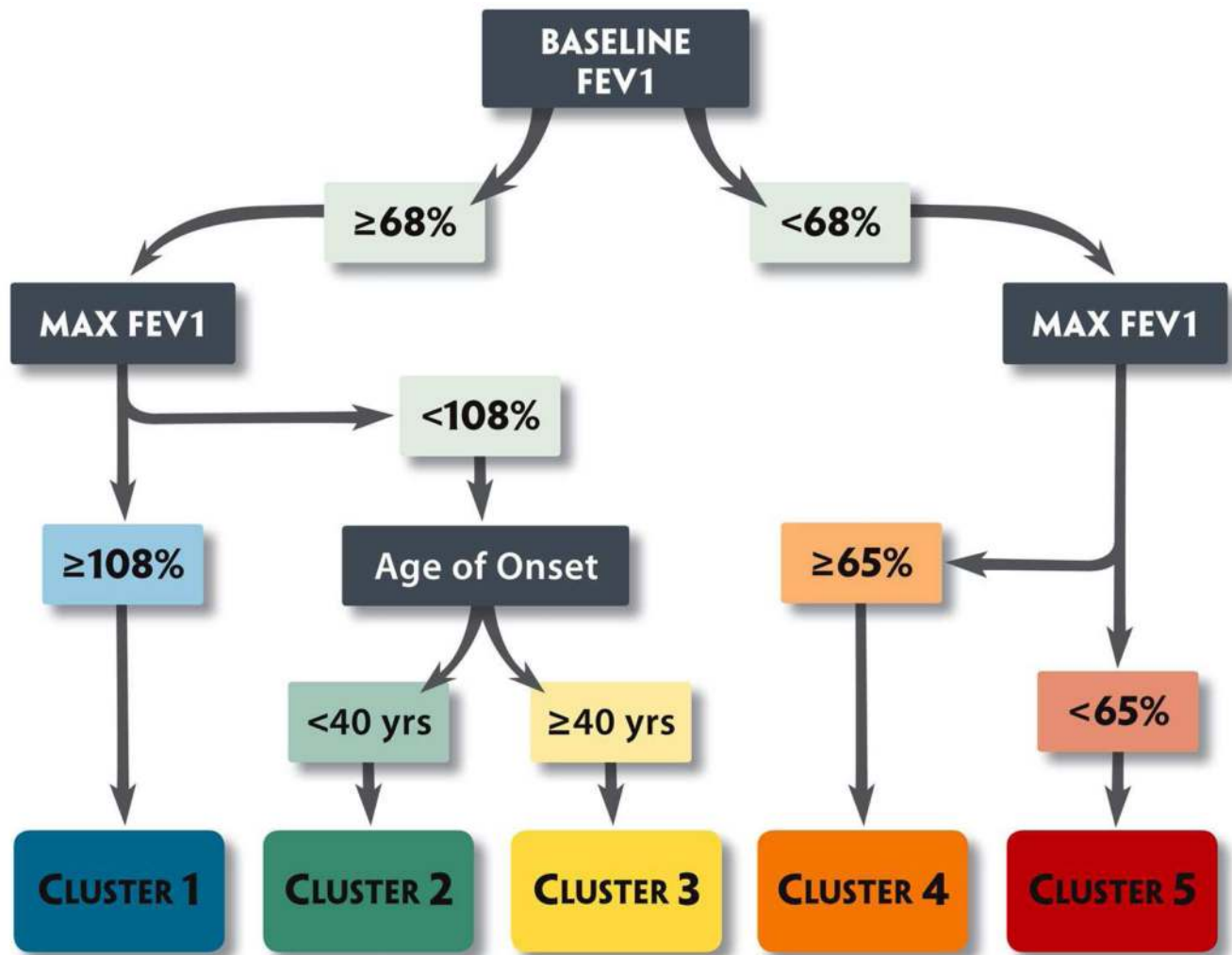


Figure 2. SARP algorithm for cluster assignment in subjects > 12 years of age.¹⁶ Using three variables (1) Baseline FEV1 (with a bronchodilator withhold), (2) Maximal “Max” FEV1 (after 6-8 puffs of albuterol) and (3) age of onset of asthma, subjects can be assigned to the five clinical asthma phenotypes. Clusters 3, 4 and 5 are the **severe** asthma clusters; *Color Key: Yellow, late onset nonatopic asthma; Orange, severe atopic asthma; Red, severe asthma with fixed airflow.*

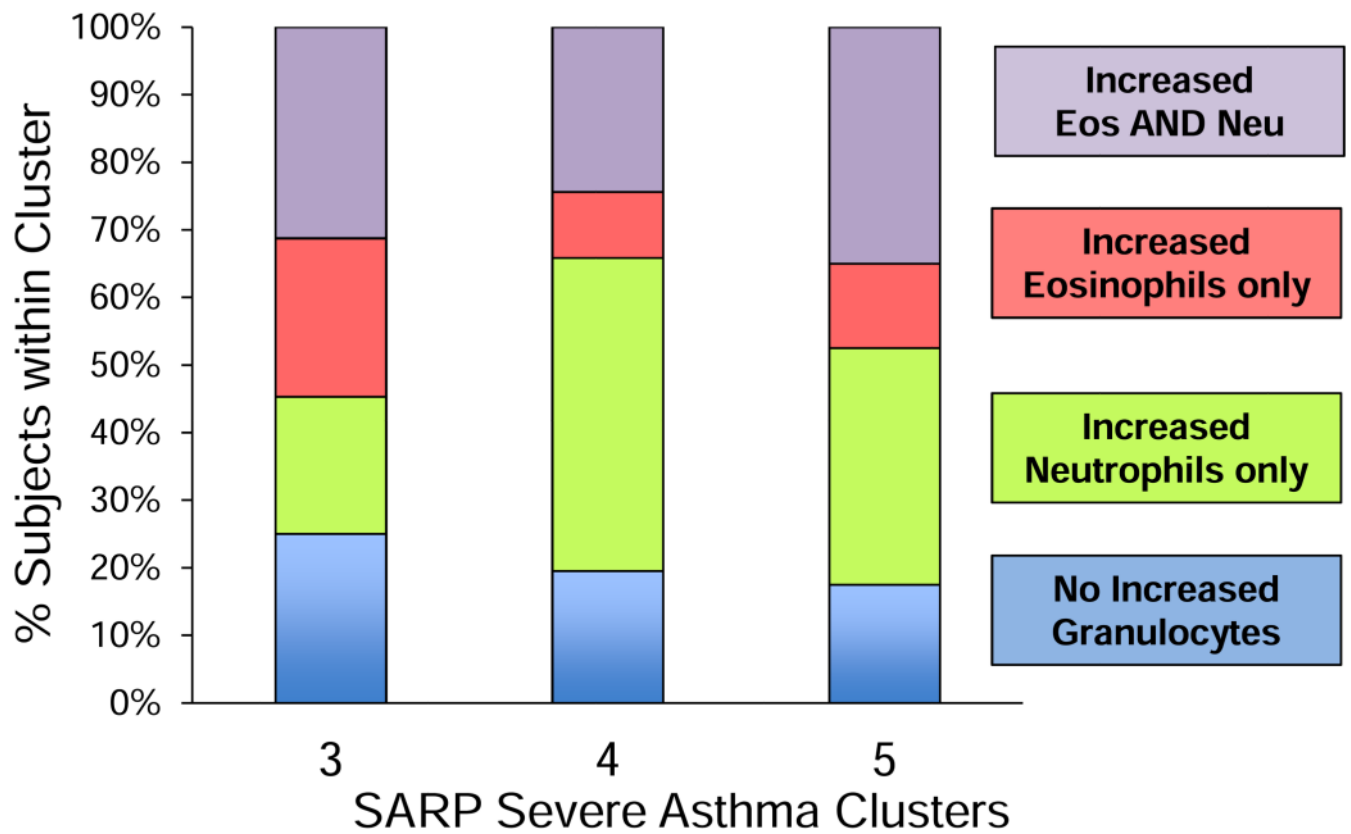


Figure 3.

Sputum inflammatory profiles in Adult SARP **severe** asthma cluster phenotypes show heterogeneity within each cluster with no clear predominant pattern. Inflammatory profiles were determined for individual subjects based on % eosinophils ($\geq 2\%$) and % neutrophils $\geq 40\%$ in induced sputum as previously described.³⁶ *Color Key: Blue*, paucigranulocytic; *Green*, neutrophil predominant; *Red*, eosinophil predominant; *Purple*, mixed granulocytic.

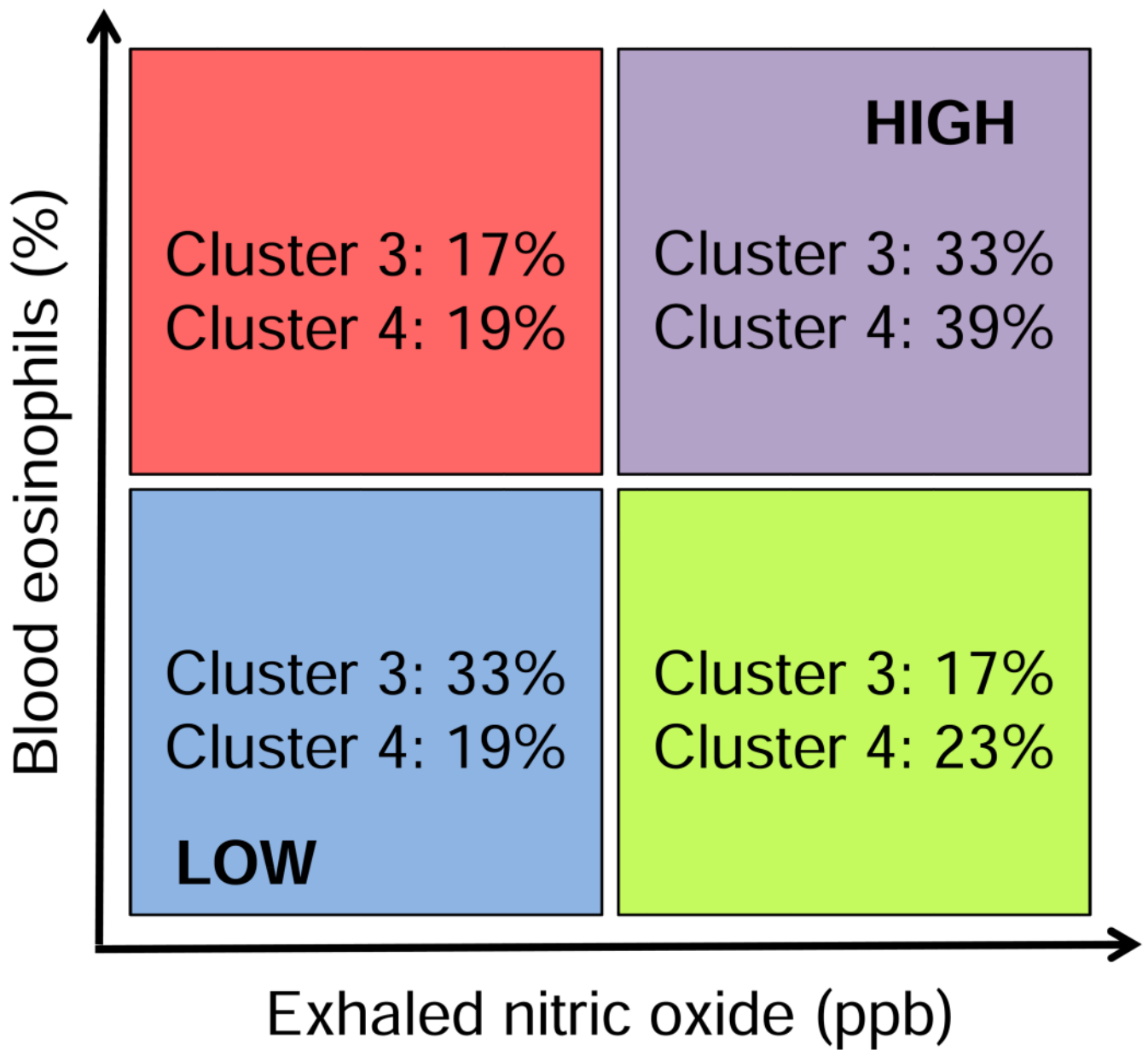


Figure 4. Association between exhaled nitric oxide values and blood eosinophils in the SARP pediatric **severe** asthma clinical clusters.¹⁵ Percentages reflect the percentage of children in the cluster. Although there was modest agreement between the biomarkers, heterogeneity in biomarker presentation was present in both clusters.

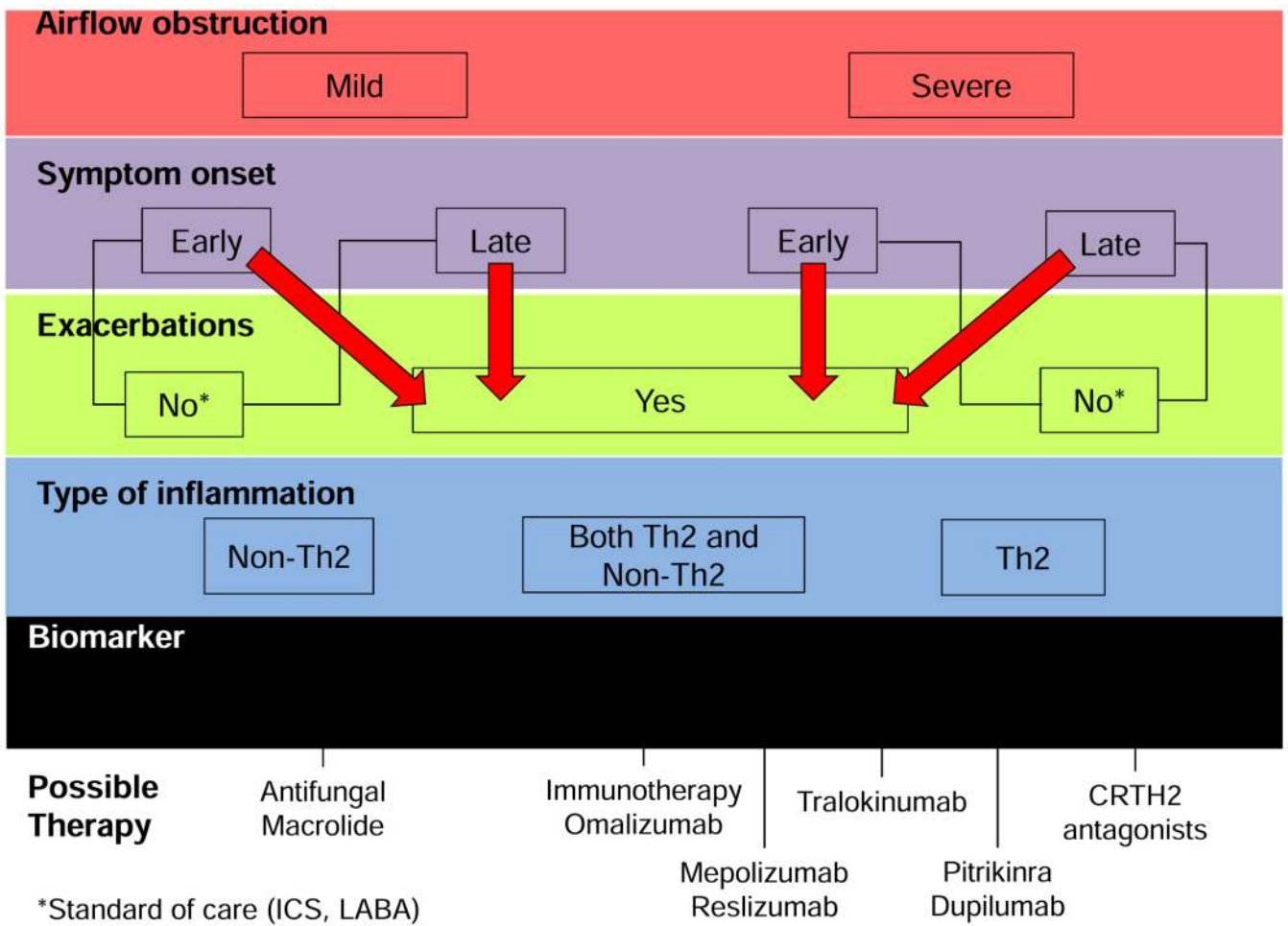


Figure 5. Potential approach for selection of biological therapy in severe asthma patients, utilizing phenotyping by clinical characteristics and biomarker assessment. IgE = immunoglobulin E, IL = interleukin, CRTH2 = chemokine receptor homologous molecule expressed on Th2 lymphocyte, PDE4 = phosphodiesterase 4

Table 1
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	Co-morbid, 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
Healthcare 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
Co-morbid features	Sinus disease, gastroesophageal reflux, obesity	Less frequent co-morbidity	Less frequent co-morbidity	Pneumonia, hypertension, obesity	Sinus disease, hypertension, obesity

Adapted from Reference 15 (Pediatric Cluster Analysis) and, 16 (Adult Cluster Analysis).

Abbreviations: ICS= inhaled corticosteroid, OCS = chronic oral corticosteroid

Table 2
“Severe” Asthma Clusters Identified by Other Investigators outside of the Severe Asthma Research Program (SARP)

Reference	Population	Age group	N	Number of clusters identified	Number of “severe” clusters	Description of “severe” clusters	
Halдар et al. (2008) ²⁴	Secondary care, refractory asthma	Adults	187	4	4	1	Early onset, atopic
						2	Late onset, obese, non-eosinophilic
						3	Early onset, atopic with high symptom expression
						4	Late onset, few symptoms but active eosinophilic inflammation
Kim et al. (2013) ²⁵	Secondary care, asthma	Adults	2,567	4	1	Adult onset obstructive asthma	
Amelink et al. (2013) ²⁶	Secondary care, adult-onset asthma	Adults	200	3	2	1	Severe eosinophilic inflammation
						2	Frequent symptoms, high healthcare utilization and low sputum eosinophils
Schatz et al. (2014) ²⁷	Severe or difficult-to-treat asthma	Children	518	5	5	1	White males, no tobacco exposure
						2	Females, no tobacco exposure
						3	Predominantly non-atopic with airflow obstruction
						4	Passive smoke exposure with airflow obstruction and elevated IgE
						5	Non-white race with airflow obstruction and elevated IgE
Schatz et al. (2014) ²⁷	Severe or difficult-to-treat asthma	Adolescents and adults	3,612	5	5	1	White female, adult-onset asthma with low IgE
						2	Early onset, atopic with elevated IgE
						3	White male with airflow obstruction
						4	Non-white asthma with elevated IgE
						5	Adult onset with aspirin sensitivity
Newby et al. (2014) ²⁸	Severe, refractory asthma	Adults	349	5	5	1	Early onset, atopic
						2	Late onset, obese with frequent exacerbations
						3	Least severe asthma, non-atopic with normal lung function
						4	Late onset, eosinophilic asthma

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Reference	Population	Age group	N	Number of clusters identified	Number of "severe" clusters	Description of "severe" clusters
						5 Severe but reversible airflow obstruction
Zaithra et al. (2016) ²⁹	Secondary care, difficult-to-treat asthma	Adults	125	4	3	1 Late onset with airflow obstruction 2 Obese females 3 Early onset with airflow obstruction
Lefaudeux et al. (2017) ³⁰	Mild-to-severe asthma	Adults	418	4	4	1 Well controlled 2 Late onset with airflow obstruction, obesity and smoking 3 Airflow obstruction but no smoking 4 Obese females with no smoking or airflow obstruction