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Severe Asthma in Childhood: Recent Advances in Phenotyping and Pathogenesis

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Abstract

Purpose of the review—Children with severe asthma have a high degree of respiratory morbidity despite treatment with high doses of inhaled corticosteroids and are therefore very difficult to treat. This review will discuss phenotypic and pathogenic aspects of severe asthma in childhood, as well as remaining knowledge gaps.

Recent findings—As a group, children with severe asthma have a number of distinct phenotypic features compared to children with mild-to-moderate asthma. Clinically, children with severe asthma are differentiated by greater allergic sensitization, increased exhaled nitric oxide, and significant airflow limitation and air trapping that worsens as a function of age. These findings are accompanied by structural airway changes and increased and dysregulated airway inflammation and oxidant stress which may explain the differential nature of corticosteroid responsiveness in this population. Because children with severe asthma themselves are a heterogeneous group, current efforts are focused on improved definition and sub-phenotyping of the disorder. While the clinical relevance of phenotyping approaches in severe asthma is not yet clear, they may provide important insight into the mechanisms underlying the disorder.

Summary—Improved classification of severe asthma through unified definitions, careful phenotypic analyses, and mechanism-focused endotyping approaches may ultimately advance knowledge and personalized treatment.

Keywords

Severe asthma; difficult asthma; children; phenotype; endotype

Introduction

While the implementation of asthma clinical practice guidelines has led to important reductions in overall asthma morbidity and mortality over the past two decades [1], there

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Conflicts of interest

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remains a relatively small yet significant group of patients with severe asthma who suffer from ongoing respiratory symptoms despite appropriate treatment with inhaled corticosteroids **(ICS)** [2, 3]. Although there is some symptom heterogeneity within this subpopulation, affected patients share the risk for adverse outcomes, including life-threatening exacerbations and ultimately, asthma-related death [4, 5]. Patients with severe asthma therefore account for up to 50% of all asthma-related costs given the disproportionate medication requirements and healthcare utilization associated with the disorder [6, 7].

Interest in the underlying biological mechanisms of severe asthma and specialized diagnostic and management strategies for the disorder has increased substantially in recent years. This has resulted in the formation of several international severe asthma research initiatives, from which a number of pivotal publications have ensued (Table 1) [8–12]. These efforts have ultimately resulted in a rapid increase in the number of indexed (PubMed) publications on severe asthma over the past two decades (Figure 1). However, while the body of available literature on severe asthma has grown, there remain few publications on children. This knowledge gap has important public health consequences given the high underlying prevalence of asthma in children and the significant burden of asthma disease in this age group [13–15]. This review will therefore discuss recent findings related to severe asthma in children that shed new light on the burden and peculiarities of the disorder. Because clinical management approaches to the child with severe asthma have been the subject of several recent reviews [16–19], this review will focus instead on phenotypic and pathogenic aspects of severe asthma in childhood, as well as remaining knowledge gaps.

What is severe asthma? The struggle for a common definition

Undoubtedly, one of the greatest challenges in the field is the definition of severe asthma as a unique disease entity. Some controversy stems from poor understanding of asthma itself, which is clearly a heterogeneous syndrome associated with a constellation of clinical features [20]. Indeed, in a recent review of publications involving relatively large ($n > 100$) cohorts of children with asthma diagnosed between 6 and 18 years, 122 publications yielded 60 different definitions of asthma that had a large impact on prevalence estimates and asthma predictive probabilities [21]. Nonetheless, several concerted efforts have been made to standardize the definition of severe asthma in order to advance the field.

An important advance came from the recognition that asthma severity and control are related but not interchangeable concepts. Whereas asthma control refers to the extent to which asthma symptoms or associated features are alleviated by treatment, asthma severity refers to the difficulty in controlling asthma with treatment (i.e., the activity of the underlying disease state) [22, 23]. These distinctions were incorporated into a uniform definition of severe asthma by the World Health Organization **(WHO)** during a workshop in 2009. According to the WHO definition, severe asthma is defined as “uncontrolled asthma which can result in risk of frequent severe exacerbations (or death) and/or adverse reactions to medications and/or chronic morbidity (including impaired lung function or reduced lung growth in children)” [24]. Severe asthma therefore includes three groups: 1) untreated severe asthma due to failure of diagnosis, lack of access to medical care, or non-adherence to therapy, 2) difficult-to-treat severe asthma from co-morbid conditions or adverse environmental circumstances, and 3) treatment-resistant severe asthma, which encompasses asthma for which control is not achieved despite intensive therapy and asthma for which control can only be maintained with intensive therapy (Figure 2) [24, 25]. This definition has a number of global advantages. In low- or middle-income countries where asthma is highly prevalent, asthma may be undiagnosed due to limited training and accessibility of

medical professionals or may be undertreated due to limited availability of asthma controller medications. This definition will capture these individuals and will therefore permit more meaningful estimates of the prevalence of severe asthma worldwide. This will ultimately promote health care planning and policy for public health purposes and will facilitate epidemiologic comparisons across different populations. The prevalence of severe asthma is also expected to increase as a result.

Because the WHO definition of severe asthma was drafted for global application, the American Thoracic Society **(ATS)** and the European Respiratory Society **(ERS)** convened a similar workshop in 2011 to develop a definition of severe asthma for countries in which there is reasonable access to asthma medications (publication expected in 2012). This workshop built upon the ATS definition of severe asthma proposed 10 years earlier [26] and distinguishes only between patients with treatment-resistant severe asthma and patients in whom the asthma is difficult to treat. According to the new ATS-ERS definition, once the asthma diagnosis is confirmed and differentiated from difficult-to-treat asthma, severe asthma is defined as the requirement for treatment with high-dose ICS plus a second controller medication. This definition applies to two groups: 1) patients who require intensive treatment to maintain asthma control, and 2) others who fail to achieve control with this treatment regimen (personal communication, Sally Wenzel, ATS-ERS workshop chair). This approach is in keeping with that proposed by the WHO and attempts to identify individuals at high risk from the disease and for medication-related side effects. While research on the application and utility of these emerging definitions of severe asthma is clearly needed, these attempts to improve classification of the disorder are expected to lead to refinement in clinical and mechanistic explorations that are essential for the development of novel therapeutics.

Phenotyping severe asthma: what is it and why does it matter?

For the purpose of this review, the term “phenotype” refers to observable characteristics, often with no direct relationship to disease process, such as airway physiology, triggers, and inflammatory parameters [27]. However, there is no consensus definition of what a “phenotype” is and therefore the term is used in different ways by different groups. For instance, geneticists frequently refer to a “phenotype” as any observable trait of an organism. In the clinical realm, a “phenotype” may be viewed along the spectrum of a “useful but entirely artificial construct” to “an underlying disease entity that, like biological species, awaits discovery” [28]. These controversies have formed the subject of two recent reviews on childhood asthma [28, 29]. While the clinical benefit of phenotyping severe asthma is not yet clear, it may be the key to major advances in the field, which is presently plagued by a lack of clear genetic markers for disease onset and severity [30, 31] and highly heterogeneous disease presentation in terms of symptoms, exacerbations, and pharmacologic responses [32–34]. However, until convincing data are available, the decision whether or not to phenotype severe asthma ultimately rests with the theoretical underpinnings of the investigative team.

Severe asthma as a unique phenotype: clinical studies

Severe asthma presents in childhood as a heterogeneous disorder determined by unique socio-cultural, environmental and biological factors, including suboptimal adherence to prescribed asthma therapies [35–37]. Although early investigations in childhood severe asthma identified a highly atopic group of children with persistent airflow obstruction, airway eosinophilia and reticular basement membrane thickening despite corticosteroid treatment [38–40], the presence of unique severe asthma “phenotype” in children has been questioned since asthma *per se* in children tends to be more episodic with a high

exacerbation frequency despite relatively normal lung function [41]. Therefore, over the past decade, the Epidemiology and Natural History of Asthma: Outcomes and Treatment Regimens **(TENOR)** study group and the National Heart, Lung and Blood Institute's Severe Asthma Research Program **(SARP)** led concerted efforts to identify the unique features of children with severe versus mild-to-moderate asthma. Both groups found that children with severe asthma had a high burden of asthma symptoms and increased frequency of asthma exacerbations despite high-dose inhaled and oral corticosteroid treatment [2, 42, 43]. Furthermore, children with severe asthma were also more likely to experience a subsequent asthma exacerbation requiring systemic corticosteroids, an emergency visit, or hospitalization when followed prospectively after enrollment [2, 4], a finding that was strongest in children with baseline airflow limitation [2].

Other interesting findings from SARP and TENOR have centered on comparisons of children and adults with severe asthma (Table II). Although children and adults with severe asthma share a similar burden of symptoms, emergency department visits and hospitalizations are more frequent in children [2, 42] and are greatest in children with daily symptoms [4]. Furthermore, unlike adults with severe asthma wherein markers of atopy are relatively less prevalent [3], children with severe asthma are highly atopic with increased peripheral blood eosinophilia, aeroallergen sensitivity, and elevated serum IgE concentrations [2, 42, 44]. Whereas exhaled nitric oxide concentrations are not consistently elevated in adults with severe asthma [3], by contrast, children with severe asthma have sustained increases in exhaled nitric oxide [2] in keeping with the reactive, at-risk, adult severe asthma phenotype [45]. Airflow limitation and air trapping are also present in children with severe asthma [2, 42], albeit to a lesser degree than what is commonly seen in adults [46]. Interestingly, whereas pre-pubertal girls with severe asthma had no residual air trapping after maximal bronchodilation, boys with severe asthma had incomplete reversal of air trapping with persistent elevations in the ratio of residual volume to total lung capacity **(RV/TLC)** [47]. This finding suggests that the adult physiological patterns of severe asthma are already present in school-age boys but may not yet be fully developed in girls. Thus the years surrounding puberty may represent a critical window where the phenotype of severe asthma in children intensifies and worsens.

Given the limited number of longitudinal studies in children with severe asthma, the natural history of severe asthma is poorly understood. Thus an important unanswered question is the stability of the severe asthma phenotype in children over time. In the TENOR study, 38% of children with poorly controlled severe asthma had improvement in their asthma symptoms after 2 years of follow-up [4]. However, 62% of children remained persistently very poorly controlled and were six times more likely to have severe exacerbations [4]. A similar subset of pre-pubertal children with severe asthma enrolled in SARP also demonstrated declines in the forced expiratory volume in one second **(FEV_1)**, forced vital capacity **(FVC)**, and post-bronchodilator FEV_1 percent predicted values during the early adolescent years [48]. Children with the most significant declines were those who had ongoing daily symptoms and a greater magnitude of allergic sensitization [48]. These findings are similar to those of the Childhood Asthma Management Research Program [49, 50] and the Dunedin Multidisciplinary Health and Development Study [51, 52] which demonstrated increased and persistent airflow limitation in children with persistent versus remitting asthma that was associated with greater aeroallergen sensitization and increased airway hyperresponsiveness during early childhood. The Melbourne Asthma study further noted early and irreversible loss of lung function by age 14 in children with severe asthma [53, 54], suggesting that the changes in lung function in severe asthma occur early during the course of the disease. Whether these observations represent a reduction in lung growth or progression of structural airway remodeling is not clear [55].

Severe asthma as a unique phenotype: translational studies

Considerably fewer studies have focused on the mechanistic underpinnings of severe asthma in children, in part due to research limitations in children. One example involves bronchoscopy, which typically can only be done for clinical purposes in children and therefore is associated with significant challenges stemming from selection bias. Yet despite these challenges, critical findings have been made. Importantly, structural airway alterations are apparent in children with severe asthma, like adults, and include greater airway smooth muscle mass [56], increased reticular basement membrane **(RBM)** thickening [39, 57] and epithelial damage and angiogenesis [58, 59]. While airway mucosal and tissue eosinophilia are often accompanying findings [38, 60], these structural airway changes may also be present in the absence of a prominent eosinophilic infiltrate [59] and may instead develop as a function of age [61, 62] and asthma duration [60, 63, 64]. Interestingly, airway eosinophilia and RBM thickening are not readily identifiable in 12–24 month infants with wheezing disorders [61] but are present in some preschool children after 24 months of age [60]. Although other preschool children have more neutrophilic-predominant patterns of inflammation with increased IL-8 expression [65–67], these findings suggest that there is a classical and perhaps severe form of asthma that is identifiable very early in life and is distinct from other wheezing disorders. However, contrary to what is seen in fibrotic conditions, the ratio of fibril to matrix in the RBM of children and adults with asthma is normal and is not associated with increased interstitial collagen [68]. These findings challenge the notion that asthma is a fibrotic disorder and therefore additional studies are needed to understand how these airway structural changes evolve across the early lifespan.

The airway structural changes that accompany severe asthma do not occur in isolation but rather are accompanied by a number of other inflammatory features. In contrast to children with mild-to-moderate asthma, children with severe asthma have altered regulation of the antioxidant, glutathione, in the epithelial lining fluid that corresponds to the magnitude of airflow obstruction [69]. These disturbances of airway glutathione are further associated with increased lipid peroxidation and DNA nucleoside oxidation byproducts [69, 70], increased nitric oxide oxidation products [71], increased catabolism of endogenous S-nitrosothiols [72], and impaired airway macrophage function, including altered innate immune defense [70, 73]. These findings may account for the increased severity of respiratory infections as well as the relative corticosteroid resistance of this population. Despite best attempts at corticosteroid therapy, children with severe asthma have decreased histone deacetylase activity in airway macrophages [70] as well as sustained expression of pro-inflammatory cytokines and chemokines resulting in a unique molecular phenotype that is neither Th1- nor Th2- predominant [74]. These observations are likely mediated by post-translational modification of key proteins and transcription factors such as nuclear factor (erythroid-derived 2)-like 2 [75] and suggest that that interventions to restore airway redox status may be warranted in children with severe asthma.

Sub-phenotypes within severe asthma

These prior efforts suggest that there is indeed a unique group of children with severe asthma who, as a group, differ considerably from children with mild-to-moderate asthma with regard to a number of clinical, pathophysiologic and molecular features. However, within the group of children severe asthma, clearly there are a number of sub-phenotypes given the observed heterogeneity in the disorder. These questions have resulted in the application of non-biased cluster analyses to diverse samples of highly characterized patients to determine “clusters” or groups of patients with shared phenotypic characteristics. This approach was recently applied to large samples of adults with asthma and revealed unique subgroups with differences in lung function, age of asthma onset, inflammatory features and

clinical treatment responses [20, 76]. The SARP investigators also applied the same approach to a highly characterized sample of children and identified four unique cluster phenotypes of asthma defined by different degrees of lung function, asthma duration, and asthma controller medication use (Figure 3) [77]. Children with ATS-defined severe asthma [26] were present in all four clusters, thus confirming its marked heterogeneity even in childhood [77]. Furthermore, no cluster corresponded to the asthma severity classifications proposed in asthma treatment guidelines [78, 79]. Additional studies are now needed to understand the clinical relevance of these clusters, including their stability over time and their predictive validity with regard to a number of important disease outcomes.

Conclusion - From phenotype to endotype: Next steps

Although considerable advances have been made in the understanding of severe asthma in children over the past decade, the next decade will inevitably be focused on personalized medicine for the disorder [80]. In contrast to the “one-size-fits-all” approach to asthma treatment provided by current asthma treatment guidelines [78, 79], the next decade will likely see major revisions to these guidelines based on emerging phenotypic findings [81], including the highly differential nature of the corticosteroid response in children with severe asthma [34]. A number of asthma clinical trials have already included analyses of pre-selected phenotypic predictors [82, 83] and differential responses within treatment groups [84]. However, the biology linking phenotypic characteristics to clinical responses remains unknown. While the quest for biomarkers of severe asthma in children has yielded interesting developments with regard to urinary leukotriene E_4 [85, 86] and vitamin D [87] analyses, more attention on the “endotype” of asthma (i.e., the distinct disease entity present in a phenotype that is defined by a specific biological mechanism) is clearly needed [27]. Whereas current treatment guidelines assume that: 1) asthma is a unified disorder with a common inflammatory mechanism, 2) there is concordance between inflammation and symptoms, and 3) the nature of the inflammation is corticosteroid responsive [78, 79], developments in asthma endotyping are likely to challenge this paradigm in the next decade. This would represent a huge advance for both practitioners and patients alike and may be an important next step toward mitigating the morbidity and mortality that accompanies severe asthma in children, which remains a heterogeneous condition that is extremely difficult to treat.

Acknowledgments

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Key Points

- Children with severe asthma are a heterogeneous group that includes children with severe, therapy-resistant asthma and children in whom the asthma is difficult-to-treat.
- Although there is no consensus definition of “phenotype,” it typically refers to observable characteristics that may or may not be related to disease, such as airway physiology, triggers, and inflammatory parameters.
- While the phenotype of severe asthma in children as a group is unique from that of children with mild-to-moderate asthma, there are also sub-phenotypes within severe asthma.
- The clinical relevance of asthma phenotypes ultimately rests with endotyping, which focuses on the biological mechanisms that underlie a distinct disease entity present within a phenotype.

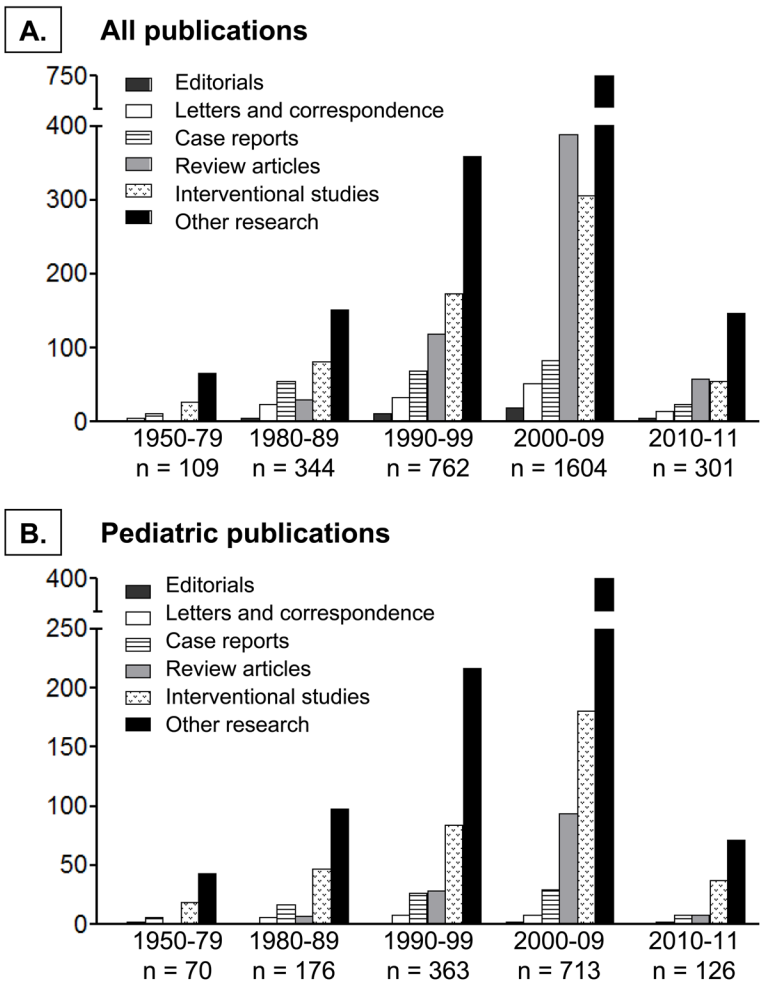

Figure 1.

Publications on (A) severe asthma and (B) severe asthma in children from the 1950's to present. Publications were limited to those indexed on PubMed and written in English. Searches were made for "severe asthma," "difficult asthma," and "difficult-to-treat asthma," excluding "acute asthma" and animal studies.

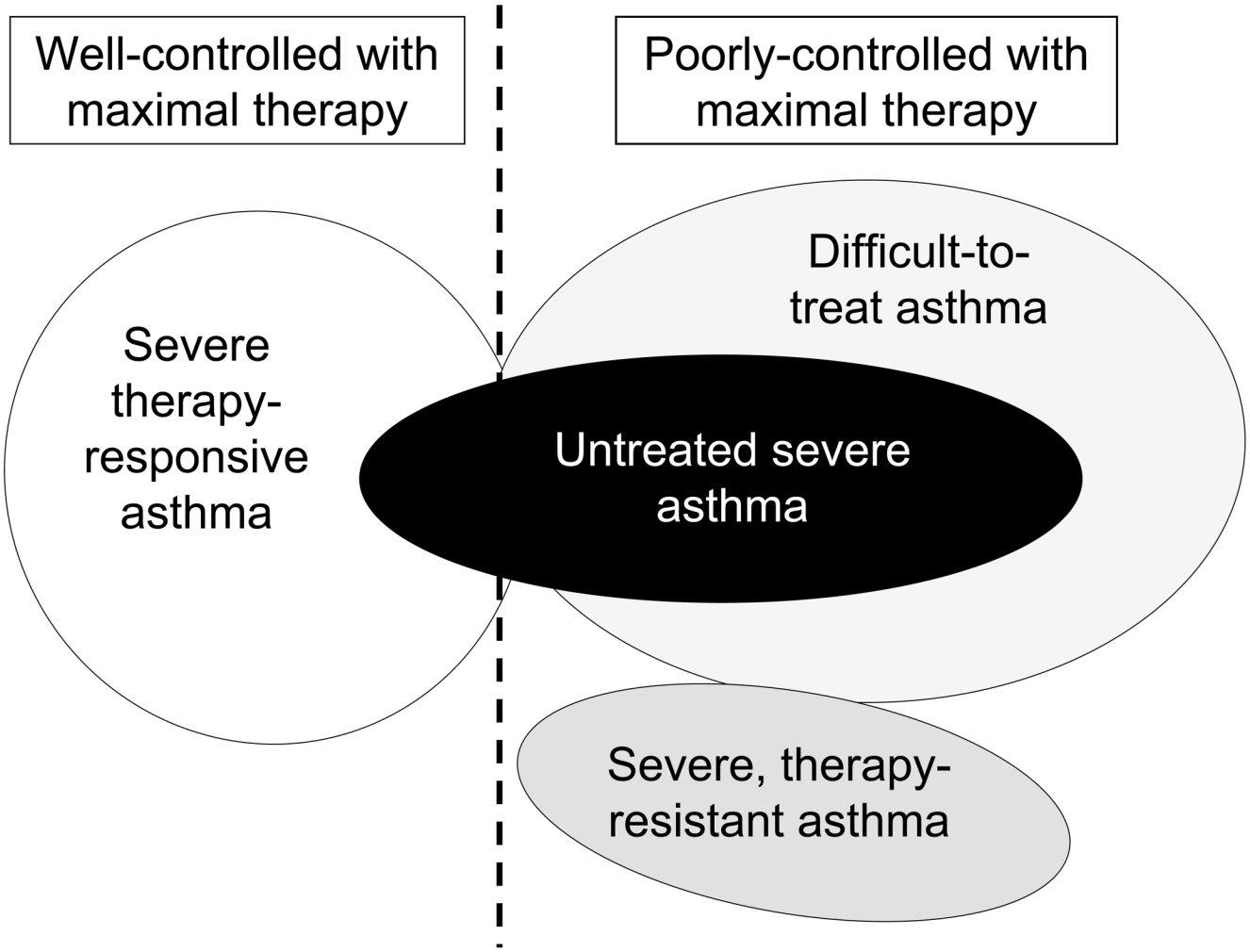

Figure 2.
The WHO definition of severe asthma.

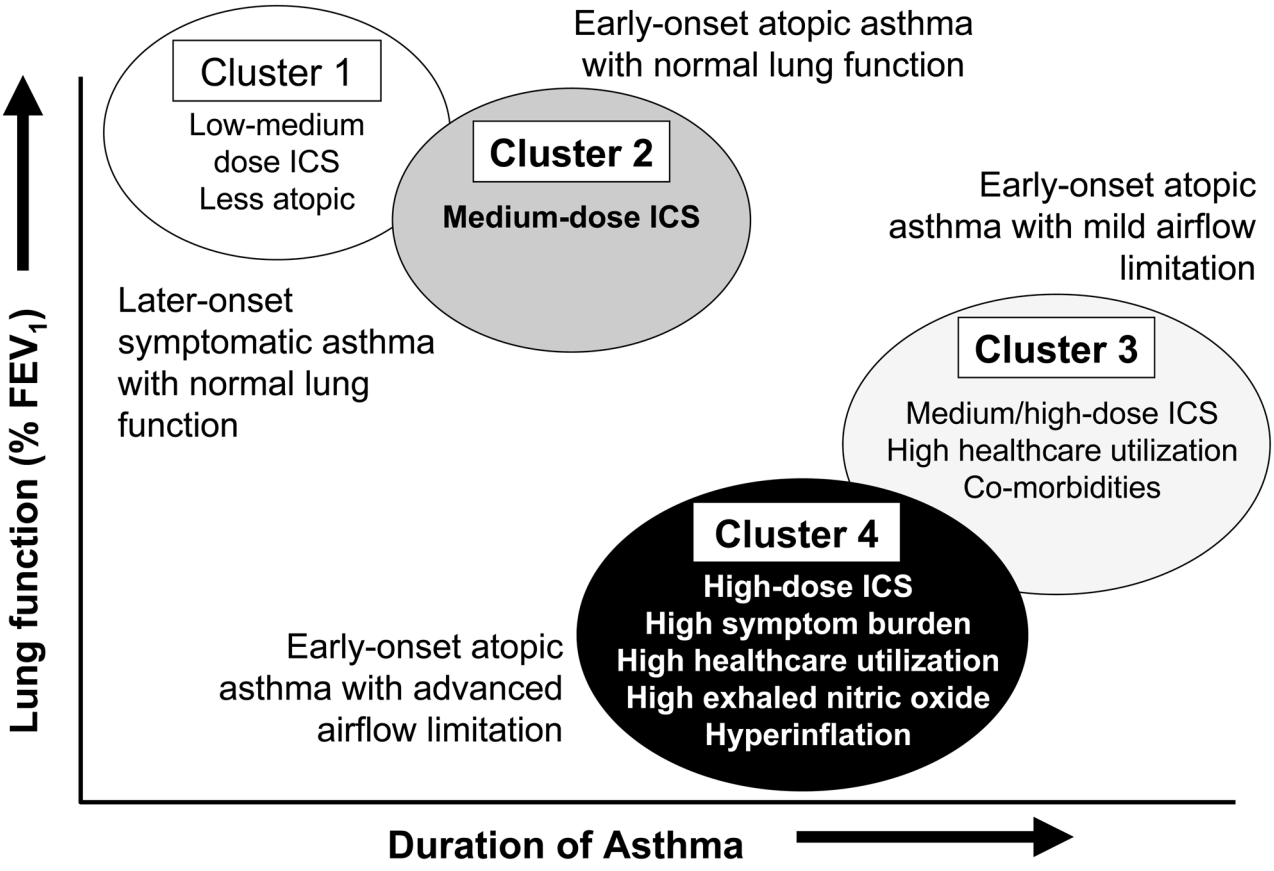

Figure 3.
Unbiased hierarchical cluster analysis reveals four clusters of asthma with shared phenotypic features. Although clusters 3 and 4 tend to be more "severe," children with ATS-defined severe asthma are present in all clusters, thus highlighting the heterogeneity of the disorder [77].

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Table 1

Name	Clinical centers	Patients enrolled	Original reference
European Network for Understanding Mechanisms of Severe Asthma (ENFUMOSA)	Twelve clinical specialty centers in nine European countries	Aged 17–65 years with asthma diagnosed by a specialist receiving ICS treatment for at least 1 year	[8]
Epidemiology and Natural History of Asthma: Outcomes and Treatment Regimens (TENOR)	Two hundred eighty-three office-based private practice, hospital, and academic sites across the US	Aged 6 years and older with severe or difficult-to-treat asthma treated by an asthma specialist	[9]
Global Asthma and Allergy European Network (GA^2LEN)	Twenty-seven research centers and 60 collaborating centers in 16 European countries in 35 countries	Project-specific, includes birth cohorts and patients with mild-to-severe asthma across the age spectrum	[10]
National Heart, Lung and Blood Institute Severe Asthma Research Program (SARP)	Eight academic clinical specialty centers in the US and UK	Project-specific, aged 6 years and older with physician-diagnosed mild to severe asthma and healthy nonsmoking adults without asthma	[11]
Unbiased Biomarkers for the Prediction of Respiratory Disease Outcome (U-BIOPRED)	Twenty academic centers across Europe	Adults and children with severe asthma taking high-dose ICS, adults with mild-to-moderate asthma, and healthy nonsmoking adults without asthma	[12]

ICS, inhaled corticosteroids.

Table 2

	Adults (18 years+) with severe asthma		Children (6–17 years) with severe asthma	
Feature	**Observation {versus nonsevere asthma)**	**Reference**	**Observation (versus nonsevere asthma)**	**Reference**
Exacerbation severity	Frequency emergency department visits and hospitalizations with ~30% hospitalized in the previous year; 20–25% with lifetime history of intubation	[3]	Frequent emergency department visits and hospitalizations with ~55% hospitalization in the previous year; 10–15% with lifetime history of intubation	[2,42]
Allergic sensitization	Varying degrees of atopy according to age of asthma onset and phenotype cluster	[3,20▪▪]	Highly atopic with increased peripheral blood eosinophilia, aeroallergen sensitivity, and elevated serum IgE concentrations	[2,42.44▪▪]
Exhaled nitric oxide	Not distinguishing overall but associated with exacerbations in a selected phenotype	[3,45▪]	Sustained elevations	[2]
Airflow limitation	Moderate-to-severe airflow limitation, often with incomplete reversal after bronchodilation	[3,20▪▪,46]	Some (mild) airflow limitation with near-complete reversal after bronchodilation; significant acceleration of airflow limitation in some adolescents after puberty	[2,42,48▪▪]
Air trapping	Increased air trapping (increased RV/TLC) at the same threshold of airflow limitation (FEV_1/FVC)	[46]	Increased air trapping (increased RV/TLC) at baseline; reversible in girls but persistent in boys	[2,47▪▪]

FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; RV/TLC, ratio of residual volume to total lung capacity.