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Severe Asthma in Children: Lessons Learned and Future Directions

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Abstract

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.

Keywords

Severe asthma; Children; Lung function; Phenotype; Endotype; Inflammation

Introduction

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 (i.e., 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 one 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

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medication access and compliance⁴ and likely affects less than 5% (or approximately 300,000) of all asthmatic children in the United States.⁵

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 estimated incremental direct costs of asthma has been estimated at more than \$3,250 (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 multi-center program focused on the clinical and biological attributes of severe asthma in adults and children that has been ongoing since 2001. At the initiation 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 three 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 age 6 to 17 years of age. 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 one to three years. The excellent retention and interesting longitudinal features of these participants resulted in renewal of the SARP program in 2012. Whereas the first two cycles of SARP were primarily focused on asthma phenotypes (i.e., observable clinical characteristics), SARP was renewed with the purpose of elucidating asthma endotypes (i.e., biological mechanisms within phenotypes).¹³ Awards were made to seven clinical centers with the mandate that each center would enroll

25% children and that all SARP participants would complete up to three 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 sub-populations.

Definition of “severe” asthma in children

Prior to 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 two minor criteria, including use of additional asthma controller medications (i.e., long-acting beta agonists), daily use of short-acting bronchodilators for symptoms, persistent airflow obstruction evidenced by a forced expiratory volume in one second (**FEV₁**) < 80% predicted at baseline, one or more urgent care visits for asthma in the previous year, three 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 due to co-morbid 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 (ERS)/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 were the same as for adults (i.e., a minimum of 880 mcg of fluticasone equivalent/day, versus a minimum of 440 mcg of fluticasone equivalent/day for children 6–11 years).

Clinical features of children with severe asthma in SARP

As a group, children with severe asthma enrolled in SARP had a number of distinguishing clinical features. Similar to adults,¹² children with severe asthma were characterized by a high burden of asthma symptoms, but were more likely to seek medical care for acute exacerbations. At enrollment, more than three quarters of children with severe asthma in SARP had visited the emergency room for an acute exacerbation in the preceding 12 months, with many of these children requiring hospitalization for status asthmaticus (Table 1). Nearly 30 percent of all children with severe asthma in SARP also reported a lifetime history of intubation for near-fatal respiratory failure, suggesting that the children enrolled were at high risk for future asthma mortality.

Whereas adults with severe asthma do not always have atopic features,¹⁷ children with severe asthma in SARP overall had a high degree of atopy reflected by increased blood eosinophils and higher concentrations of total serum immunoglobulin E (**IgE**) compared to children with non-severe asthma (Figure 1A, 1B). Although the prevalence of sensitization to single versus multiple aeroallergens was similar regardless of asthma severity (non-severe versus severe asthma, single aeroallergen sensitization: 19% vs. 11%; multiple aeroallergen sensitization: 81% vs. 89%), patterns of aeroallergen sensitization were different between the severe and non-severe groups (Figure 1C). Children with severe asthma also had increased concentrations of exhaled nitric oxide,¹¹ but it is unclear whether the increased exhaled nitric oxide concentrations observed in these children are a unique feature of asthma severity or a reflection of underlying atopic features or T-helper type 2 (**Th2**) inflammation.¹⁸ A separate study in SARP adults found that exhaled nitric oxide values were not different between severe versus non-severe asthma but were instead elevated in those patients with greater airway reactivity, greater airway and systemic eosinophils and more aeroallergen sensitization.¹⁹ In these adult patients, increased exhaled nitric oxide values (i.e., >35 ppb) were also associated with more frequent emergency care utilization.¹⁹

Airflow limitation and air trapping were also distinguishing features of severe asthma in children,¹¹ but the degree of airflow limitation and air trapping were significantly less than that observed in adults. Whereas adults with severe asthma had prominent air trapping evidenced by a higher ratio of residual volume (**RV**) to total lung capacity (**TLC**) and a reduction in forced vital capacity (**FVC**) across the entire range of FEV₁/FVC, adults with non-severe asthma had less air trapping even in the presence of airflow obstruction reflected by an FEV₁/FVC less than 75% of predicted values.²⁰ Adults with severe asthma further exhibited greater airway wall thickness at baseline.²¹ While heterogeneity was noted,²¹ airway wall thickness in adults with severe asthma increased further over time and this change was associated with a significant decline in post-bronchodilator FEV₁.²² Although airway imaging studies were not conducted in children, similar declines in post-bronchodilator FEV₁ percent predicted were observed over a period of three years in a small, representative subset of children with severe asthma (n = 28) enrolled at SARP during the early pubertal years.²³ In that study, post-bronchodilator FEV₁ values declined in 46% of the children with severe asthma and 29% had significant post-bronchodilator FEV₁ declines of more than 1% per year.²³ Children with the largest magnitude of lung function decline were those who had ongoing daily symptoms and an increased magnitude of

aeroallergen sensitization evidenced by more positive skin prick responses at the baseline characterization visit.²³ Whether this finding represents a reduction or lung growth or progression or airway remodeling is not clear, but suggests that the pubertal years may represent a critical window whereby airway structure-function relationships intensify and worsen in children with severe asthma.

Risk factors for severe asthma in children

Several studies in SARP have focused on risk factors for severe asthma such as sex, race, co-morbid conditions, and environmental exposures. These risk factors are discussed below.

Sex

In adults, severe asthma may be slightly more prevalent in women versus men,¹² whereas in children, it may be more prevalent in boys versus girls.^{11, 24} The features of severe asthma may also vary according to sex. For example, boys with severe asthma enrolled in SARP had significantly more baseline airflow obstruction and reversed incompletely with bronchodilation, in contrast to girls with severe asthma.²⁵ Furthermore, whereas girls with severe asthma had no residual air trapping after bronchodilation, boys with severe asthma had incomplete reversal of air trapping with persistent elevations in the RV/TLC ratio, suggesting that the adult patterns of severe asthma are already present in school-age boys but may not yet be fully developed in girls.²⁵ The mechanisms responsible for this are unclear but may be related to sex hormones. Other SARP studies in adults demonstrate that airflow and lung diffusing capacity vary over the menstrual cycle,²⁶ and further, that women with perimenstrual asthma have more asthma symptoms and urgent healthcare utilization potentially related to prostaglandin alterations given the higher prevalence of aspirin sensitization in this group.²⁷

Race

Severe asthma may also be disproportionately represented among certain racial groups. Children with severe asthma enrolled in SARP were more likely to be Black (Table 1), but it is unclear whether this reflects convenience sampling by the SARP centers since many of these centers serve an inner-city, urban population. However, a separate analysis of Black versus White adults enrolled in SARP did reveal differences in a number of features, suggesting that asthma in Blacks may be phenotypically unique.²⁸ For example, Black adults with severe asthma had a higher body mass index and more airway obstruction than White adults with severe asthma. Moreover, in multivariable analyses, serum IgE levels, skin test reactivity, and family history of asthma were strongly associated with severe asthma in Blacks but were not associated with severe asthma in Whites.²⁸ However, Black SARP participants with severe asthma were less likely to be employed and were more likely to be exposed to second-hand smoke,²⁸ so it is unclear whether these findings represent a unique phenotype or other socioeconomic and environmental factors. Nonetheless, separate genetic analyses in SARP participants have revealed some interesting results. One study identified a unique variant that predicted serum IgE in Black and admixed populations.²⁹ Other studies in SARP adults³⁰ and in larger admixed populations³¹ also suggest that genetic variants that contribute to asthma susceptibility may differ between Blacks and

Whites and argue for further research on biological and genetic determinants of racial disparities.^{30, 31} However, the relationships between racial disparity and severe asthma are undoubtedly complex and more studies are needed to understand the role of residual confounding from socioeconomic status, health beliefs and access to healthcare in Black and other racial populations.

Co-morbid conditions

Co-morbid risk factors such as gastroesophageal reflux, sinopulmonary infections, and pneumonia requiring antibiotic therapy were more frequent in children¹¹ and adults¹² with severe asthma, particularly in older patients with a later onset of disease and those patients with the lowest lung function and highest exposure to systemic corticosteroids.^{17, 32}

Although sleep disorders were not systematically assessed in children, sleep quality was generally poor in adults with non-severe and severe asthma even after adjustment for other co-morbid conditions.^{33, 34} However, adults with severe asthma were at highest risk for obstructive sleep apnea, which was further associated with poor asthma control and other inflammatory indices.^{33, 34}

By contrast, obesity, defined by a body mass index at or above the 95% percentile for children or 30 or more kg/m² for adults, was highly prevalent in both children and adults with severe asthma. Interestingly, there was a significant association between body mass index and the duration of asthma in SARP participants, but only in those participants with childhood-onset asthma.³⁵ It remains unclear whether this obesity-asthma association is due to greater corticosteroid exposure³⁶ and/or cardiopulmonary deconditioning from activity limitation,³⁷ or to specific biological^{38, 39} or physiological⁴⁰ mechanisms that increase the risk of adverse asthma outcomes. Indeed, obese children with asthma were more likely to report non-specific chest symptoms such as dyspnea and were significantly more likely to receive systemic corticosteroids.⁴¹

Environmental exposures

Environmental tobacco smoke exposure is highly prevalent among children with asthma⁴² and has been associated with poorer asthma control, including an increased risk of asthma-related hospitalization.^{43, 44} Studies of smoke exposure and asthma severity in children have not yet been performed in SARP, but analyses have been conducted in SARP adults.

Although all SARP participants were non-smokers with less than 5 pack years of tobacco use, one study found that SARP adults with detectable levels of urinary cotinine had increased airway hyperresponsiveness to methacholine, increased short-acting bronchodilator medication use, and significantly greater airway obstruction with lower FEV₁ % predicted and FEV₁/FVC values.⁴⁵ Adults with detectable levels of urinary cotinine also had decreased activity of the airway antioxidant, superoxide dismutase,⁴⁵ which is likely attributable to an increased oxidative burden from cigarette smoke and oxidative modification of the superoxide dismutase protein.⁴⁶ Alternatively, environmental tobacco smoke might promote airway obstruction through direct injury to airway epithelial cells. Indeed, a study of endobronchial biopsies from SARP adults noted striking epithelial alterations in severe asthma including increased proliferation, increased apoptosis and decreased cell death suppression.⁴⁷ These changes are likely multifactorial in nature and

may be accelerated by environmental exposures in concert with other underlying inflammatory factors.

Heterogeneity of children with severe asthma

Although the SARP definition of severe asthma does identify patients with distinct asthma features, significant heterogeneity is present within this group. More recent efforts in SARP have focused on unraveling this heterogeneity through non-biased approaches such as cluster analysis. In SARP adults, cluster analysis identified 5 clusters (i.e., phenotypes) of asthma distinguished primarily by pre- and post-bronchodilator values of lung function and the age of asthma onset.³² In post-hoc analyses, increased airway sputum neutrophils, either alone or in combination with increased airway eosinophils, were differentiating features of the most “severe” clusters and were further associated with more frequent lifetime hospitalizations for status asthmaticus, greater airflow obstruction and increased medication requirements.^{48, 49} Subsequent cluster analyses in adult participants from SARP⁵⁰ and other programs^{51–54} have yielded similar as well as other unique phenotypic clusters. However, whether these clusters or “phenotypes” of asthma are also present in children is unclear, and the existence of a neutrophil-dominated phenotype in children is controversial. Although a small bronchoscopic study of children with severe asthma enrolled in SARP did observe elevated neutrophil counts in children with severe asthma, these counts were not different from children with milder asthma and were further associated with airway eosinophils in the majority of participants studied.⁵⁵ A separate study similarly found no evidence of airway neutrophilia in children with severe asthma and concluded that eosinophils were the predominant inflammatory cell.⁵⁶

Nonetheless, it is recognized that children with severe asthma are a heterogeneous group of patients with highly varied clinical features and asthma-related outcomes. To better understand this heterogeneity, a cluster analysis was also performed on all children with asthma enrolled in SARP based on 12 variables that could be derived from the clinical setting: 1) sex, 2) race, 3) ICS dose, 4) the duration of asthma, 5) baseline FEV₁ percent predicted, 6) post-bronchodilator FEV₁ percent predicted, 7) short-acting beta-agonist usage over the previous 3 months, 8) symptom frequency, 9) allergic sensitization, 10) exhaled nitric oxide, 11) the number of asthma controller medications, and 12) healthcare utilization in the previous year. However, results were driven primarily by three variables (asthma duration, the number of asthma controller medications and baseline FEV₁ percent predicted values) that resulted in correct classification of 93% of original participants.⁵⁷ Children in Cluster 1 (30% of participants) had normal lung function and relatively mild disease, while children with Cluster 2 (32% of participants) had slightly lower lung function and increased symptoms and medication use. Children in Cluster 3 (20% of participants) had the highest prevalence of co-morbid conditions such as pneumonia as well as increased bronchial responsiveness to methacholine and lower lung function, while children in Cluster 4 (18% of participants) had the most advanced airflow obstruction and the greatest burden of symptoms and associated medication use.⁵⁷ Similar to the analysis in adults,³² children with SARP-defined severe asthma were present in all clusters,⁵⁷ highlighting the heterogeneity of the disorder. Moreover, no cluster corresponded perfectly to proposed definitions of asthma severity and these findings potentially argue for refined approaches for the classification of

asthma severity.¹⁷ Separate cluster analyses of asthmatic children across the severity spectrum outside of SARP have also yielded clusters of asthma that differed according to allergic sensitization, race, asthma duration, airway obstruction, medication utilization, exacerbations, and inflammatory biomarkers.^{58–61} Although these approaches might be useful in the quest for personalized medicine for severe asthma, replication and validation of clustering approaches for asthma is needed. The SARP clusters have been reproduced in adult^{62–64} and pediatric populations,⁶⁵ but a recent study in adults found that asthma clusters had no prognostic value in the prediction of future asthma control, treatment requirements or exacerbations.⁶⁴ However, application of the SARP pediatric cluster algorithm to a heterogeneous, pediatric clinical trial population did identify groups of children with distinct differential and even limited responses to asthma therapies.⁶⁵

Potential endotypes of asthma severity in children

Mechanistic studies in SARP have primarily focused on adults, in part due to challenges associated with sample collection in children. Induced sputum was not performed in SARP participants less than 18 years of age due to potential safety concerns resulting from limited experience and available literature on children with severe asthma at the time. Furthermore, whereas adult SARP participants were routinely consented for research-related bronchoscopy with bronchoalveolar lavage and endobronchial biopsy,⁶⁶ bronchoscopies for the sole purpose of research were not performed on children. Rather, children who underwent bronchoscopy for clinical indications submitted leftover samples for research at selected SARP sites.

SARP mechanistic studies in adults have been previously reviewed⁶⁷ and have focused on the unique properties of airway mast cells,⁶⁸ epithelial cells,^{47, 69} eosinophils and neutrophils⁴⁹ and the airway vasculature^{26, 70} in severe asthma subpopulations. Large data studies such as genetic analyses are currently ongoing but several key findings from SARP have been reported, including genetic variations in chitinase expression,⁷¹ the interleukin-6 receptor,⁷² and genes associated with total serum IgE,⁷³ lung function,^{74, 75} and asthma immunopathogenesis⁷⁶ that may contribute to asthma severity in adults and children. Molecular phenotyping of cytokine panels has also been applied to bronchoalveolar lavage fluid from severe and non-severe adults and has identified several phenotypes including a high neutrophil phenotype, a bronchodilator response phenotype, a high eosinophil phenotype, and a bronchial hyperactive phenotype irrespective of asthma severity.⁷⁷ A similar analysis in children with severe versus non-severe asthma also identified unique cytokine and chemokine patterns. Although the majority of children with asthma included in that analysis had evidence of Th2-mediated inflammation, children with SARP-defined severe asthma also had evidence of increased T-helper type 1 (**Th1**) inflammation and increased expression of neutrophil chemoattractants.⁵⁵ However, heterogeneity was noted suggesting that sub-phenotypes are likely present but were of too low a number to be detected with invasive sampling.

Other SARP studies have examined the associations between specific inflammatory cytokines and asthma outcomes in children. Whereas one study demonstrated associations between high tumor necrosis alpha expression and poor asthma control,⁷⁸ others have shown

associations between increased airway transforming growth factor beta-1 expression⁷⁹ and increased urinary bromotyrosine and F(2)-isoprostanes⁸⁰ and airflow obstruction in children. Urinary bromotyrosine levels have further been shown to predict clinical responsiveness to inhaled corticosteroid therapy in adults, particularly when assessed in combination with exhaled nitric oxide values.⁸¹ Other studies in adults have also identified alterations in plasma arginine bioavailability⁸² and lipoxygenase-derived eicosanoid synthesis⁸³ in severe asthma which may also be of relevance to children.

SARP studies have also focused on airway nitric oxide biology and nitrosative/nitrative stress from the reaction of reactive nitrogen species with protein tyrosine residues. Although reactive nitrogen species can be generated from a variety of sources, acidification of airway pH can contribute to nitric oxide and reactive nitrogen species formation in patients with asthma⁸⁴ and may be associated with airflow obstruction and airway neutrophilia in asthmatic subgroups.⁸⁵ Airway reactive nitrogen species and protein nitration are also increased as a function of asthma severity in both adults⁸⁶ and children⁸⁷ and are further associated with other oxidative processes including depletion and/or inactivation of the airway antioxidants glutathione,⁸⁸ catalase⁸⁶ and superoxide dismutase.⁴⁶ This oxidant imbalance has important functional consequences for asthma patients including impairment of airway innate immune cell function,^{89, 90} which may increase the severity of respiratory infection, and disruption of the global airway thiol redox balance that is required for anti-inflammatory signaling^{91, 92} and glucocorticoid receptor function.⁹³ Decreased glutathione availability also decreases the formation of S-nitrosoglutathione, an endogenous smooth muscle relaxant, which is decreased in subgroups of children and adults with early-onset atopic asthma.^{94, 95} Current SARP efforts are utilizing large-data approaches to better understand nitric oxide-related endotypes. For example, one recent study observed differences in the plasma metabolome between asthmatics with high versus low exhaled nitric oxide values, whereby nitric oxide “high” patients had higher levels of branched chain amino acids and bile acids.⁹⁶ Two other studies focused on airway epithelial cells have also identified a novel metabolome driving nitrative stress in severe asthma patients⁹⁷ as well as Th2-related and novel gene expression pathways underlying exhaled nitric oxide clinical phenotypes¹⁸ that are worthy of further study.

Conclusions and future directions for SARP

Findings from SARP suggest that severe asthma is a heterogeneous disorder with diverse clinical, molecular, and cellular inflammatory characteristics. Children, like adults, do have differentiating features of severe asthma but are not “small adults.” Moreover, children with severe asthma also have a number of phenotypes and likely biological endotypes, which have not yet been fully elucidated. An important knowledge gap is how (and whether) the phenotype of severe asthma in children changes over time. Given the cross-sectional design of the original SARP, current SARP efforts are now focused on longitudinal study of children and adults with severe and non-severe asthma to better understand the natural history of the disorder as well as phenotypic heterogeneity and related endotypes over time. The ultimate goal of SARP is to apply this knowledge to adults and children with severe asthma to improve existing and emerging phenotypic-directed treatments and to advance personalized medicine for the disorder.

Abbreviations

ATS	American Thoracic Society
ERS	European Respiratory Society
FEV₁	Forced expiratory volume in one second
FVC	Forced vital capacity
ICS	Inhaled corticosteroid
IgE	Immunoglobulin E
RV	Residual volume
SARP	SARP
Th1	T-helper type 1
Th2	T-helper type 2
TLC	Total lung capacity

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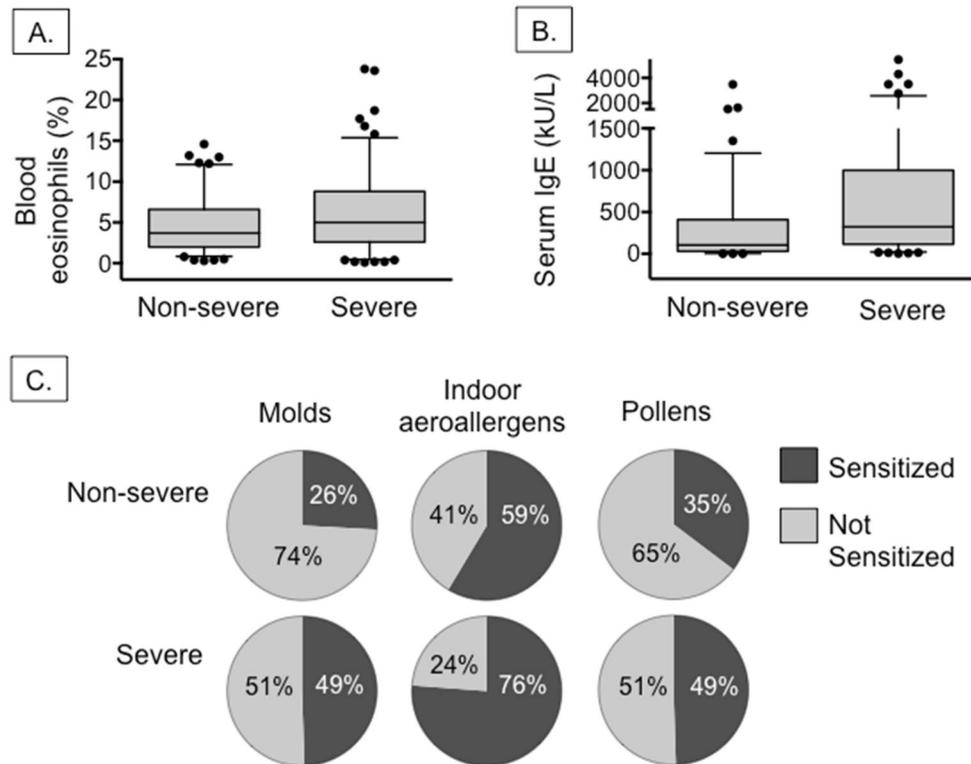


Figure 1.

(A) Blood eosinophils, (B) serum IgE, and (C) the prevalence of aeroallergen sensitization in children 6–17 years with severe and non-severe asthma enrolled in SARP. Boxplot horizontal lines reflect the median value and whiskers represent the 5th to 95th percentile. Severe versus non-severe asthma, median eosinophils: 5.0 vs 3.7, $p = 0.005$; median IgE: 322 vs. 105, $p < 0.001$.

Table 1

Features of children with severe asthma enrolled in SARP. Values represent the number (%) or median (IQR).

Feature	Severe asthma, 6–11 years N = 68	Severe asthma, 12–17 years N = 73
Sex		
Males	34 (50)	44 (60)
Females	34 (50)	29 (40)
Race		
White	14 (21)	14 (19)
Black	47 (69)	49 (67)
Other	7 (10)	10 (14)
Age of asthma onset	1 (1, 2)	1 (1, 3)
Co-morbid conditions		
Obesity	18 (27)	18 (25)
Pneumonia	44 (66)	48 (67)
Sinusitis	25 (37)	38 (53)
Gastroesophageal reflux	24 (36)	37 (51)
Second-hand tobacco smoke exposure	9 (13)	23 (32)
Healthcare utilization (previous year)		
Emergency department visit	53 (78)	56 (77)
Hospitalization	43 (63)	34 (47)
Intubation for asthma-related respiratory failure (ever)	20 (29)	26 (36)
Daily asthma symptoms (past 3 months)	40 (60)	47 (65)
Aeroallergen sensitization ^I		
Positive tests (out of 12)	3 (0, 5)	4 (2, 7)
Any sensitization	44 (86)	43 (84)
Mold sensitization	18 (35)	82 (63)
Pollen sensitization	21 (41)	28 (55)
Indoor allergen sensitization	40 (78)	38 (75)
Blood eosinophils		
% Eosinophils	5 (3, 10)	5 (5, 15)
Absolute eosinophils (k/UL)	0.3 (0.1, 0.6)	0.3 (0.2, 0.8)
Blood eosinophils 4%	34 (58)	44 (65)
Blood eosinophils 0.3 k/UL	35 (51)	46 (63)
Serum IgE		
Serum IgE (kU/L)	293 (80, 969)	412 (200, 1329)
Serum IgE 150 kU/L	36 (68)	35 (66)
Exhaled nitric oxide		

Feature	Severe asthma, 6–11 years N = 68	Severe asthma, 12–17 years N = 73
Exhaled nitric oxide (ppb)	20 (9, 40)	45 (37, 135)
Exhaled nitric oxide > 35 ppb	14 (33)	29 (60)
Baseline pulmonary function		
FVC (% predicted)	100 (94, 110)	101 (80, 117)
FEV ₁ (% predicted)	90 (77, 104)	85 (66, 90)
FEV ₁ /FVC	0.78 (0.69, 0.84)	0.72 (0.64, 0.72)
RV/TLC	0.30 (0.22, 0.33)	0.28 (0.18, 0.31)
FEV ₁ < 80% predicted	20 (30)	31 (43)
FEV ₁ /FVC < 0.85	37 (55)	57 (79)
Post-bronchodilator pulmonary function		
FVC (% predicted)	112 (106, 126)	105 (87, 124)
FEV ₁ (% predicted)	103 (94, 122)	98 (80, 108)
FEV ₁ /FVC	0.83 (0.75, 0.87)	0.81 (0.75, 0.88)
RV/TLC	0.26 (0.23, 0.32)	0.26 (0.16, 0.28)
FEV ₁ (% reversal from baseline)	12 (4, 32)	17 (8, 21)
FEV ₁ < 80% predicted	4 (6)	13 (19)
FEV ₁ /FVC < 0.85	23 (37)	33 (47)
Methacholine PC ₂₀ (mg/mL)	1.4 (0.5, 4.1)	0.5 (0.2, 7.1)

¹ Defined by positive skin prick test responses to 12 aeroallergens. Age 6–11, n = 51; age 12–17, n = 51