# Heterogeneity of severe asthma in childhood: Confirmation by cluster analysis of children in the National Institutes of Health/National Heart, Lung, and Blood Institute Severe Asthma Research Program

**Anne M. Fitzpatrick, PhD,[a] W. Gerald Teague, MD,[b] Deborah A. Meyers, PhD,[c] Stephen P. Peters, MD, PhD,[c] Xingnan Li, PhD,[c] Huashi Li, MS,[c] Sally E. Wenzel, MD,[d] Shean Aujla, MD,[d] Mario Castro, MD,[e] Leonard B. Bacharier, MD,[e] Benjamin M. Gaston, MD,[b] Eugene R. Bleecker, MD,[c] and Wendy C. Moore, MD,[c] for the National Institutes of Health/National Heart, Lung, and Blood Institute Severe Asthma Research Program*** *Atlanta, Ga, Charlottesville, Va, Winston-Salem, NC, Pittsburgh, Pa, and St Louis, Mo*

**Background: Asthma in children is a heterogeneous disorder with many phenotypes. Although unsupervised cluster analysis is a useful tool for identifying phenotypes, it has not been applied to school-age children with persistent asthma across a wide range of severities.**

**Objectives: This study determined how children with severe asthma are distributed across a cluster analysis and how well these clusters conform to current definitions of asthma severity.**

**Methods: Cluster analysis was applied to 12 continuous and composite variables from 161 children at 5 centers enrolled in the Severe Asthma Research Program.**

**ResultsFour clusters of asthma were identified. Children in cluster 1 (n = 48) had relatively normal lung function and less atopy. Children in cluster 2 (n = 52) had slightly lower lung function, more atopy, and increased symptoms and medication use. Cluster 3 (n = 32) had greater comorbidity, increased bronchial responsiveness, and lower lung function. Cluster 4 (n = 29) had the lowest lung function and the greatest symptoms and medication use. Predictors of cluster assignment were asthma duration, the number of asthma controller medications, and baseline lung function. Children with severe asthma were present in all clusters, and no cluster corresponded to definitions of asthma severity provided in asthma treatment guidelines.**

**Conclusion: Severe asthma in children is highly heterogeneous. Unique phenotypic clusters previously identified in adults can also be identified in children, but with important differences. Larger validation and longitudinal studies are needed to determine the baseline and predictive validity of these phenotypic clusters in the larger clinical setting. (J Allergy Clin Immunol 2011;127:382-9.)**

***Key words:*** *Allergic sensitization, asthma, severe asthma, asthma guidelines, children, cluster analysis, lung function, phenotype*

Asthma in children is a chronic, persistent disorder characterized by airway inflammation and episodic airflow obstruction in response to specific triggers.[1] Whereas some children with asthma have intermittent symptoms that are improved with short-acting bronchodilators, many have classic, persistent symptoms requiring daily treatment with inhaled corticosteroids (ICSs).[2,3] Children with severe asthma are differentiated by ongoing symptoms and airway inflammation despite treatment with high doses of ICSs and other controller medications.[4-6] Although the prevalence of severe asthma is low, these children have extreme morbidity[4,5] and account for 30% to 50% of all pediatric asthma health care costs.[7,8]

Children with severe asthma are a challenging group of patients who can be difficult to treat. Although national and international guidelines from the Global Initiative for Asthma (GINA) and the National Asthma Education and Prevention Program (NAEPP) emphasize the importance of assessing asthma severity in children

From [a]the Department of Pediatrics, Emory University School of Medicine, Atlanta; [b]the Department of Pediatrics, University of Virginia School of Medicine; [c]the Center for Human Genomics, Wake Forest University School of Medicine, Winston-Salem; [d]the University of Pittsburgh School of Medicine; and [e]the Washington University School of Medicine, St Louis.

*A complete listing of Severe Asthma Research Program investigators is provided in the acknowledgments.

Supported by National Institutes of Health grants RO1 HL069170, RO1 HL069167, RO1 HL069174, RO1 HL69149, and RO1 HL091762 and in part by the Center for Developmental Lung Biology, Children's Healthcare of Atlanta, and PHS grants UL1 RR025008, KL2 RR025009, TL1 RR025010, and UL1 RR024992 from the Clinical and Translational Science Award Program, National Institutes of Health, National Center for Research Resources.

Disclosure of potential conflict of interest: A. M. Fitzpatrick has received research support from the National Heart, Lung, and Blood Institute Severe Asthma Research Program. W. G. Teague is a speaker for Merck, has received research support from the National Institutes of Health and the American Lung Association, and is a volunteer for Not One More Life. D. A. Meyers has received research support from the National Institutes of Health. S. P. Peters has received research support from the National Institutes of Health, National Heart, Lung, and Blood Institute Severe Asthma Research Program. M. Castro is a consultant for Electrocore, NKTT, Schering, Asthmatx, and Cephalon; is on the advisory board for Genentech; is a speaker for AstraZeneca, Boehringer-Ingelheim, Pfizer, Merck, and GlaxoSmithKline; has received grants from Asthmatx, Amgen, Ception, Genentech, Medimmune, Merck, Novartis, the National Institutes of Health, and GlaxoSmithKline; and has received royalties from Elsevier. L. B. Bacharier has received honoraria from AstraZeneca and has received honoraria from and is on the advisory board for Genentech, GlaxoSmithKline, Merck, Schering-Plough, and Aerocrine. B. M. Gaston has received research support from the National Institutes of Health and has served as an expert witness on the topic of exhaled nitric oxide for Apieron. E. R. Bleecker is an advisor and consultant for Aerovance, AstraZeneca, Boehringer-Ingelheim, Genentech, GlaxoSmithKline, Merck, Novartis, Pfizer, and Wyeth and has received research support from Aerovance, Amgen, AstraZeneca, Boehringer-Ingelheim, Centocor, Ception, Genentech, GlaxoSmithKline, the National Institutes of Health, Novartis, Pfizer, and Wyeth. The rest of the authors have declared that they have no conflict of interest.

Received for publication July 8, 2010; revised November 8, 2010; accepted for publication November 12, 2010.

Available online January 6, 2011.

Reprint requests: Anne M. Fitzpatrick, PhD, 2015 Uppergate Drive, Atlanta, GA 30322. E-mail: anne.fitzpatrick@emory.edu.

0091-6749/$36.00



doi:10.1016/j.jaci.2010.11.015

*Abbreviations used*
ATS: American Thoracic Society
GINA: Global Initiative for Asthma
ICS: Inhaled corticosteroid
LABA: Long-acting β-agonist
NAEPP: National Asthma Education and Prevention Program
NHLBI: National Heart, Lung, and Blood Institute
SARP: Severe Asthma Research Program

before the initiation of therapy, severe asthma is defined primarily by lung function abnormalities, persistent symptoms, and exacerbations despite appropriate therapy.[3,9] This approach underestimates the phenotypic heterogeneity of the disorder[10] and may further lead to suboptimal asthma treatment, because the majority of children with persistent asthma have relatively normal lung function during symptom-free periods with abnormal pulmonary function only during acute exacerbations.[11,12] Indeed, $FEV_1$ does not correlate well with the magnitude of asthma symptoms in children,[13] and values less than 80% predicted have a low sensitivity (approximately 40%) for distinguishing asthma severity in this population.[14] These findings suggest that more specific approaches are needed to differentiate asthma heterogeneity in children to assess better the risk and impairment associated with the disorder as well as to guide clinical asthma therapies.

Cluster analysis is an unsupervised analytical approach that is useful in the refinement of pediatric asthma diagnosis and severity assessments because of its ability to distinguish complex phenotypes without *a priori* (and therefore biased) definitions of disease severity.[15-17] In adults with chronic obstructive pulmonary disease and asthma,[18,19] cluster analyses have revealed distinct phenotypes of obstructive airway disease that may ultimately require modified approaches for their identification and diagnosis as well as different therapeutic interventions. Cluster analysis derived from the Severe Asthma Research Program (SARP) of the National Heart, Lung, and Blood Institute (NHLBI) has resulted in 5 novel clusters of asthma phenotypes in adults that do not correspond to the levels of asthma severity as outlined by current guidelines.[19] Although that study[19] and others[20] emphasized the importance of age of asthma onset in distinguishing the asthma clusters, no cluster analysis has been undertaken in childhood asthma. Given the significant heterogeneity in children with asthma, the purpose of this study was to apply unsupervised cluster analysis to a diverse sample of children enrolled in SARP to determine (1) whether phenotypic clusters that conform to established definitions of severe and nonsevere asthma are identifiable in children, and (2) how these clusters relate to definitions of asthma severity as proposed by the American Thoracic Society (ATS),[15] the NAEPP,[3] and GINA.[9] Because children enrolled in SARP are characterized with comprehensive phenotyping similar to the adult subjects,[4,21] we raised the question whether previously identified clusters of early-onset asthma in adults[19] would also be detected in children with similar phenotypic characteristics.

## METHODS

The SARP is an NHLBI-supported research program with recruitment of children 6 to 17 years of age across 5 centers in the United States. Each of the SARP centers is affiliated with a major university teaching program, and children are recruited into SARP from the outpatient clinics and inpatient hospital wards of those academic centers. As a result, children enrolled in SARP are more likely to have difficult asthma and are representative of a referral population of children who receive care at academic versus community centers. The protocol was approved by each center's institutional review board. Informed consent was obtained from the legal guardians of each child, and verbal and written consent was obtained from participating children.

All children 6 to 17 years of age who underwent standardized characterization in SARP were eligible for inclusion. Eligible children had never smoked and had physician-diagnosed asthma and historical evidence of bronchial hyperresponsiveness or at least 12% $FEV_1$ bronchodilator reversibility either at baseline or during an acute exacerbation. Children were classified as having severe asthma according to ATS workshop criteria (see this article's Table E1 in the Online Repository at www.jacionline.org).[15] This definition assumes that comorbid conditions have been treated or addressed and that the patient is adherent with prescribed asthma treatment. Thresholds for high-dose ICS were adjusted for children and defined as ≥440 μg fluticasone equivalent per day for children less than 12 years and ≥880 μg of fluticasone equivalent per day for children 12 to 17 years of age (see this article's Table E2 in the Online Repository at www.jacionline.org).[4] All children enrolled received a stable dose of ICS for at least 6 months. All were stable at the time of characterization with no signs of acute respiratory illnesses. Children presenting to the SARP clinic with an acute worsening of asthma control were treated accordingly and were reassessed at a later date.

### Characterization procedures

Participants underwent comprehensive phenotypic characterization consisting of questionnaires, serum IgE and eosinophil quantification, allergy skin prick testing, and bronchial responsiveness to methacholine as previously described.[4,21] Exhaled nitric oxide was determined with both offline (Sievers NOA 280-I; Ionic Instruments, Boulder, Colo) and online (NIOX; Aerocrine, Solna, Sweden) methods in accordance with published recommendations.[22] Spirometry (KoKo PDS; Ferraris, Louisville, Colo) was performed at baseline and after bronchodilator reversibility testing with 4, 6, and 8 inhalations of albuterol sulfate (90 μg per inhalation) to determine the best response to short-acting β-agonists. Lung volumes were measured with a body plethysmograph (MedGraphics Elite Series; MEDGRAPHICS, St Paul, Minn). Spirometry predicted values were obtained by using the equations of Wang et al,[23] and plethysmographic lung volume predicted values were obtained by using the Crapo[24] predicted equations.

### Variable reduction

The entire SARP dataset provided more than 500 variables that were reduced to 12 variables before cluster analysis. Continuous variables included the duration of asthma in months, baseline $FEV_1$ percent predicted, and the best postbronchodilator $FEV_1$ percent predicted. Categorical variables included sex, race (white, black, or other) and ICS group (none, low-dose, or high-dose). Semiquantitative variables included β-agonist use over the previous 3 months, the frequency of symptoms, the magnitude of atopic sensitization, and exhaled nitric oxide quartile. Composite variables were derived from binary or discrete questionnaire data and were developed by study physicians with experience in the study and treatment of childhood asthma to cover the broad spectrum of routine asthma assessment in the clinical setting (see this article's Table E3 in the Online Repository at www.jacionline.org).[19] These composite variables included the number of asthma controller medications and health care use in the previous year. For the composite variable health care use in the previous year, subjects were assigned a rank on the basis of the most severe use reported by the individual. Further description and performance of the variables for atopic sensitization and exhaled nitric oxide quartile appears in this article's Tables E4 and E5 in the Online Repository at www.jacionline.org. All variables were equally weighted in the analysis. Subjects with missing data were excluded.

### Statistical analysis

Cluster analysis was performed with SAS version 9.1 (SAS Institute Inc, Cary, NC) as previously described (see this article's Methods section in the