Published in final edited form as:
J Allergy Clin Immunol. 2011 February ; 127(2): 382–389.e1-13. doi:10.1016/j.jaci.2010.11.015.

Heterogeneity of Severe Asthma in Childhood: Confirmation by Cluster Analysis of Children in the NIH/NHLBI Severe Asthma Research Program (SARP)

Anne M. Fitzpatrick, Ph.D.[1], **W. Gerald Teague, M.D.**[2], **Deborah A. Meyers, Ph.D.**[3], **Stephen P. Peters, M.D., Ph.D.**[3], **Xingnan Li, PhD**[3], **Huashi Li, M.S.**[3], **Sally E. Wenzel, M.D.**[4], **Shean Aujla, M.D.**[4], **Mario Castro, M.D.**[5], **Leonard B. Bacharier, M.D.**[5], **Benjamin M. Gaston, M.D.**[2], **Eugene R. Bleecker, M.D.**[3], and **Wendy C. Moore, M.D.**[3] **For the NIH/NHLBI Severe Asthma Research Program**

[1]Emory University School of Medicine, Department of Pediatrics, Atlanta, Georgia

[2]University of Virginia School of Medicine, Department of Pediatrics, Charlottesville, Virginia

[3]Wake Forest University School of Medicine, Center for Human Genomics, Winston-Salem, North Carolina

[4]University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania

[5]Washington University School of Medicine, St. Louis, Missouri

Abstract

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 (SARP).

Results—Four clusters of asthma were identified. Children in Cluster 1 (n = 48) had relatively normal lung function and less atopy, while children in Cluster 2 (n = 52) had slightly lower lung function, more atopy, and increased symptoms and medication usage. Cluster 3 (n = 32) had greater co-morbidity, increased bronchial responsiveness and lower lung function. Cluster 4 (n = 29) had the lowest lung function and the greatest symptoms and medication usage. 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.

Please address correspondence to: Anne M. Fitzpatrick, 2015 Uppergate Drive, Atlanta, Georgia 30322, Phone: (404) 727-9112, Fax: (404) 712-0920, anne.fitzpatrick@emory.edu.

CLINICAL IMPLICATIONS

Cluster analysis identifies distinct phenotypes of asthma in children that do not correspond to definitions of asthma severity proposed by current guidelines. Clusters of asthma in adults can also be indentified in children, but with important differences.

Conclusions—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.

Keywords

Allergic sensitization; Asthma; Severe asthma; Asthma guidelines; Children; Cluster analysis; Lung function; Phenotype

INTRODUCTION

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 (ICS) (2,3). Children with severe asthma are differentiated by ongoing symptoms and airway inflammation despite treatment with high doses of ICS and other controller medications (4–6). Although the prevalence of severe asthma is low, these children have extreme morbidity (4,5) and account for 30–50% of all pediatric asthma healthcare 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 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, the forced expiratory volume in one second (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 better assess 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 National Heart, Lung and Blood Institute's (NHLBI) Severe Asthma Research Program (SARP) has resulted in five novel clusters of asthma phenotypes in adults that do not correspond to the levels of asthma severity as outlined by current guidelines (19). While 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 which conform to established definitions of severe and non-severe 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

SARP is an NHLBI-supported research program with recruitment of children 6–17 years of age across five 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 6–17 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 (online repository Table E1) (15). This definition assumes that co-morbid 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 mcg of fluticasone equivalent per day for children less than 12 years and ≥ 880 mcg of fluticasone equivalent per day for children 12–17 years of age (online repository Table E2) (4). All children enrolled received a stable dose of ICS for at least six 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 immunoglobulin E (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, CO) and online (NIOX®, Aerocrine, Solna, Sweden) methods in accordance with published recommendations (22). Spirometry (KoKo® PDS, Ferraris, Louisville, CO) was performed at baseline and after bronchodilator reversibility testing with 4, 6, and 8 inhalations of albuterol sulfate (90μg per inhalation) to determine the best response to short-acting beta agonists. Lung volumes were measured with a body plethysmograph (MedGraphics® Elite Series,™ St. Paul, MN). Spirometry predicted values were obtained using the equations of Wang (23) and plethysmographic lung volume predicted values were obtained using the Crapo predicted equations (24).

Variable reduction

The entire SARP dataset provided more than 500 variables that were reduced to 12 variables prior to cluster analysis. Continuous variables included the duration of asthma in months,

baseline FEV_1 percent predicted and the best post-bronchodilator FEV_1 percent predicted. Categorical variables included gender, race (Caucasian, African American or Other) and ICS group (none, low-dose, or high-dose). Semi-quantitative variables included beta-agonist use over the previous three 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 (online repository Table E3) (19). These composite variables included the number of asthma controller medications and healthcare utilization in the previous year. For the composite variable healthcare utilization in the previous year, subjects were assigned a rank based on the most severe utilization reported by the individual. Further description and performance of the variables for atopic sensitization and exhaled nitric oxide quartile appears in the online supplement in Tables E4 and E5. 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 (19). Ward's minimum-variance hierarchical clustering method was performed using an agglomerative (bottom-up) approach and Ward's linkage (Online repository Figure E1). At each generation of clusters, samples were merged into larger clusters to minimize and maximize with within-subjects and between-subjects sum of squares, respectively. Analysis of variance with Tukey's post-hoc testing and chi-square tests were used to determine differences between groups. To determine the strongest predictors of cluster assignment, stepwise discriminant analysis of the cluster variables was performed with the Fisher method (25) as previously described (26) using an F-value entry probability of 0.05 and removal probability of 0.10. Cross-validation was performed by extracting each case and treating it as test data against the remaining cases.

RESULTS

Results from 273 children (mean age 10 years) enrolled in SARP across five centers in Atlanta, Georgia, Winston-Salem, North Carolina, Pittsburgh, Pennsylvania, St. Louis, Missouri, and Charlottesville, Virginia were available for analysis. Of these, 112 were missing one or more of the cluster variables and were excluded. The features of excluded children did not differ from those of the final sample (Online repository Table E6). The final sample included 161 children. Features of the sample are presented in Table I. Whereas treatment with combination ICS and long-acting beta-agonist (LABA) therapy was prevalent even among children with mild-to-moderate asthma (Table I), the study sample is representative of children with difficult asthma treated at academic medical centers.

Cluster analysis

Using the agglomerative cluster approach, a dendogram was generated and revealed four clusters of children with shared phenotypic characteristics (online repository Figure E1). The presence of four clusters was confirmed when the cluster analysis was repeated with alternative linkage methods, including the average between groups and centroid linkage. These clusters were distinguished by age, race, asthma onset and duration, a history of sinusitis and gastroesophageal reflux, the degree of atopic sensitization, and exhaled nitric oxide (Table II). Clusters also differed according to medication and healthcare utilization (Table III) and lung function (Table IV). These lung function differences between clusters persisted even after stratification by age of enrollment (online repository Table E7, E8).

Cluster 1—Forth-eight children were grouped into Cluster 1 (termed “late-onset symptomatic asthma”). This cluster had the lowest prevalence of severe asthma defined by ATS criteria (n = 15, 31%) and GINA or NAEPP criteria (n = 1, 2%) (Figure 1, online repository Table E9). Ten (67%) of the children with ATS-defined severe asthma in this cluster were hospitalized within the previous year, and six (40%) were hospitalized for the first time. This cluster was younger with more non-Hispanic whites and was differentiated by an older age of symptom onset and shorter asthma duration. Although many children in this cluster had markers of atopy with positive allergy skin prick tests, the magnitude of allergic sensitization was relatively less compared to the other clusters, with lower exhaled nitric oxide concentrations. Eighty-eight percent (n = 42) of children in this cluster had an asthma exacerbation necessitating a physician encounter, and 23% (n = 11) were hospitalized. Despite having bronchial hyperresponsiveness to methacholine, these children had relatively normal lung function (or mild airflow limitation) with minimal hyperinflation (air trapping) and decreased airway resistance. Children in Cluster 1 were treated with relatively fewer controller medications including a significantly lower daily dose of ICS. Although 21% of this cluster did report daily short-acting bronchodilator use, this finding may be related in part to prophylactic treatment of exercise-induced symptoms. Approximately 69% (n = 33) of the children in this group reported that sports were a primary trigger of asthma symptoms.

Cluster 2—Fifty-two children were assigned to Cluster 2 (termed “early-onset atopic asthma with normal lung function”). Whereas 61% (n = 28) of children in this cluster had ATS-defined severe asthma, only 4% (n = 2) had severe asthma by GINA or NAEPP criteria (Figure 1). Children were similar in age and race to Cluster 1 but had an earlier age of asthma onset, a longer duration of asthma symptoms and increased markers of atopy, although exhaled nitric oxide was not significantly different from Cluster 1. Healthcare utilization was again prominent and 88% (n = 46) of children in this cluster had a physician encounter for an acute asthma exacerbation within the previous year, and 33% (n = 17) were hospitalized. Although children in this group were treated more frequently with controller medications as well as higher daily doses of ICS, lung function including spirometric and lung volume variables, as well as best post-bronchodilator responses, were similar to those observed in Cluster 1. However, 52% (n = 27) reported daily short-acting bronchodilator use. Because 37% (n = 19) of children in this group also reported asthma symptoms with daily activities such as walking up stairs, it is unlikely that short-acting bronchodilator use was solely due to prophylactic therapy before exercise.

Cluster 3—Thirty-two children were grouped into Cluster 3 (termed “early-onset atopic asthma with mild airflow limitation and co-morbidities”). Similar to Cluster 2, 63% (n = 12) had ATS -defined severe asthma, while only 16% (n = 5) had severe asthma by GINA or NAEPP criteria (Figure 1). This cluster included fewer non-Hispanic whites with an earlier onset of asthma symptoms and the longest asthma duration. Children in Cluster 3 also had elevated exhaled nitric oxide concentrations compared to Clusters 1 and 2 and significant co-morbidities, including a higher prevalence of gastroesophageal reflux and chronic sinusitis requiring antibiotic treatment. Children in this cluster were also more likely to be treated with oral corticosteroids. Seventy-two percent (n = 23) had a physician encounter for an asthma exacerbation within the previous year and 41% (n = 13) were hospitalized. This cluster was further differentiated by the degree of airflow limitation and hyperinflation. Although children in cluster 3 had an enhanced bronchodilator response, airflow limitation was not completely reversed after 6 to 8 inhalations of albuterol. Children in this cluster also had a lower total lung capacity, increased airway resistance and greater bronchial hyperresponsiveness to methacholine. More than half of this group (n = 18, 56%) used

short-acting bronchodilators on a daily basis and 47% (n = 15) reported asthma symptoms with daily activities such as walking and climbing stairs.

Cluster 4—Twenty-nine children were assigned to Cluster 4 (termed "early-onset atopic asthma with advanced airflow limitation"). Eighty-six percent (n = 24) of children in this cluster were classified as having severe asthma according to ATS criteria, while only 14% (n = 4) met GINA or NAEPP criteria for severe asthma (Figure 1). Cluster 4 included the highest prevalence of Blacks and was similar to Cluster 3 with regard to asthma onset and asthma duration, although there were fewer co-morbidities. This cluster was further differentiated by the highest exhaled nitric oxide values and the highest extent of healthcare utilization. Ninety-seven percent (n = 28) of children in this group saw a physician for an acute exacerbation within the previous year and 48% (n = 22) were hospitalized, with 28% (n = 8) requiring intensive care. Children in Cluster 4 were therefore treated with the highest daily doses of ICS, and most were receiving at least three asthma controller medications. This cluster was also differentiated by the lowest lung function, including baseline airflow limitation and hyperinflation that were not completely reversed with bronchodilator administration. Similar to Cluster 3, children in this cluster also had increased airway resistance and greater bronchial responsiveness to methacholine. Lower total lung capacity was also observed in this cluster, although this finding was restricted to children 12–17 years of age (online repository Table E7, E8). Daily symptoms requiring short-acting bronchodilator treatment were also common in this group (n = 16, 55%), and nearly one-half (n = 14, 48%) reported asthma symptoms with activities of daily living.

Predictors of cluster assignment

Asthma duration ($p < 0.001$), the number of asthma controller medications ($p = 0.001$), and baseline FEV_1 percent predicted values ($p < 0.001$) were identified as the strongest predictors of cluster assignment in this sample (Wilk's $\lambda = 0.071$, $\chi^2 = 401.99$, $p < 0.001$; online repository Table E10). These three variables alone resulted in correct classification of 93% of the original subjects (Figure 2) and 92% of cross-validated grouped cases (Online repository Table E11).

DISCUSSION

Asthma in children is a complicated and heterogeneous disorder with distinct phenotypes. Using an unsupervised cluster analysis in children with a wide range of asthma severity characterized in the SARP network, we have identified four clusters of childhood asthma with shared phenotypic features. Similar to the previous SARP report that described increased allergic sensitization in clusters of adults with early-onset asthma (21,28), clusters of childhood asthma were all atopic, although the magnitude of allergic sensitization differed between groups. Asthma duration, the number of asthma controller medications and baseline lung function were also major determinants of asthma phenotype in this cluster analysis. While children with ATS-defined severe asthma were present in all clusters, and no single cluster corresponded well to the definitions of asthma severity proposed in published guidelines (3,9). This is likely due to overly stringent lung function requirements (i.e., $FEV_1 < 60\%$) for childhood severe asthma (12), which were extrapolated from adult reference norms (3,9). These findings highlight the complexity and unique differences of childhood asthma and emphasize the need for unbiased approaches to refine current guidelines for asthma diagnosis and treatment in children.

In a previous cluster analysis of adults enrolled in SARP, Moore et al. (19) observed five distinct clusters of asthma that differed primarily in the age of asthma onset, allergic sensitization, baseline lung function, bronchodilator reversibility, medication usage, and

healthcare utilization. Two of these clusters were associated with early-onset atopic asthma and normal or relatively mild airflow obstruction, while two others were associated with airflow obstruction that displayed different degrees of bronchodilator reversibility (19). Using a similar characterization method, we have identified four similar clusters of asthma in children, although the degree of lung function impairment was significantly less. Whereas baseline FEV_1 percent predicted values were 75–84% in Clusters 3 and 4, clusters of adults with early-onset atopic asthma had baseline FEV_1 percent predicted values of 43–57% (19). Similarly, the magnitude of FEV1 bronchodilator administration was significantly greater in children and suggests that “fixed” airflow limitation is not a distinguishing feature of severe asthma in this age group. Interestingly, children in Clusters 3 and 4 did have evidence of hyperinflation (air trapping) both at baseline and after bronchodilator administration, but to a much lesser extent than what has been previously reported in adults (19,21).

While the stability of airflow obstruction and hyperinflation in childhood asthma is not entirely clear, there is increasing evidence that an important sub-group of children with persistent wheezing and asthma symptoms acquires significant baseline airflow limitation by the early adult years (29–31). In the Melborne birth cohort study (32), children with severe asthma at 10 years of age had the lowest FEV_1 and FEV_1/forced vital capacity ratios throughout the first 42 years of life (32). Thus the magnitude of airflow limitation in childhood asthma may represent an important marker of progressive asthma that worsens and results in more severe disease in adults over time. Even in children with mild-to-moderate asthma, approximately 30% have declines in the post-bronchodilator FEV_1 percent predicted value of more than 1% per year regardless of treatment with ICS (33). This observation may be related to impaired lung growth (34), which could result in accelerated lung function decline in the adult years. Further study is needed to understand how lung function changes and evolves in these clusters with age.

Unlike previous cluster analyses of asthma in adults (18–20), healthcare utilization was not a robust discriminator of cluster assignment in children. Although children in Cluster 4 had the highest degree of healthcare utilization, the majority of children in each cluster had physician contact for an asthma exacerbation within the previous year. While this observation may be an artifact of the study sample since children in SARP were recruited from academic medical centers, this finding is also consistent with the episodic nature of childhood asthma. Indeed, there is an important distinction between the severity of exacerbations and overall asthma control (10,35). Whereas asthma severity refers to the required level of therapy during active treatment of asthma symptoms (i.e., the magnitude of disease activity), asthma control refers to the extent to which asthma symptoms are alleviated by treatment (36). Although asthma control often predicts the risk of future exacerbations (37), children can have severe exacerbations despite limited symptoms and normal lung function prior to the event (38). These children are difficult to evaluate, because many are not symptomatic between exacerbations and medications may be discontinued. Future revision of definitions of asthma severity may need to take this observation into account, since the intensity of treatment in these children may not be the best indicator of impairment and future risk.

An important strength of this study is that cluster analysis, by definition, is unsupervised and thus the identified clusters conform to shared phenotypic features and not *a priori* severity assignments. This study nonetheless does have limitations. First, it is unclear whether children enrolled in SARP differ systematically from children who refused participation. Although selection bias is a concern in all observational studies, this bias may influence the conclusions drawn and the generalization of our results, particularly since the SARP sample was enriched for children with difficult asthma who are evaluated at academic medical centers. However, the clinical characteristics associated with asthma severity in this sample,

including lung function measures, markers of allergic sensitization and exhaled nitric oxide values, are similar to what has been previously reported in other samples of children with severe asthma (5,6,12). Regardless, our sample may not accurately identify different phenotypes of milder asthma severity that are likely encountered in clinical practice. Thus expansion of our study to children with more mild intermittent forms of asthma would likely have resulted in additional subjects and therefore sub-clustering within Clusters 1 and 2. Second, while enrollment of additional non-Hispanic white subjects would have led to a more geographically representative sample, the disproportionate grouping of blacks in Clusters 3 and 4 likely reflects important ethnic differences in asthma phenotypes. Because healthcare utilization was highly prevalent in each cluster, the disproportionate racial distributions are not solely attributable to healthcare access. Indeed, other genetic-based studies have shown that black subjects with asthma have the earliest age of asthma onset, the strongest family history of asthma and the lowest baseline FEV_1 percent predicted values compared to white and Hispanic subjects (39). Third, it is also important to note that the results obtained from cluster analysis may be dependent on the cluster technique used. Because a cluster analysis will always find patterns in data, regardless of the organization of the dataset, there is not a single “best” method for performing the analysis. Thus the inclusion of more children would likely have resulted in further sub-clustering within our four identified clusters. For this reason, these results must be interpreted within the larger clinical context. While all children in this study were stable at the time of assessment, the stability of these clusters over time and in response to different or novel asthma interventions (including pharmacologic therapies) is unknown. Thus the predictive aspects of these clusters are also unclear and will require validation in future longitudinal studies of childhood asthma. A separate validation in a different and perhaps larger sample of children with severe asthma would also be useful to better understand the heterogeneity of the disorder.

In conclusion, we have identified four clusters of childhood asthma in the NIH/NHLBI SARP. Foremost, these data emphasize that asthma, particularly severe asthma, is a highly heterogeneous disorder. Importantly, no identified cluster corresponded in entirety to definitions of severe asthma proposed by national and international guidelines or the ATSWhile this may reflect our variable selection, the consensus-based definitions of severe asthma may also require further validation in children. Whereas the GINA and NAEPP criteria for severe asthma are based primarily on symptoms and lung function, our pediatric asthma clusters were determined as much by the magnitude of atopy and duration of asthma as by airflow limitation and hyperinflation. Exhaled nitric oxide concentrations and the age of asthma symptom onset were also differentiating features of the clusters, while healthcare utilization was a lesser determinant. These data highlight the complexity and heterogeneity of childhood asthma and support the need for additional studies, including validation of these clusters in other samples of children with severe asthma. If these clusters are indeed clinically meaningful, then cluster analysis and other unsupervised approaches may ultimately assist with the refinement of current guidelines for asthma diagnosis and treatment in children.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

The Severe Asthma Research Program (SARP) is a multicenter asthma research group funded by the NHLBI and consisting of the following contributors (Principal Investigators are marked with an asterisk): *Brigham & Women's Hospital* - Elliot Israel*, Bruce D. Levy, Michael E. Wechsler, Shamsah Kazani, Gautham Marigowda; *Cleveland Clinic* - Serpil C. Erzurum*, Raed A. Dweik, Suzy A.A. Comhair, Emmea Cleggett-Mattox, Deepa George,

Marcelle Baaklini, Daniel Laskowski; *Emory University* - Anne M. Fitzpatrick, Denise Whitlock, Shanae Wakefield; *Imperial College School of Medicine* - Kian Fan Chung*, Mark Hew, Patricia Macedo, Sally Meah, Florence Chow; *University of Iowa* – Eric Hoffman*, Janice Cook-Granroth; *University of Pittsburgh* - Sally E. Wenzel*, Fernando Holguin, Silvana Balzar, Jen Chamberlin; *University of Texas-Medical Branch* - William J. Calhoun*, Bill T. Ameredes; *University of Virginia* - Benjamin Gaston*, W. Gerald Teague*, Denise Thompson-Batt; *University of Wisconsin* - William W. Busse*, Nizar Jarjour, Ronald Sorkness, Sean Fain, Gina Crisafi; *Wake Forest University* - Eugene R. Bleecker*, Deborah Meyers, Wendy Moore, Stephen Peters, Rodolfo M. Pascual, Annette Hastie, Gregory Hawkins, Jeffrey Krings, Regina Smith; *Washington University in St Louis* - Mario Castro*, Leonard Bacharier, Jaime Tarsi; *Data Coordinating Center* - Douglas Curran-Everett*, Ruthie Knowles, Maura Robinson, Lori Silveira; *NHLBI* - Patricia Noel, Robert Smith

This work was supported by National Institute of Health grants RO1 HL069170, RO1 HL069167, RO1 HL069174, RO1 HL69149, RO1 HL091762 and was supported 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

ABBREVIATIONS

ATS	American Thoracic Society
FEV_1	Forced expiratory volume in one second
FVC	Forced vital capacity
GINA	Global Initiative for Asthma
ICS	Inhaled corticosteroids
IgE	Immunoglobulin E
LABA	Long-acting beta-agonist
NAEPP	National Asthma Education and Prevention Program
NHLBI	National Heart, Lung and Blood Institute
PC20	Provocative dose (of methacholine) required to drop FEV_1 by ≥20%
RV	Residual volume
Raw	Airway resistance
SARP	NHLBI Severe Asthma Research Program
TLC	Total lung capacity

REFERENCES

1. Lemanske RF Jr, Busse WW. Asthma: clinical expression and molecular mechanisms. J Allergy Clin Immunol. 2010; 125:S95–S102. [PubMed: 20176271]
2. Long-term effects of budesonide or nedocromil in children with asthma. The Childhood Asthma Management Program Research Group. N Engl J Med. 2000; 343:1054–1063. [PubMed: 11027739]
3. Expert Panel Report 3 (EPR-3): Guidelines for the Diagnosis and Management of Asthma-Summary Report 2007. J Allergy Clin Immunol. 2007; 120:S94–S138. [PubMed: 17983880]
4. Fitzpatrick AM, Gaston BM, Erzurum SC, Teague WG. Features of severe asthma in school-age children: Atopy and increased exhaled nitric oxide. J Allergy Clin Immunol. 2006; 118:1218–1225. [PubMed: 17157650]
5. Bossley CJ, Saglani S, Kavanagh C, Payne DN, Wilson N, Tsartsali L, et al. Corticosteroid responsiveness and clinical characteristics in childhood difficult asthma. Eur Respir J. 2009; 34:1052–1059. [PubMed: 19541710]
6. Chipps BE, Szefler SJ, Simons FE, Haselkorn T, Mink DR, Deniz Y, et al. Demographic and clinical characteristics of children and adolescents with severe or difficult-to-treat asthma. J Allergy Clin Immunol. 2007; 119:1156–1163. [PubMed: 17397912]

7. Godard P, Chanez P, Siraudin L, Nicoloyannis N, Duru G. Costs of asthma are correlated with severity: a 1-yr prospective study. Eur Respir J. 2002; 19:61–67. [PubMed: 11843329]
8. Sullivan SD, Rasouliyan L, Russo PA, Kamath T, Chipps BE. Extent, patterns, and burden of uncontrolled disease in severe or difficult-to-treat asthma. Allergy. 2007; 62:126–133. [PubMed: 17298420]
9. Bateman ED, Hurd SS, Barnes PJ, Bousquet J, Drazen JM, FitzGerald M, et al. Global strategy for asthma management and prevention: GINA executive summary. Eur Respir J. 2008; 31:143–178. [PubMed: 18166595]
10. Bush A, Menzies-Gow A. Phenotypic differences between pediatric and adult asthma. Proc Am Thorac Soc. 2009; 6:712–719. [PubMed: 20008882]
11. Spahn JD, Cherniack R, Paull K, Gelfand EW. Is forced expiratory volume in one second the best measure of severity in childhood asthma? Am J Respir Crit Care Med. 2004; 169:784–786. [PubMed: 14754761]
12. Bacharier LB, Strunk RC, Mauger D, White D, Lemanske RF, Sorkness CA. Classifying asthma severity in children: Mismatch between symptoms, medication use, and lung function. Am J Respir Crit Care Med. 2004; 170:426–432. [PubMed: 15172893]
13. Sharek PJ, Mayer ML, Loewy L, Robinson TN, Shames RS, Umetsu DT, et al. Agreement among measures of asthma status: a prospective study of low-income children with moderate to severe asthma. Pediatrics. 2002; 110:797–804. [PubMed: 12359798]
14. Lang AM, Konradsen J, Carlsen KH, Sachs-Olsen C, Mowinckel P, Hedlin G, et al. Identifying problematic severe asthma in the individual child--does lung function matter? Acta Paediatr. 2010; 99:404–410. [PubMed: 20040073]
15. Proceedings of the ATS workshop on refractory asthma: current understanding, recommendations, and unanswered questions. American Thoracic Society. Am J Respir Crit Care Med. 2000; 162:2341–2351. [PubMed: 11112161]
16. Liard R, Leynaert B, Zureik M, Beguin FX, Neukirch F. Using Global Initiative for Asthma guidelines to assess asthma severity in populations. Eur Respir J. 2000; 16:615–620. [PubMed: 11106201]
17. Von Mutius E. Presentation of new GINA guidelines for paediatrics. The Global Initiative on Asthma. Clin Exp Allergy. 2000; 30 Suppl 1:6–10. [PubMed: 10849467]
18. Weatherall M, Travers J, Shirtcliffe PM, Marsh SE, Williams MV, Nowitz MR, et al. Distinct clinical phenotypes of airways disease defined by cluster analysis. Eur Respir J. 2009; 34:812–818. [PubMed: 19357143]
19. Moore WC, Meyers DA, Wenzel SE, Teague WG, Li H, Li X, et al. Identification of asthma phenotypes using cluster analysis in the Severe Asthma Research Program. Am J Respir Crit Care Med. 2010; 181:315–323. [PubMed: 19892860]
20. Haldar P, Pavord ID, Shaw DE, Berry MA, Thomas M, Brightling CE, et al. Cluster analysis and clinical asthma phenotypes. Am J Respir Crit Care Med. 2008; 178:218–224. [PubMed: 18480428]
21. Moore WC, Bleecker ER, Curran-Everett D, Erzurum SC, Ameredes BT, Bacharier L, et al. Characterization of the severe asthma phenotype by the National Heart, Lung, and Blood Institute's Severe Asthma Research Program. J Allergy Clin Immunol. 2007; 119:405–413. [PubMed: 17291857]
22. ATS/ERS recommendations for standardized procedures for the online and offline measurement of exhaled lower respiratory nitric oxide and nasal nitric oxide, 2005. Am J Respir Crit Care Med. 2005; 171:912–930. [PubMed: 15817806]
23. Wang X, Dockery DW, Wypij D, Fay ME, Ferris BG Jr. Pulmonary function between 6 and 18 years of age. Pediatr Pulmonol. 1993 Feb; 15(2):75–88. [PubMed: 8474788]
24. Crapo RO. Spirometry: quality control and reproducibility criteria. Am Rev Respir Dis. 1991; 143:1212–1213. [PubMed: 2048802]
25. Fisher RA. The use of multiple measurements in taxonomic problems. Annals Eugenics. 1936; 7:179–188.
26. Fitzpatrick AM, Higgins M, Holguin F, Brown LA, Teague WG. The molecular phenotype of severe asthma in children. J Allergy Clin Immunol. 2010; 125:851–857. [PubMed: 20371397]

27. Buchvald F, Baraldi E, Carraro S, Gaston B, De Jongste J, Pijnenburg MW, et al. Measurements of exhaled nitric oxide in healthy subjects age 4 to 17 years. J Allergy Clin Immunol. 2005; 115:1130–1136. [PubMed: 15940124]
28. Miranda C, Busacker A, Balzar S, Trudeau J, Wenzel SE. Distinguishing severe asthma phenotypes: role of age at onset and eosinophilic inflammation. J Allergy Clin Immunol. 2004; 113:101–108. [PubMed: 14713914]
29. Rasmussen F, Taylor DR, Flannery EM, Cowan JO, Greene JM, Herbison GP, et al. Risk factors for airway remodeling in asthma manifested by a low postbronchodilator FEV1/vital capacity ratio: a longitudinal population study from childhood to adulthood. Am J Respir Crit Care Med. 2002; 165:1480–1488. [PubMed: 12045120]
30. Sears MR, Greene JM, Willan AR, Wiecek EM, Taylor DR, Flannery EM, et al. A longitudinal, population-based, cohort study of childhood asthma followed to adulthood. N Engl J Med. 2003; 349:1414–1422. [PubMed: 14534334]
31. Stern DA, Morgan WJ, Halonen M, Wright AL, Martinez FD. Wheezing and bronchial hyper-responsiveness in early childhood as predictors of newly diagnosed asthma in early adulthood: a longitudinal birth-cohort study. Lancet. 2008; 372:1058–1064. [PubMed: 18805334]
32. Phelan PD, Robertson CF, Olinsky A. The Melbourne Asthma Study: 1964–1999. J Allergy Clin Immunol. 2002; 109:189–194. [PubMed: 11842286]
33. Covar RA, Spahn JD, Murphy JR, Szefler SJ. Progression of asthma measured by lung function in the childhood asthma management program. Am J Respir Crit Care Med. 2004; 170:234–241. [PubMed: 15028558]
34. Strunk RC, Weiss ST, Yates KP, Tonascia J, Zeiger RS, Szefler SJ. Mild to moderate asthma affects lung growth in children and adolescents. J Allergy Clin Immunol. 2006; 118:1040–1047. [PubMed: 17088127]
35. Reddel H, Ware S, Marks G, Salome C, Jenkins C, Woolcock A. Differences between asthma exacerbations and poor asthma control. Lancet. 1999; 353:364–369. [PubMed: 9950442]
36. Reddel HK, Taylor DR, Bateman ED, Boulet LP, Boushey HA, Busse WW, et al. An official American Thoracic Society/European Respiratory Society statement: asthma control and exacerbations: standardizing endpoints for clinical asthma trials and clinical practice. Am J Respir Crit Care Med. 2009; 180:59–99. [PubMed: 19535666]
37. Bateman ED, Reddel HK, Eriksson G, Peterson S, Ostlund O, Sears MR, et al. Overall asthma control: the relationship between current control and future risk. J Allergy Clin Immunol. 2010; 125:600–608. [PubMed: 20153029]
38. Carroll CL, Schramm CM, Zucker AR. Severe exacerbations in children with mild asthma: characterizing a pediatric phenotype. J Asthma. 2008; 45:513–517. [PubMed: 18612906]
39. Lester LA, Rich SS, Blumenthal MN, Togias A, Murphy S, Malveaux F, et al. Ethnic differences in asthma and associated phenotypes: collaborative study on the genetics of asthma. J Allergy Clin Immunol. 2001; 108:357–362. [PubMed: 11544453]

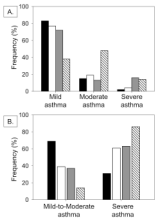

Figure 1.

(A) Frequency of children with mild, moderate and severe asthma defined by NAEPP or GINA guidelines and (B) frequency of children with mild-to-moderate and severe asthma defined by ATS criteria in each cluster (Cluster 1, black bars; Cluster 2, white bars; Cluster 3, gray bars; Cluster 3, hatched bars).

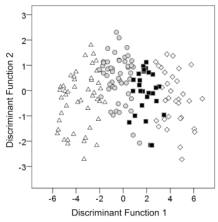

Figure 2.

Scatterplot of the discriminant functions generated from discriminant analysis of asthma duration, the extent of asthma controller therapy, and baseline FEV_1 percent predicted values. Each data point represents a single subject. The plot depicts clustering and separation of Cluster 1 (white triangles), Cluster 2 (gray circles), Cluster 3 (black squares), and Cluster 4 (white diamonds) using these three variables.

Table I

Features of the sample. Severe asthma was defined according to ATS criteria (4,14). Data represent the mean ± SD or the frequency (%), unless otherwise specified.

	Mild-to-Moderate n = 72	Severe Asthma n = 89	p-value
Age in years	11 ± 3	11 ± 3	0.879
Male	40 (56)	49 (55)	0.571
Caucasian	38 (53)	24 (27)	0.001
African American	27 (38)	56 (63)	
Other			
Emergency room visit (previous year)	22 (31)	64 (72)	< 0.001
Hospitalization (previous year)	6 (8)	49 (55)	< 0.001
History of intubation (ever)	2 (3)	22 (25)	0.002
Parental history of asthma	41 (58)	62 (70)	0.022
History of atopic dermatitis	35 (49)	54 (61)	0.114
History of pneumonia	30 (42)	57 (64)	0.001
History of sinusitis	26 (31)	35 (39)	0.255
History of gastroesophageal reflux	8 (11)	31 (35)	0.001
Daily ICS dose (μg fluticasone equivalent per day)	227 ± 211	893 ± 225	< 0.001
No ICS	18 (25)	0	< 0.001
Montelukast	38 (53)	88 (99)	< 0.001
ICS + LABA	31 (43)	77 (87)	< 0.001
Daily short-acting bronchodilators	17 (24)	54 (61)	< 0.001
Daily oral corticosteroids	0	13 (15)	< 0.001
Number of aero-allergen skin prick responses (out of 12), median (range)[1]	1 (0 – 9)	4 (0 – 12)	< 0.001
Serum IgE (kU/L), median (range)[1]	142 (2 – 3484)	344 (3 – 5458)	< 0.001
Blood eosinophils (%), median (range)[1]	3.9 (0.3 – 23.8)	4.4 (0.1 – 23.6)	0.684
Baseline FEV_1 (% predicted)	94 ± 14	85 ± 21	0.002
Best FEV_1 (% predicted)	104 ± 14	98 ±19	0.021
Methacholine (PC_{20}), median (range)[1]	2.1 (0.1 – 24.3)	0.9 (0.1 – 23.1)	0.047

[1]Data were logarithmically transformed prior to analysis

J Allergy Clin Immunol. Author manuscript; available in PMC 2012 February 1.

Table II

Demographic and atopic features of subjects. Data represent the mean ± SD or the frequency (%), unless otherwise specified.

	Total sample (n = 161)	Cluster 1 Late-onset symptomatic asthma with normal lung function (n = 48)	Cluster 2 Early-onset atopic asthma with normal lung function (n = 52)	Cluster 3 Early-onset atopic asthma with mild airflow limitation (n = 32)	Cluster 4 Early-onset atopic asthma with advanced airflow limitation (n = 29)	p-value[1]
Age in years	11 ± 3	9 ± 3	10 ± 2	15 ± 2	12 ± 2	< 0.001
Male	89 (55)	22 (46)	27 (52)	21 (66)	19 (66)	0.205
Caucasian	62 (39)	26 (54)	25 (48)	8 (25)	3 (10)	< 0.001
African American	83 (52)	15 (31)	25 (48)	19 (59)	24 (83)	
Other	14 (9)	7 (15)	2 (4)	5 (16)	2 (7)	
Age of asthma diagnosis (months)	38 ± 39	73 ± 46	30 ± 29	14 ± 12	19 ± 17	< 0.001
Duration of asthma (months)	99 ± 51	38 ± 23	95 ± 15	170 ± 15	129 ± 13	< 0.001
Body mass index >90th percentile	47 (29)	13 (27)	16 (31)	12 (38)	6 (21)	0.522
Parental history of asthma	103 (64)	29 (60)	33 (64)	19 (59)	22 (76)	0.398
History of atopic dermatitis	89 (55)	24 (50)	29 (56)	15 (47)	21 (72)	0.179
History of pneumonia	87 (54)	23 (48)	27 (52)	22 (69)	15 (52)	0.299
History of sinusitis	61 (38)	16 (33)	14 (27)	21 (66)	10 (35)	0.003
History of gastroesophageal reflux	39 (24)	7 (15)	13 (25)	11 (34)	8 (28)	0.028
Number of skin prick responses (out of 12), median (range)[2]	3 (0 – 12)	1 (0 – 12)	3 (0 – 12)	4 (0 – 10)	3 (0 – 8)	0.007
Serum IgE (kU/L), median (range)[2]	548 (2 – 5458)	105 (2 – 3484)	405 (3 – 3511)	216 (25 – 5458)	361 (7 – 1800)	0.005
Blood eosinophils (%) median (range)[2]	4.1 (0.1 – 23.8)	2.9 (0.4 – 13.2)	5.5 (0.4 – 23.8)	3.9 (0.2 – 13.9)	5.4 (0.1 – 23.6)	0.053
Exhaled nitric oxide						
Offline (ppb, n = 80)[2]	9 (2 – 46)	7 (2 – 30)	9 (4 – 31)	12 (4 – 27)	14 (7 – 46)	0.021

	Total sample (n = 161)	Cluster 1 Late-onset symptomatic asthma with normal lung function (n = 48)	Cluster 2 Early-onset atopic asthma with normal lung function (n = 52)	Cluster 3 Early-onset atopic asthma with mild airflow limitation (n = 32)	Cluster 4 Early-onset atopic asthma with advanced airflow limitation (n = 29)	p-value[1]
Online (ppb, n = 81)[2]	20 (3 – 260)	12 (3 – 63)	16 (4 – 74)	21 (6 – 260)	30 (4 – 169)	0.041

[1] p-value from analysis of variance or Chi-square analysis between the four clusters.

[2] Data were logarithmically transformed prior to analysis

Table III

Medication use and healthcare utilization. Data represent the mean ± SD or the frequency (%).

	Total sample (n = 161)	Cluster 1 Late-onset symptomatic asthma with normal lung function (n = 48)	Cluster 2 Early-onset atopic asthma with normal lung function (n = 52)	Cluster 3 Early-onset atopic asthma with mild airflow limitation (n = 32)	Cluster 4 Early-onset atopic asthma with advanced airflow limitation (n = 29)	p-value[1]
No ICS	17 (11)	11 (23)	1 (2)	5 (16)	0	< 0.001
Low-to moderate dose ICS	54 (34)	21 (44)	20 (38)	7 (22)	5 (17)	
High-dose ICS	90 (56)	16 (33)	31 (59)	20 (63)	24 (83)	
Daily ICS dose (μg fluticasone)[1]	587 ± 393	399 ± 332	622 ± 354	623 ± 450	829 ± 364	< 0.001
Daily beta-agonist use	77 (44)	10 (21)	27 (52)	18 (56)	16 (55)	0.002
Controller medications						
No controller medications	14 (9)	9 (19)	2 (4)	3 (9)	0	0.015
Montelukast only	6 (4)	2 (4)	0	4 (13)	0	0.018
ICS only	13 (8)	6 (13)	4 (8)	1 (3)	2 (7)	0.496
ICS + LABA or montelukast	31 (19)	16 (33)	9 (17)	3 (9)	3 (10)	0.021
ICS + LABA + montelukast	97 (60)	15 (31)	37 (71)	21 (66)	24 (83)	< 0.001
Omalizumab	3 (2)	0	2 (4)	0	1 (3)	0.386
Oral corticosteroids	12 (7)	0	4 (8)	5 (16)	3 (10)	0.062
At least one oral corticosteroid burst	120 (75)	31 (65)	41 (79)	23 (72)	26 (90)	0.128
Number of oral corticosteroid bursts[2]	2 ± 3	2 ± 2	3 ± 3	4 ± 4	3 ± 2	0.018
Healthcare utilization (previous year)[2]						
None	22 (14)	6 (13)	6 (12)	9 (28)	1 (3)	0.037
Physician visit for acute symptoms	149 (93)	42 (88)	46 (88)	23 (72)	28 (97)	0.037
Emergency room visit	87 (54)	20 (42)	32 (62)	18 (56)	17 (59)	0.217
Hospital admission	55 (3)	11 (23)	17 (33)	13 (41)	14 (48)	0.116
ICU admission	33 (21)	8 (17)	10 (19)	7 (22)	8 (28)	0.702

	Total sample (n = 161)	Cluster 1 Late-onset symptomatic asthma with normal lung function (n = 48)	Cluster 2 Early-onset atopic asthma with normal lung function (n = 52)	Cluster 3 Early-onset atopic asthma with mild airflow limitation (n = 32)	Cluster 4 Early-onset atopic asthma with advanced airflow limitation (n = 29)	p-value[1]
Intubation (ever)	19 (15)	0	9 (21)	4 (20)	6 (24)	0.018

[1] p-value from Chi-square analysis between the four clusters.

[2] Data are mutually exclusive (subjects were ranked by the most severe level of healthcare utilization)

Table IV

Lung function variables. Data represent the mean ± SD or the frequency (%), unless otherwise specified.

	Total sample (n = 161)	Cluster 1 Late-onset symptomatic asthma with normal lung function (n = 48)	Cluster 2 Early-onset atopic asthma with normal lung function (n = 52)	Cluster 3 Early-onset atopic asthma with mild airflow limitation (n = 32)	Cluster 4 Early-onset atopic asthma with advanced airflow limitation (n = 29)	p-value[1]
Baseline spirometry						
FVC (% predicted)	99 ± 14	102 ± 15	101 ± 11	93 ± 18	92 ± 12	0.002
FEV_1 (% predicted)	89 ± 19	96 ± 19	91 ±15	84 ± 21	75 ± 16	< 0.001
FEV_1/FVC	0.78 ± 0.11	0.82 ± 0.11	0.79 ± 0.09	0.72 ± 0.10	0.73 ± 0.10	< 0.001
Post-bronchodilator spirometry						
FVC (% predicted)	105 ± 16	109 ± 16	105 ± 13	100 ± 20	99 ± 17	0.038
FEV_1 (% predicted)	101 ± 17	109 ± 19	103 ±13	97 ± 19	90 ± 12	< 0.001
FEV_1/FVC	0.84 ± 0.08	0.86 ± 0.08	0.86 ± 0.06	0.82 ± 0.08	0.79 ± 0.11	0.003
Change in % predicted FEV_1	15 ± 16	13 ± 15	14 ± 14	18 ± 19	20 ± 19	0.220
Baseline lung volumes						
TLC (% predicted)	99 ± 13	102 ± 13	100 ± 11	92 ± 11	95 ± 16	0.034
RV (% predicted)	127 ± 49	122 ± 49	126 ± 42	122 ± 53	139 ± 58	0.618
RV/TLC	0.28 ± 0.11	0.26 ± 0.08	0.26 ± 0.08	0.29 ± 0.15	0.34 ± 0.15	0.025
Raw (% predicted)	132 ± 68	108 ± 46	120 ± 63	185 ± 68	154 ± 84	< 0.001
Post-bronchodilator lung volumes						
TLC (% predicted)	98 ± 12	99 ± 10	102 ± 11	91 ± 9	94 ± 14	0.004
RV (% predicted)	116 ± 39	115 ± 31	116 ± 46	115 ± 49	116 ± 34	0.998
RV/TLC	0.25 ± 0.08	0.26 ± 0.07	0.24 ± 0.08	0.27 ± 0.14	0.26 ± 0.07	0.613
Raw (% predicted)	83 ± 33	74 ± 36	79 ± 36	99 ± 41	83 ± 33	0.170
Methacholine PC_{20} (mg), median (range)[2]	1.32 (0.16 – 23.14)	1.20 (0.09 – 3.05)	1.13 (0.12 – 3.02)	0.43 (0.06 – 3.18)	0.63 (0.25 – 2.21)	0.018

[1] p-value from analysis of variance between the four clusters.

[2]Data were logarithmically transformed prior to analysis.