Asthma phenotypes in inner-city children

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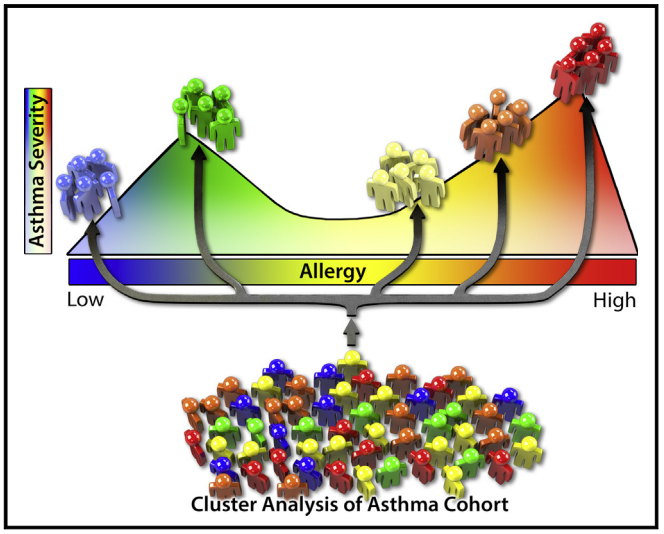
GRAPHICAL ABSTRACT



Background: Children with asthma in low-income urban areas have high morbidity. Phenotypic analysis in these children is lacking, but may identify characteristics to inform successful tailored management approaches.

Objective: We sought to identify distinct asthma phenotypes among inner-city children receiving guidelines-based management.

Methods: Nine inner-city asthma consortium centers enrolled 717 children aged 6 to 17 years. Data were collected at baseline and prospectively every 2 months for 1 year. Participants' asthma and rhinitis were optimally managed by study physicians on the basis of guidelines. Cluster analysis using 50 baseline and 12 longitudinal variables was performed in 616 participants completing 4 or more follow-up visits.

Results: Five clusters (designated A through E) were distinguished by indicators of asthma and rhinitis severity, pulmonary physiology, allergy (sensitization and total serum

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IgE), and allergic inflammation. In comparison to other clusters, cluster A was distinguished by lower allergy/inflammation, minimally symptomatic asthma and rhinitis, and normal pulmonary physiology. Cluster B had highly symptomatic asthma despite high step-level treatment, lower allergy and inflammation, and mildly altered pulmonary physiology. Cluster C had minimally symptomatic asthma and rhinitis, intermediate allergy and inflammation, and mildly impaired pulmonary physiology. Clusters D and E exhibited progressively higher asthma and rhinitis symptoms and allergy/inflammation. Cluster E had the most symptomatic asthma while receiving high step-level treatment and had the highest total serum IgE level (median, 733 kU/L), blood eosinophil count (median, 400 cells/mm^3), and allergen sensitizations (15 of 22 tested). Conclusions: Allergy distinguishes asthma phenotypes in urban children. Severe asthma often coclusters with highly allergic children. However, a symptomatic phenotype with little allergy or allergic inflammation was identified. (J Allergy Clin Immunol 2016;138:1016-29.)

Key words: *Allergen sensitization, allergy, airway inflammation, bronchial hyperresponsiveness, asthma phenotypes, asthma severity, IgE, hierarchical cluster, inner-city asthma, rhinitis*

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Hallmarks of asthma include varying degrees of episodic dyspnea, wheezing, or coughing, in association with airway obstruction, bronchial hyperresponsiveness (BHR), and airway inflammation. Considering the heterogeneity of features, severity, and therapeutic responses inherent in asthma, characterizing discrete phenotypes is essential to improving and personalizing asthma care. Unsupervised cluster analysis, a statistical method commonly applied in clinical studies to group participants with similar characteristics, has been used to identify discrete asthma phenotypes in several cohorts of varying ages, demographic characteristics, and underlying asthma severity.[1-8]

Children living in low-income urban regions of the United States have high morbidity and asthma severity.[9] Little is known about the asthma phenotypes in these at-risk children and whether there are phenotypes that are less likely to respond to specific interventions, including standard guidelines-based therapy. To meet this need, we designed and conducted the National Institutes of Health/National Institute of Allergy and Infectious Diseases–sponsored Inner-City Asthma Consortium Asthma Phenotypes in the Inner City (APIC) study. In this report, we present our findings from an unsupervised cluster analysis.

Abbreviations used
APIC: Asthma Phenotypes in the Inner City
BHR: Bronchial hyperresponsiveness
CAMP: Childhood Asthma Management Program
FENO: Fractional exhaled nitric oxide
FVC: Forced vital capacity
HCA: Hierarchical clustering algorithm
PC_{20}: Provocative concentration to induce a 20% decline in FEV_1

METHODS

Study population

The APIC study was designed as a prospective, epidemiological investigation of 6- to 17-year-old children with asthma from low-income areas of 9 US cities (Baltimore, Md; Boston, Mass; Chicago, Ill; Cincinnati, Ohio; Dallas, Tex; Denver, Colo; Detroit, Mich, New York, NY, and Washington, DC). The protocol was approved by institutional review boards from each center, and written informed consent was obtained from the legal guardians of participating children. Assent was obtained from 561 children according to institutional review board requirements. Between August 2011 and September 2013, 845 children were screened, 795 met eligibility criteria, and 717 completed the study entry visit (V0). These children were scheduled for bimonthly visits for 1 year (V1-V6) and received guidelines-based management of their asthma and rhinitis as well as additional evaluations. Completion of 4 or more postenrollment visits was required for inclusion in this cluster analysis. For asthma, a predefined, computerized National Asthma Education and Prevention Program Expert Panel Report-3–based treatment algorithm was used by the study clinicians to adjust the participant's controller regimen at each visit on the basis of asthma symptoms, spirometry results, and recent exacerbations.[10] For rhinitis, medications were prescribed in accordance with the Allergic Rhinitis and its Impact on Asthma recommendations.[11] The frequency and degree of bothering of nasal symptoms were captured and an algorithm was used to adjust treatment. Detailed descriptions of asthma and rhinitis management algorithms, data collection, and scoring systems for the APIC study are included in Pongracic et al.[12]

Study assessments

Each participant was characterized using a set of 50 baseline variables measured at screening or V0 as well as the within-participant mean and variance of 6 asthma severity variables measured at every visit between V0 and V6 (12 variables). These variables were selected for inclusion on the basis of a review of previous asthma cluster analyses in the literature and a consensus among APIC investigators.

A complete list of the variables entered into the hierarchical clustering algorithm (HCA) is provided in Table E1 in this article's Online Repository at www.jacionline.org. The variables were representative of several domains that were designated solely for descriptive purposes: demographic characteristics, family history, allergy history, asthma history, environmental exposures, body mass index, serum vitamin D level, stress, allergen sensitization, allergic inflammation, pulmonary physiology, asthma severity, and rhinitis.

Statistical methods

Variable reduction. Variables representing specific allergen sensitization through skin prick test or specific IgE were grouped together using an HCA based on Pearson correlations.[13] Using the result of the cluster analysis as a guide, allergens were grouped into the following 7 categories: molds, dust mites, cockroaches, rodents, pets, pollen/peanut, and foods. Instead of using separate variables for each individual allergen, separate variables representing sensitization in each of the 7 categories were created and used as variables in the clustering algorithm.

Hierarchical clustering analysis. R version 3.2.2 was used for analyses. Before analysis, any missing data at screening or V0 were imputed using a single imputation based on a fully conditional specification approach. Unless otherwise noted, all results were based on imputed data. To identify clusters of participants who were similar to each other based on the variables of interest, an agglomerative HCA was used. This algorithm works by measuring similarity between 2 participants, or 2 groups of participants, using a distance metric such that the distance between 2 participants who are alike is small whereas the distance between 2 participants who are dissimilar is large. In this case, distance between any 2 participants was calculated using a tree-based clustering algorithm that addresses multicollinearity among variables[14] while distance between any 2 clusters was calculated using a Ward's minimum-variance linkage clustering approach.[15] This algorithm was selected because it has been shown to have better performance than many commonly used algorithms for HCA in data sets with a large number of continuous and categorical variables that contain outliers, have skewed distribution, or are known to be highly collinear.[16]