Childhood asthma clusters and response to therapy in clinical trials

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Background: Childhood asthma clusters, or subclasses, have been developed by computational methods without evaluation of clinical utility.
Objective: To replicate and determine whether childhood asthma clusters previously identified computationally in the Severe Asthma Research Program (SARP) are associated with treatment responses in Childhood Asthma Research and Education (CARE) Network clinical trials.
Methods: A cluster assignment model was determined by using SARP participant data. A total of 611 participants 6 to 18 years old from 3 CARE trials were assigned to SARP pediatric clusters. Primary and secondary outcomes were analyzed by cluster in each trial.
Results: CARE participants were assigned to SARP clusters with high accuracy. Baseline characteristics were similar between SARP and CARE children of the same cluster. Treatment response in CARE trials was generally similar across clusters. However, with the caveat of a smaller sample size, children in the early-onset/severe-lung function cluster had best response with fluticasone/salmeterol (64% vs 23% 2.5× fluticasone and 13% fluticasone/montelukast in the Best ADd-on Therapy Giving Effective Responses trial; $P = .011$) and children in the early-onset/comorbidity cluster had the least clinical efficacy to treatments (eg, −0.076% change in FEV_1 in the Characterizing Response to Leukotriene Receptor Antagonist and Inhaled Corticosteroid trial).
Conclusions: In this study, we replicated SARP pediatric asthma clusters by using a separate, large clinical trials network. Early-onset/severe-lung function and early-onset/comorbidity clusters were associated with differential and limited response to therapy, respectively. Further prospective study of therapeutic response by cluster could provide new insights into childhood asthma treatment. (J Allergy Clin Immunol 2014;133:363-9.)

Key words: *Asthma, clustering, clinical trials, replication, pediatric, therapy response*

Asthma is likely not a single disease, but rather a syndrome comprising multiple complex phenotypes.[1] Researchers have recognized this and have attempted to subclassify asthma by using expert opinion or computational techniques such as clustering.

Expert panels have also subclassified asthma. For example, the National Asthma Education and Prevention Program Expert

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Abbreviations used
BADGER: Best ADd-on Therapy Giving Effective Responses
CARE: Childhood Asthma Research and Education
CLIC: Characterizing Response to Leukotriene Receptor Antagonist and Inhaled Corticosteroid
LDA: Linear discriminant analysis
PACT: Pediatric Asthma Controller Trial
QDA: Quadratic discriminant analysis
SARP: Severe Asthma Research Program

Panel Report 3[2] has classified asthma severity as intermittent, mild-persistent, moderate-persistent, and severe-persistent.[2] Once therapy is initiated, asthma control is defined on the basis of symptoms and lung function. A similar classification has been used in the Global Initiative for Asthma.[3] In both the Expert Panel Report 3 and the Global Initiative for Asthma, asthma phenotypes, applicable to large patient groups, are defined on the basis of the amount of therapy necessary to achieve adequate control. However, one phenotype may consist of subphenotypes, each with a different optimal treatment.

While asthma guidelines have led to improvements in asthma care, it has been argued that they do not reflect the heterogeneous nature of the disease. Miller et al[4] identified a lack of classification agreement among guidelines, physician assessment, and health care usage. Wenzel[1] proposed new asthma phenotype definitions based on clinical history, triggers, and inflammatory markers.

There is extensive literature on asthma clustering for phenotype identification using clinical, genetic, and imaging data.[5-13] For example, Moore et al[6] studied adults from the Severe Asthma Research Program (SARP) and identified 5 adult asthma clusters. Few studies have focused on clustering in childhood asthma. Fitzpatrick et al[14] studied 6- to 17-year-old SARP children (N = 161), roughly one-half with severe asthma. The authors described 4 pediatric clusters distinct from the adult clusters: cluster 1 had late-onset (mean age, 73 months) symptomatic asthma with normal lung function (late-onset/normal-lung); cluster 2 had early-onset (mean age, 30 months) atopic asthma with mild airflow limitation (early-onset/normal-lung); cluster 3 had earliest-onset (mean age, 14 months) atopic asthma with mild airflow limitation and greater comorbidity (early-onset/comorbidity); and cluster 4 had early-onset (mean age, 17 months) atopic asthma with advanced airflow limitation and the greatest medication use (early-onset/severe-lung). The SARP analysis[14] was intended to identify pediatric asthma clusters but was unable to evaluate the clinical utility of this differentiation.

Although clustering methodology has provided an additional perspective in asthma phenotypes, computationally derived phenotypes have not been evaluated for applicability to other asthma populations or clinical utility. Therefore, we used a large well-characterized population of children who participated in the Childhood Asthma Research and Education (CARE) Network clinical trials to determine, first, whether SARP pediatric asthma clusters could be replicated in a new population and, second, whether these clusters were associated with response to therapy.

METHODS

The study population consisted of 6- to 18-year-old children with asthma (N = 611) enrolled in 3 CARE Network clinical trials.[15-17] The trials are summarized in Table I. Briefly, the Pediatric Asthma Controller Trial (PACT)[16] was a 3-arm (1× fluticasone, 0.5× fluticasone plus salmeterol, or montelukast) double-blind study of children with mild-moderate asthma and used percentage of asthma control days as the primary outcome. The Characterizing Response to Leukotriene Receptor Antagonist and Inhaled Corticosteroid (CLIC)[15] trial was a crossover study comparing fluticasone 100 μg 1 inhalation twice daily and montelukast in children with mild-moderate asthma and used percent change in FEV_1 as its primary outcome. The Best ADd-on Therapy Giving Effective Responses (BADGER)[17] trial was a triple crossover study evaluating step-up therapy for children with mild-moderate asthma uncontrolled on low doses of inhaled corticosteroids (100 μg of fluticasone twice daily = 1×). Treatments included 2.5× fluticasone, 1× fluticasone plus salmeterol, and 1× fluticasone plus montelukast. The primary outcome was the best treatment based on a composite evaluation considering prednisone usage for exacerbations, asthma control days, and percent change in FEV_1. The present post hoc analysis was submitted to the University of Wisconsin Institutional Review Board and determined exempt from review.

Cluster assignment procedure

Linear discriminant analysis (LDA) was the model used by Fitzpatrick et al[14] to classify participants into SARP clusters with percent-predicted FEV_1, asthma duration, and number of controller medications as variables. The CARE data set, which the model would later be applied to, did not contain the number of controller medications. Therefore, leave-one-out cross-validation[18,19] was used to evaluate LDA and quadratic discriminant analysis (QDA) using SARP data FEV_1 and asthma duration variables. The LDA models with 2 and 3 variables were compared with the Wilks' lambda *F* test. (See Methods, LDA and QDA, in the Online Repository at www.jacionline.org for assumptions and risks of LDA and QDA.)

Compared with LDA, the QDA classification model had better performance and was used to assign CARE participants to SARP pediatric clusters. Missing data were replaced by using multiple imputation.[20] Three participants in the BADGER trial were missing FEV_1 percent-predicted measurements. (See Methods, Multiple imputation).

Demographics and run-in clinical characteristics were summarized with complete nonmissing data by using descriptive statistics and compared across clusters by using ANOVA for continuous measures and Fisher exact test for categorical measures.

Association of clusters with clinical trials outcome

We analyzed the association of clusters and treatment outcomes for the PACT, the CLIC trial, and the BADGER trial. Possible interactions between treatment and cluster were evaluated for the primary outcome and secondary outcomes (percent asthma control days, percent change in FEV_1, and time to first exacerbation) for each trial. Percent asthma control days in the PACT were analyzed by using a quasi-binomial generalized linear model with a logit link; percent asthma control days in the CLIC and BADGER trials were analyzed by using a quasi-binomial generalized estimating equations model with an independent working correlation matrix.[21] Linear regression models were used to analyze percent change in FEV_1 for the PACT; mixed-effect linear models were used to analyze repeated measurements of percent change in FEV_1 for CLIC and BADGER trials. Time to first exacerbation was analyzed by using a Cox proportional hazards model for all 3 studies; frailty models[22] accounted for repeated measurements on the same participant in CLIC and BADGER trials. Differences in best treatment by cluster in the BADGER trial were assessed by using a Monte Carlo test based on Pearson's χ^2 statistic for independence in a 2×2 table.

RESULTS

Classification model and assignment

For early-onset/normal-lung, late-onset/normal-lung, early-onset/comorbidity, and early-onset/severe-lung clusters, cross-validated QDA recall using SARP data with FEV_1 and asthma duration was 96%, 94%, 97%, and 90%, while precision was 96%, 94%, 94%, and 93%, respectively (see Table E1 in this