Can we predict fall asthma exacerbations? Validation of the seasonal asthma exacerbation index

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Background: A Seasonal Asthma Exacerbation Predictive Index (saEPI) was previously reported based on 2 prior National Institute of Allergy and Infectious Diseases Inner City Asthma Consortium trials.

Objective: This study sought to validate the saEPI in a separate trial designed to prevent fall exacerbations with omalizumab therapy.

Methods: The saEPI and its components were analyzed to characterize those who had an asthma exacerbation during the Preventative Omalizumab or Step-Up Therapy for Fall Exacerbations (PROSE) study. We characterized those inner-city children with and without asthma exacerbations in the fall period treated with guidelines-based therapy (GBT) in the absence and presence of omalizumab.

Results: A higher saEPI was associated with an exacerbation in both the GBT alone ($P < .001$; area under the curve, 0.76) and the GBT + omalizumab group ($P < .01$; area under the curve, 0.65). In the GBT group, younger age at recruitment, higher total IgE, higher blood eosinophil percentage and number, and higher treatment step were associated with those who had an exacerbation compared with those who did not. In the GBT + omalizumab group, younger age at recruitment, increased eosinophil number, recent exacerbation, and higher treatment step were also associated with those who had an exacerbation. The saEPI was associated with a high negative predictive value in both groups.

Conclusions: An exacerbation in children treated with GBT with or without omalizumab was associated with a higher saEPI along with higher markers of allergic inflammation, treatment step, and a recent exacerbation. Those that exacerbated on omalizumab had similar features with the exception of some markers of allergic sensitization, indicating a need to develop better markers to predict poor response to omalizumab therapy and alternative treatment strategies for children with these risk

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factors. The saEPI was able to reliably predict those children unlikely to have an asthma exacerbation in both groups. (J Allergy Clin Immunol 2017;140:1130-7.)

Key words: *Fall asthma exacerbation, omalizumab, guidelines-based therapy, asthma exacerbation predictors, Seasonal Asthma Exacerbation Predictive Index (saEPI)*

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Asthma is a chronic disease with widespread impact, affecting approximately 6.8 million children in the US in 2012, which is about 9.3% of the US population of children.[1] Asthma exacerbations are an increasingly important outcome in the determination of efficacy of asthma therapy, due to the high burden of disease, as well as significantly increased health care costs in patients who exacerbate.[2] Children in the inner city are at higher risk for asthma-related morbidity and mortality, for a variety of reasons.[3]

The National Institute of Allergy and Infectious Diseases has sponsored the Inner City Asthma Consortium (ICAC) since 1991, with a focus on reducing disparities for children with asthma residing in the inner-city.[4] A previous retrospective ICAC analysis used data from 2 previous trials (Asthma Control Evaluation [ACE][5] and Inner City Anti-IgE Therapy for Asthma [ICATA][6]) to identify season-specific risk factors for asthma exacerbations and to develop a Seasonal Asthma Exacerbation Predictive Index (saEPI) (see Table E1 in this article's Online Repository at www.jacionline.org).[7] This index consisted of 8 variables, which were each given a low, medium, or high point value. The composite index score was then used to determine exacerbation risk during each season (see the Methods for more detail). The fall season is a time of particular risk of exacerbation for children with asthma,[8-12] beginning about 2 weeks after the start of the school year.[13] The ICAC's Preventative Omalizumab or Step-up Therapy for Fall Exacerbations (PROSE) study[14] included a run-in period prior to the beginning of school, with a treatment period initiated at school start dates, affording a unique opportunity to reexamine the saEPI specifically for this fall period.

Our primary objective was to test the reliability of the saEPI in a population of children treated with the consensus Expert Panel Recommendations[15] (which we have called guidelines-based therapy or GBT), with and without the addition of omalizumab. Our hypothesis was that those with a high saEPI would be more likely to have an asthma exacerbation on GBT. Our secondary objectives were (1) to determine whether these predictors might change in the presence of anti-IgE, and (2) to determine whether providers with access to varying amounts of data would be able to use portions of the index to effectively predict the risk of an asthma exacerbation.

Abbreviations used
AUC: Area under the curve
FENO: Fractional exhaled nitric oxide
GBT: Guidelines-based therapy
ICAC: Inner City Asthma Consortium
ICS: Inhaled corticosteroids
NPV: Negative predictive value
PPV: Positive predictive value
ROC: Receiver operating characteristic
saEPI: Seasonal Asthma Exacerbation Predictive Index

METHODS

Study group

The PROSE study randomized 486 children with an asthma diagnosis (or asthma symptoms) for >1 year, an exacerbation requiring systemic corticosteroids or hospitalization within the prior 14 to 19 months, at least 1 positive skin test to a perennial allergen in the last year, residence in a low-income census tract, body weight and IgE appropriate for omalizumab dosing, and insurance coverage for asthma medications. Participants were randomized at a ratio of 3:3:1 to GBT + omalizumab arm (n = 223), a GBT + inhaled corticosteroid boost arm (n = 155), or GBT only arm (n = 89) (see PROSE study for further details).[14] The following data were collected during the run-in period: spirometry, fractional exhaled nitric oxide (FENO), total IgE, and blood eosinophils (percentage and total number). Response predictors were collected at randomization. For this analysis, participants from the GBT and GBT + omalizumab groups were analyzed *post hoc* to determine the characteristics of those that had an exacerbation during the fall treatment period (starting 4-6 weeks from fall school start plus 90 days) in these 2 treatment groups. The inhaled corticosteroids (ICSs) boost arm was not included in this analysis as the goal was to validate the results of previous evaluations of GBT only, as well as to determine whether characteristics were different in the group receiving biologic therapy (omalizumab). Those in the ICS boost arm were limited to participants receiving step 2 through 4 treatment, whereas participants in the other 2 groups could exceed these limits, thus the ICS boost arm was not felt to accurately reflect the target population under study.

The saEPI

The saEPI was developed by assigning cutoff values to 8 risk variables and assigning point values to the risk variable range (low risk = 0 points, medium risk = 1 point, high risk = 2 points) with a composite score ranging from 0 to16 (Table E1). Variables included age, allergic propensity (total IgE and allergen skin test positivity), percentage of blood eosinophils, exacerbation in the prior season, ICS step, FEV_1/forced vital capacity (FVC), and FENO. An additional parameter tested separately included total eosinophil count.

Statistical analysis

The primary objective of these analyses was the validation of the previously derived predictors of future asthma exacerbations[7] for both the GBT and GBT + omalizumab arm. For the comparison between treatment groups (Table I) and between exacerbation within treatment groups (Tables II and III) we used the Mann-Whitney *U* test and the chi-square test for continuous and categorical variables respectively, to test for independence. The graphical relation between the saEPI and the dichotomous exacerbation (Fig 1), measured during the 90 days double-blind phase of the study, was constructed using a univariate logistic regression model, and a chi-square test was used to test their association.

Multivariate logistic regression analyses were conducted to quantify the risk factors and saEPI associations with exacerbations during the double-blind period. Likelihood-ratio chi-square tests were used to compare the fit of nested models and to provide a test of significance for the added variables to the model (see Table E2 in this article's Online Repository at www.jacionline.org). The order in which the variables were entered into the analyses was determined *a priori*, according to ease and cost of obtaining the clinical measurements.

The purpose of relative importance[16] is to quantify the relative contribution of an individual variable to the model's total explanatory value by considering averaging over all possible orderings of variables in the model. These are computer-intensive methods that have become achievable[17] as a result of recent advances in computational capabilities.

Discrimination was calculated by receiver operating characteristic (ROC) curves and area under the curve (AUC or c statistic), and optimal cutpoint[18] for the score were derived from the ROC.

Log-transformations of skewed data (FENO, total IgE) were used for partial multivariate analyses. $P < .05$ was considered statistically significant. All statistical analyses were performed using the R system for statistical computing