Seasonal risk factors for asthma exacerbations among inner-city children

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Background: Asthma exacerbations remain common, even in children and adolescents, despite optimal medical management. Identification of host risk factors for exacerbations is incomplete, particularly for seasonal episodes.
Objective: We sought to define host risk factors for asthma exacerbations unique to their season of occurrence.
Methods: This is a retrospective analysis of patients aged 6 to 20 years who comprised the control groups of the Asthma Control Evaluation study and the Inner City Anti-IgE Therapy for Asthma study. Univariate and multivariate models were constructed to determine whether patients' demographic and historical factors, allergic sensitization, fraction of exhaled nitric oxide values, spirometric measurements, asthma control, and treatment requirements were associated with seasonal exacerbations.
Results: The analysis included 400 patients (54.5% male; 59.0% African American; median age, 13 years). Exacerbations occurred in 37.5% of participants over the periods of observation and were most common in the fall (28.8% of participants). In univariate analysis impaired pulmonary function was significantly associated with greater odds of exacerbations for all seasons, as was an exacerbation in the previous season for all seasons except spring. In multivariate analysis exacerbation in the previous season was the strongest predictor in fall and winter, whereas a higher requirement for inhaled corticosteroids was the strongest predictor in spring and summer. The multivariate models had the best predictive power for fall exacerbations (30.5% variance attributed).
Conclusions: Among a large cohort of inner-city children with asthma, patients' risk factors for exacerbation vary by season. Thus information on individual patients might be beneficial in strategies to prevent these seasonal events. (J Allergy Clin Immunol 2015;■■■:■■■-■■■.)

Key words: *Asthma, seasons, biomarkers, asthma exacerbations, IgE, exhaled nitric oxide, allergy, eosinophils, pulmonary function*

Asthma exacerbations remain a major factor contributing to the morbidity and even mortality of pediatric patients with asthma.[1] Moreover, asthma exacerbations account for a large proportion

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This project has been funded in whole or in part with Federal funds from the National Institute of Allergy and Infectious Diseases, National Institutes of Health, Department of Health and Human Services, under contract nos. NO1-AI-25496, NO1-AI-25482, HHSN272200900052C, and HHSN272201000052I. Additional support was provided by the National Center for Research Resources, National Institutes of Health, under grants RR00052, M01RR00533, UL1 RR024982, M01RR00071, 5M01RR020359-04, 1UL1RR025771, 1UL1RR025780, 1UL1RR024156, UL1RR031988, UL1RR025741, and UL1TR000451. Lincoln Diagnostics provided the Multi-Test, and GlaxoSmithKline (GSK) provided study drug for Asthma Control Evaluation study participants. Novartis Pharmaceuticals provided study drug under a clinical trial agreement with the University of Wisconsin–Madison, Dey Pharma provided EpiPens, and SC Johnson provided household pest control for Inner City Anti-IgE Therapy for Asthma study participants. None of these companies had a role in the development or approval of the protocol, conduct of the trial, data analysis, manuscript preparation, or the decision to submit for publication.

Disclosure of potential conflict of interest: S. J. Teach has received research support from the National Institutes of Health (NIH)/National Institute of Allergy and Infectious Diseases (NIAID) and Novartis; is employed by the Children's National Health System; has received research support from the NIH/NIAID, the Kohls Foundation, the Stewart Foundation, and PCORI; and has received royalties from UpToDate. S. J. Szefler has received research support and travel support from the NIAID Inner-City Asthma Consortium; has received consultancy fees from Merck, Boehringer Ingelheim, GlaxoSmithKline, and Genentech; has received research support from GlaxoSmithKline; has received lecture fees from Merck; and has a patent with the National Heart, Lung, and Blood Institute (NHLBI) CARE Network. H. E. Mitchell and A. Calatroni has received research support from the NIH/NIAID. J. Wildfire and G. R. Bloomberg have received research support and travel support from the NIH/NIAID. C. M. Kercsmar has received research support from the NIH, is a board member for GlaxoSmithKline, and has received royalties from UpToDate. A. H. Liu has received lecture fees from Merck Sharp & Dohme and is a Data Safety Committee member for GlaxoSmithKline. M. M. Makhija has received travel support from the NIAID Inner-City Asthma Consortium. E. Matsui has received research support from the NIH, is a board member for the US Environmental Protection Agency Science Advisory Board, and is employed by Johns Hopkins University. W. Morgan has received research support and travel support from the NIAID/NIH and the University of Wisconsin-Madison; has received consultancy fees from Genentech and the Cystic Fibrosis Foundation; is employed by the University of Arizona; has received research support from AsthmaNet NIH/NHLBI, the Cystic Fibrosis Foundation, Mt Sinai College of Medicine, and the NIH/NHLBI; and has received lecture fees from the American Thoracic Society and the American College of Chest Physicians. G. O'Connor has received research support from the NIH. W. W. Busse has been supported by the NHLBI/NIH; is a board member for Merck; has received consultancy fees from Novartis, GlaxoSmithKline, Genentech, Roche, Pfizer, Boston Scientific, Circassia, ICON, AstraZeneca, Sanofi, Amgen, MedImmune, NeoStem, Takeda, and Boehringer Ingelheim; has received research support from the NIAID/NIH and the NHLBI/NIH; and has received royalties from Elsevier. P. J. Gergen declares that he has no relevant conflicts of interest.

Received for publication August 21, 2014; revised December 17, 2014; accepted for publication December 19, 2014.

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0091-6749/$36.00

http://dx.doi.org/10.1016/j.jaci.2014.12.1942

Abbreviations
ACE: Asthma Control Evaluation
BMI: Body mass index
FENO: Fraction of exhaled nitric oxide
FVC: Forced vital capacity
ICATA: Inner City Anti-IgE Therapy for Asthma study
ICS: Inhaled corticosteroid
OR: Odds ratio

of the direct and indirect medical costs associated with the disease.[2,3] Although guideline-directed care reduces the frequency of asthma exacerbations among children, these events continue to occur in many patients.[4] Given the importance of exacerbations to the overall burden of asthma, attention has focused on the causes of these events, including viral respiratory tract infections, airborne allergens, pollutants, and stress.[5] Although asthma exacerbations can occur at any time during the year, seasonal patterns exist, and in children exacerbation rates are highest in the fall and lowest in the summer.[6-8] The seasonal increase in fall exacerbations is highly consistent and, based on studies from Canada, has been referred to as the "September epidemic."[9] Fall exacerbations have been attributed to an increased frequency of rhinovirus respiratory tract infections among children when they return to school.[10,11] However, other factors, such as allergic sensitization and an increase in exposure to environmental allergens, have also been proposed to work in combination with viral respiratory tract infections to trigger fall asthma exacerbations.[12] Although the environmental contributors to asthma exacerbations are well recognized and appreciated, patients' characteristics associated with a susceptibility to these events on a seasonal basis have not been completely defined nor has the importance of these factors in determining possible differences in the timing of exacerbations.

An achievement of optimal asthma control includes efforts to reduce the frequency of exacerbations.[13] Understanding which characteristics are associated with an increased risk for asthma exacerbation is a critical step to prevent these events and might include seasonal modification of treatment. Toward that goal, a predominant finding in predicting who is at risk for asthma exacerbation has been the observation that prior exacerbations are the best predictor of future exacerbations.[14-17] Although this finding has important utility, its tautological nature suggests that incompletely defined additional factors might also predict exacerbations. Furthermore, there has been little research that explores risk factors for exacerbations in individual seasons other than the fall or whether these risk factors can be predicted and, as a consequence, whether this information might improve approaches to prevent seasonal exacerbations. Consequently, we hypothesized that specific patients' characteristics might be associated with seasonal asthma exacerbations. Such characteristics could act to identify which patients are at high risk for seasonal asthma exacerbations and therefore might serve as a framework to identify more effective treatment strategies to prevent these events.

METHODS

Overview

This analysis examines risk factors for asthma exacerbations in 400 control group participants from 2 recent studies from the Inner-City Asthma Consortium: the Asthma Control Evaluation (ACE) study (n = 253)[4] and the Inner City Anti-IgE Therapy for Asthma (ICATA) study (n = 147).[18] Seasonal and year-round predictors are considered by using both univariate and multivariate analytic techniques. Of note, in both the ACE and ICATA studies, all participants (including control subjects) were given guideline-based treatment by asthma specialists before randomization and throughout the year-long follow-up. In the ACE study fraction of exhaled nitric oxide (FENO) was added to the evaluation regimen to determine treatment for the intervention group. For the ICATA study, omalizumab was added to guideline treatment for the intervention group. In both studies the guideline-treated control and intervention groups were closely monitored for symptoms and exacerbations during the follow-up year. Both studies were approved by each institution's institutional review board. Study details, including study sites and inclusion and exclusion criteria, are included in Table E1 in this article's Online Repository at www.jacionline.org. Both studies enrolled largely minority participants with persistent asthma from urban neighborhoods. Important differences between the trials include the ages of enrolled participants (12-20 years for the ACE study and 6-20 years for the ICATA study), the proportion of Hispanics enrolled (22.9% for the ACE study and 42.2% for the ICATA study), and the requirement that patients in the ICATA study have a combined body weight and total serum IgE level suitable for omalizumab dosing and a positive skin prick test response to at least 1 perennial allergen; however, 85% of patients in the ACE study also met this requirement.

ACE population and study design

A total of 546 participants aged 12 to 20 years with asthma were enrolled in the ACE study at 10 large urban research centers in the United States.[4] The ACE study had a randomized, double-blind, parallel-group design. At screening visits, each participant was assessed for asthma symptoms, previous treatment, pulmonary function, allergen skin prick test sensitivity, total serum IgE levels, and allergen-specific IgE levels. Participants were evaluated at 7 additional visits at 6- to 8-week intervals, with symptom assessments and pulmonary function testing at each visit. Treatment was adjusted according to guideline-based algorithms[13] with or without taking into consideration FENO values. All study drugs were provided. Exacerbations were defined as a need for systemic corticosteroids, hospitalization, or both.

ICATA population and study design

The ICATA study was a randomized, double-blind, placebo-controlled, parallel-group, multicenter trial that compared omalizumab with placebo added to guideline-based therapy in 419 inner-city children, adolescents, and young adults (aged 6-20 years) with persistent allergic asthma.[18] Similar to the ACE study, at screening visits, each participant was assessed for asthma symptoms, previous treatment, pulmonary function, allergen skin prick test sensitivity, total serum IgE levels, and allergen-specific IgE levels. Asthma medications covered by the participants' insurance plans were prescribed but were not supplied, with the exception of omalizumab or placebo study injections and oral prednisone for exacerbations. Like the ACE study, exacerbations were defined by the need for systemic corticosteroids, hospitalization, or both.

Statistical analyses

Participants from the ACE and ICATA studies were pooled for all analyses to increase sample size and to improve generalizability. Exacerbation predictors are described as either "baseline" or "previous season." Baseline predictors were measured at or before study randomization, whereas previous season predictors were postrandomization measures collected before the start of the season of interest. For example, the FEV_1/forced vital capacity (FVC) ratio from the summer was used to predict exacerbations in the fall. The exacerbation outcome was binary (≥1 exacerbation vs no exacerbations in a given season). The initial 90 days of follow-up exacerbation data were not included as outcomes because there was no prior season prediction data; however, data from this period were used as predictors for the following season. A minimum of 45 days of follow-up for exacerbations in a given season was required for inclusion in the analysis. All participants with at least 5