

Asthma exacerbations: Looking back to the future

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The morbidity and mortality associated with asthma continues to be driven by asthma exacerbations.¹ In recent years, our understanding of the mechanisms and triggers precipitating asthma exacerbations has greatly improved. However, this understanding has not been fully matched by our ability to accurately predict which patients are at greatest risk for these life-threatening events or determine whether there are seasonal differences between risk factors. Both the Global Initiative for Asthma (GINA)² and National Asthma Education and Prevention Program³ guidelines highlight the risk domain of asthma and outline accompanying strategies to both prevent and manage such acute events.

Key to successful implementation of evidence-based asthma guidelines is the need to identify patients at risk. Two articles in this issue of the *Journal* contribute to our knowledge base in this regard, identifying host and seasonal risk factors for asthma exacerbations^{4,5} and proposing a simple risk score with the potential for widespread clinical use.⁵

The studies by Teach et al⁴ and Bateman et al⁵ both use retrospective analyses from well-regarded randomized controlled trials that have been previously published. The first cohort analyzed by Teach et al⁴ includes 400 patients aged 6 to 20 years who participated in one of 2 trials conducted by the Inner-City Asthma Consortium: the Asthma Control Evaluation trial⁶ and the Inner City Anti-IgE Therapy for Asthma Trial.⁷ The analytic cohort included participants in both trials who were allocated to the control group, which received guidelines-based asthma care. The cohort members were largely male (54.5%), minority (59% African American), and adolescent (median age, 13 years), residing in one of 10 large urban cities in the United States. Univariate and multivariate pooled analyses were applied to determine whether demographic and historical factors, allergic sensitization measures, fraction of exhaled nitric oxide and spirometric measurements, asthma control measures, and asthma treatment requirements were associated with seasonal exacerbations (winter, summer, spring, and fall). Exacerbations in both the

Asthma Control Evaluation trial and Inner City Anti-IgE Therapy for Asthma Trial were defined *a priori* as a need for systemic corticosteroids, hospitalization, or both.

Of the 400 participants, 37.5% experienced a defined asthma exacerbation, with the highest frequency of 28.8% in the fall months (September–November), followed by 19.9% in spring, 15.9% in winter, and 14.5% in summer. For the full-year univariate analysis, factors most associated with exacerbations included an exacerbation in the prior year, increased Composite Asthma Severity Index scores (as well as individual markers of asthma severity, such as decreased pulmonary function measures and higher requirements for inhaled corticosteroids [ICSs]), and a dominant T_H2 phenotype, including increased total serum IgE levels and increased blood eosinophil counts. The greatest contribution of this article is the individual season predictors. The strongest predictors for fall exacerbations included an exacerbation during the prior season (summer), markers of allergy (including positive skin test results and increased total serum IgE and allergen-specific IgE levels to house dust mite and cockroach), increased fraction of exhaled nitric oxide values, and decreased pulmonary function. Few variables predicted winter exacerbations; these were limited to an exacerbation during the previous season (fall) and decreased pulmonary function measures. Exacerbations in spring were most closely associated with an exacerbation during the previous year but not the previous season (unlike the fall and winter exacerbation predictors). Summer exacerbations were associated with impaired pulmonary function, sensitization to *Alternaria* species, increased blood eosinophil counts, higher ICS doses, and an exacerbation in the previous season.

For the multivariate prediction models, 7 risk factors were selected. The best predictive power occurred in the fall. For fall and winter seasons, a history of an exacerbation in the last season was most predictive, whereas spring and summer exacerbations were best predicted based on ICS requirements. The authors present risk scores based on these 7 available risk factors.

The second large cohort described in this issue of the *Journal* includes participants enrolled in one of 3 trials of 6 to 12 months in duration; each study evaluated the efficacy of ICS/long-acting β -adrenergic agonist combinations in adolescents and adults applied in different dosage strategies.^{8–10} These 3 trials had similar entry criteria, including participants using GINA treatment steps 3 or 4 and a history of 1 or more exacerbations in the year before enrollment. The end point of a severe exacerbation was defined in a similar manner to the study by Teach et al.⁴ Unlike that analysis, the univariate and multiple regression models did not include an exacerbation history in the model because all participants were required to have 1 or more such events for trial entry.

Bateman et al⁵ selected 16 patient and clinical characteristics based on availability from the study data: age, sex, body mass index, smoking status, time since asthma diagnosis, pulmonary function measures, 5-item Asthma Control Questionnaire scores, asthma symptom scores, bronchodilator reliever use, nocturnal

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awakenings, GINA treatment step 3 or 4, prestudy ICS dose, long-acting β -adrenergic agonist use, and the presence of allergic rhinitis. The article presents a risk score for exacerbations, using these variables for an initial analysis set and a second validation set, standardizing to a maximal sum of 100, where a higher score represents a higher risk of exacerbation within 6 months. Five dominant baseline predictors of increased exacerbation risk within 12 months were selected: GINA treatment step, mean daily number of rescue inhalations, postbronchodilator FEV₁, 5-item Asthma Control Questionnaire score, and body mass index. The authors report an exponential increase in observed risk of exacerbations (from low risk of 10% to high risk of 40%) within 12 months with increments in risk score for exacerbations based on these 5 selected predictors.

Both studies contribute important clinical insights into the risks of asthma exacerbations and offer the possibility of an improved method of high-risk patient identification. However, each analysis has limitations that must be considered.

First, both studies are limited to inclusion of risk factors collected during the performance of the parent clinical trials, with some similarities between cohorts (lung function measures, ICS dose) but also some important differences (eg, markers of atopic disease). In both cases potentially important factors have been omitted, such as a greater understanding of the influence of inflammatory phenotype in the analysis by Bateman et al⁵ and the inability to assess the effect of exacerbations in the corresponding season of the previous year by Teach et al.⁴

Second, the generalizability of the conclusions must also be considered given the limited demographic and clinical characteristics of the enrolled cohorts (including a pediatric population in the Teach et al⁴ cohort, which was primarily composed of patients with moderate-to-severe allergic asthma with a median body mass index percentile of almost 90% and including only 11% of nonblack race and non-Hispanic ethnicity vs a primarily adult population in the Bateman et al⁵ cohort). However, the analysis by Teach et al⁴ clearly highlights that seasonal differences in risk are likely to exist and that clinicians should query not only about exacerbations in the prior year but also in the prior season to better inform them of the likelihood of an impending exacerbation in the coming months. For example, those patients

considered at risk for a fall exacerbation might require increased controller therapy before the start of school in the fall to limit the frequency, severity, or both of an exacerbation (which we know is primarily virus induced).

Although the results of both the Teach et al⁴ analysis and the risk score for exacerbations require further validation through future prospective studies involving a more diverse range of asthmatic patients, we are now a step closer to achieving a more complete, systematic, and personalized approach to asthma care whereby a tailored asthma action plan alongside phenotype-specific treatments could significantly reduce the likelihood of exacerbations and markedly improve the lives of asthmatic patients.

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