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Poor outcomes and asthma hospitalizations: How important is asthma severity and how do we measure it?

Theodore A. Omachi, MD, MBA

Asthma hospitalizations may be largely preventable but are often associated with serious adverse outcomes, including death or respiratory failure necessitating mechanical ventilation. 1 Risk stratification of patients at highest risk of hospitalization and poor outcomes is important for both epidemiologic research and for the identification of patients for targeted intervention. Intuitively, the severity of a patient's underlying asthma is a factor that could be used in such risk stratification. However, the importance of asthma severity in determining asthma outcomes, such as death, has not been conclusively determined.2 Indeed, at least in children, the risk of asthma death may even be independent of the underlying severity of disease.[3] Part of the uncertainty stems from the fact that there is no agreed upon “gold standard” for categorizing asthma severity. In the United States, the National Asthma Education and Prevention Program (NAEPP) Expert Panel III recommends the use of asthma symptoms, limitation of activity, lung function, and requirement for short-acting β-agonists.[4] Consistent with this recommendation, FEV_1 and peak flow do appear to be predictive of asthma death. For example, one study found that for every 25% decline in FEV_1 below that predicted, the risk of all-cause mortality in asthma approximately doubled.[5] Even in the absence of spirometry information, however, an asthma severity score, determined by dyspnea symptoms, asthma medication usage (including frequency of prior systemic steroid usage), and prior asthma hospitalizations and intubations, is prospectively associated with mortality in patients who have previously been hospitalized with asthma.[6] 7 Nonetheless, although the NAEPP acknowledges the importance of short-acting β-agonist frequency in measuring asthma severity, it concludes that, for treatment purposes, the prior requirement for oral systemic corticosteroids should not be used to distinguish asthma severity in patients who otherwise meet criteria for persistent asthma based on the factors mentioned above.4

In the present issue of Allergologia et Immunopathologia, the EAGLE investigators report the results of a study comparing the characteristics of hospitalized severe asthma patients to the characteristics of hospitalized patients with less severe asthma, retrospectively utilizing a cohort of patients from Spain and Latin America. The major characteristics examined were age, gender, pre-hospitalization FEV_1, atopic status, prevalence of prior hospitalization, and change in FEV_1 or peak flow associated with the index hospitalization. Of note, the authors categorized patients as having severe asthma based on their treatment regimen. In particular, patients were categorized as having “severe asthma” if their outpatient therapeutic regimen at the time of hospitalization was the equivalent of Steps 4 or 5 of the Global Initiative for Asthma (GINA) management and prevention guidelines. Based on the GINA guidelines, for the majority of patients in the time periods under consideration, this would generally correspond to the prescription of at least medium-dose inhaled corticosteroids (Step 4) or systemic corticosteroids (Step 5).[2] The study found that patients admitted to the hospital for asthma exacerbations, who had been placed on Steps 4 or 5 outpatient asthma therapies, were at greater risk of requiring mechanical ventilation, on average required longer hospital stays, and were

Corresponding Author: Theodore A. Omachi, MD, MBA Division of Pulmonary and Critical Care Medicine Department of Medicine University of California, San Francisco 505 Parnassus Ave, Box 0111 San Francisco, CA 94143-0111 omachi@ucsf.edu.

at greater risk of in-hospital all-cause mortality as compared with patients on less intensive outpatient therapies.

Although the causal relationship between asthma therapies and outcomes was not assessed in this study, it appears unlikely that asthma therapies were responsible for poor outcomes. Indeed, prior research has demonstrated that the failure to prescribe inhaled corticosteroids, upon discharge from an asthma hospitalization, is associated with increased risk of subsequent mortality.[8] Therefore, more intensive outpatient asthma therapy is an indicator of more severe asthma, and patients on higher doses of inhaled corticosteroids or systemic corticosteroids likely have worse morbidity and mortality outcomes, associated with an asthma hospitalization, than patients on less intensive therapies because they have more severe asthma.

In the current study, the in-hospital FEV_1 (or peak flow) among patients with severe asthma was than among those with less severe asthma. Of note, however, the amount by which FEV_1 declined, as compared with pre-hospitalization values, did not appear to be greater in severe asthma patients. That is, FEV_1 (or peak flow) declined from 66% of predicted to 39% of predicted in severe asthma patients (a 27 point decline) and from 86% of predicted to 44% of predicted in non-severe asthma patients (a 42 point decline). Thus, the lower in-hospital FEV_1 in severe asthma patients was attributable to a lower baseline FEV_1 rather than a greater decline in FEV_1. This fact, combined with the older age and greater prior hospitalization rate in severe asthma patients, suggests that poor baseline health status may be just as important in determining poor in-hospital outcomes as the incremental degree of bronchoconstriction attributable to the asthma exacerbation. Because incremental bronchoconstriction may be difficult to predict, but baseline health status may more readily be assessed, this has positive implications for our ability to identify patients at risk of poor outcomes prior to hospitalization.[9]

Interestingly, the prevalence of atopy was considerably less in patients with severe asthma than in those with less severe asthma. This raises the question of whether atopic asthma is somehow less severe than asthma without atopy. For example, prior research suggests that occupational (non-atopic) asthma may be more severe than other forms of asthma.[10] It must be mentioned, however, that another explanation could be that patients with non-atopic asthma were more likely to have chronic obstructive pulmonary disease (either concurrently or because of misclassification with asthma) or that patients treated with corticosteroids were less likely to manifest an atopic response. Mitigating the latter possibility is the fact that prior research has shown that allergy skin prick tests are reasonably stable despite chronic administration of oral corticosteroids.11 Overall, the finding that severe asthma patients were less likely to have atopic asthma supports prior research with similar findings and calls for further research investigating explanatory mechanisms.[12, 13]

What are potential applications and implications of this research? Notably, it provides further validity to the concept of risk-stratification based on intensity of asthma therapeutic regimens above and beyond the requirement for short-acting β-agonists. This in turn has potential applications both for epidemiologic research as well as in clinical practice. In epidemiologic research, adjusting for asthma severity is often critical when examining outcomes, but pulmonary function testing or even survey-based batteries are often not logistically feasible or, if conducting a retrospective study, are often not available. For example, a recent study in the American Journal of Respiratory and Critical Care Medicine concluded that physical activity was associated with a reduced risk of asthma exacerbations, suggesting the respiratory benefits of regular exercise.[14] It was important in this study to account for asthma severity, as greater severity may have been independently responsible for reduced regular activity and greater risk of exacerbations. The authors appropriately did so by using an asthma symptom scores. The current study by the EAGLE investigators suggests that it may also have been

prudent to control for asthma severity by accounting for the asthma medications necessary to achieve that symptom score.

Thus, asthma severity does appear to be important in determining poor outcomes. Moreover, prior asthma therapeutic regimen requirements appear to be an important factor in measuring asthma severity. Particularly given that prior utilization information may be more readily available in large cohorts than data about airway obstruction or survey-based symptoms scores, the component of prior therapeutic requirements may be a critical means of classifying asthma severity for the purposes of both epidemiologic research and targeted disease management intervention.

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