Antibiotic Use in COPD Exacerbations

To the Editor:

I read with great interest the article by Stefan et al1 in CHEST (January 2013) regarding early antibiotic use and clinical outcomes in patients hospitalized with an exacerbation of COPD being concomitantly treated with systemic steroids. The authors concluded that early antibiotic use in combination with steroids is associated with lower rates of in-hospital mortality in patients admitted with COPD exacerbations. Several concerning aspects about the statistical analysis in this study require further clarification.

First, because of the nature of observational studies and their inherent selection bias, the authors performed propensity score matching such that patients in the late or no antibiotic arm are matched one to one with the nearest patient in the early antibiotic arm. Given that propensity score matching accounts for covariates that predict receiving the treatment in question, I believe that the absence of variables such as severity of disease, history of allergies and adverse events related to antibiotic use, and history of resistant bacterial infections in the propensity score analysis cannot be ignored and are integral to acknowledge in the propensity scoring and multivariate models. Moreover, the subsequent analysis examining the impact of antibiotic administration and antibiotic choice on outcomes cannot be interpreted unless patients with antibiotic allergies or antibiotic-resistant infections were excluded or if these variables were accounted for in the subsequent multivariate analysis.

Second, it is important to note that there are data to suggest that all patients with COPD do not benefit equally from corticosteroids. Analyses from the multicenter SCOPE (Systemic Corticosteroids in COPD Exacerbations) trial performed by the Veterans Affairs Affairs Cooperative Studies Program demonstrated that prior hospitalization for COPD in the preceding 2 years is associated with a more favorable response to systemic steroid use.2 Other clinical factors suggested to have an impact on steroid responsiveness were theophylline use, lower FEV1, at admission, and prior prednisone use. The latter two baseline characteristics were not taken into account by Stefan et al2 in the multivariate analysis examining outcomes. Ultimately, the question of optimal antibiotic choice in hospitalized patients with a COPD exacerbation remains to be answered, especially in an era of increasingly prevalent antibiotic resistance.

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References

Response

To the Editor:

We read the comments by Dr Patel regarding our recent article with great interest. Although we agree that severity of illness is an important variable for propensity score analysis, our administrative database does not include data on spirometry or other physiologic measures. While we were unable to use specific measures to assess severity of illness, we did control for multiple confounders that serve as markers for disease severity, including admissions in the year prior, multiple treatments and tests performed, comorbidities, and principal diagnosis of acute respiratory failure or COPD. In addition, our sensitivity analysis demonstrated that for a strong unmeasured confounder (eg, severe reduced FEV1), the difference in prevalence between treated and untreated patients has to be >40% to negate our findings.

Dr Patel notes our lack of information on history of allergy, adverse events to antibiotics, and resistant infection. This data, however, would impact antibiotic selection, not treatment. In addition, allergic reactions to macrolide and fluoroquinolone appear to be relatively uncommon (0.4%-3%) and most likely had little, if any, effect on the observed results. Our analysis also excluded patients treated with antibiotics not recommended by GOLD (Global Initiative for Chronic Obstructive Lung Disease) guidelines (eg, vancomycin, third and fourth generation of cephalosporine) and patients with other infection (like pneumonia).

Concerns were expressed by Dr Patel regarding the impact of other factors on the response to steroids. While we did not include theophylline use prior to hospitalization as a variable in the propensity score, we adjusted for theophylline utilization on day 1 to day 2 of hospitalization as we believe its use on the first days of hospitalization would most likely reflect prior prescription. In the study cited by Dr Patel, there was an interaction between prior hospitalization and the responsiveness to steroids,2 and we adjusted for prior admission in our study.

Dr Patel states that “ultimately, the question of optimal antibiotic choice in hospitalized patients with a COPD exacerbation remains to be answered.” We agree; however, our results suggest that trials to answer this question would need to be extremely large. In addition, these trials are not likely to take place soon, given a recent Cochrane review showing that antibiotics significantly reduce the risk of treatment failure in hospitalized patients with severe COPD exacerbations.3 Although more research is needed, antibiotics do appear to be useful for patients with acute exacerbations of COPD requiring hospitalization.