Reviewer’s report

Title: Adjunctive Corticosteroid Therapy for Inpatients with Mycoplasma pneumoniae Pneumonia

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Reviewer: Todd A Lee

Reviewer's report:

The paper describes an observational study examining the use of corticosteroid therapy in individuals with M. pneumoniae pneumonia. The goal of the paper was to determine if corticosteroids and the dose of corticosteroids were associated with differences in mortality, length of stay, costs and episodes of hyperglycemia. In the analysis, the use of steroids was not associated with morality; however, use of steroids was associated with increased length of stay, medication costs and episodes of hyperglycemia. The conclusion was that adjunctive treatment with corticosteroids is not helpful in patients with M. pneumoniae pneumonia.

Given the clinical uncertainty associated with corticosteroid use in this population, the study is addressing an important issue. There are certainly advantages of conducting this observational study in the setting where laboratory result information is available to confirm the diagnosis. However, there remain methodological challenges that are detailed in the comments below.

MAJOR CONCERNS

1. The exclusion criteria and how they impact the patients included in the analysis raise some concerns. First, the initial exclusion of individuals discharged within two days of admission is supposedly in an effort to avoid immortal time bias. However, it is not clear how this exclusion would avoid immortal time bias. It may be reasonable to exclude these individuals if they are not 'at risk' for receiving corticosteroids but the 2 day discharge doesn't seem to have an impact on immortal time so long as the person time is appropriately categorized. Second, it is not clear why individuals were excluded if they used steroids for less than three days. How was an 'unexposed group' defined if those not using corticosteroids were excluded? Moreover, exclusion of this group ensures that those exposed to steroids will have at least 3 days in the hospital which would bias the findings to longer lengths of stay in the steroid exposed groups. With this as an exclusion criterion it is not at all surprising that those in the exposed groups have longer lengths of stay. Finally, the third exclusion criterion certainly raises concern about immortal time bias which is a major concern for this study. Individuals that were included had to start treatment within 7 days of admission to be included. So, if a patient started corticosteroids on day 7 they were eligible for inclusion and
classified as steroid exposed. This is a classic case of introducing immortal time bias because these individuals are 'immortal' for the first six days in the hospital. This immortal time is attributed to the exposed groups, when in actuality the person wasn't exposed to corticosteroids until the 7th day of their stay. So these patients could not have been discharged during that time, could not have died during that timeframe and certainly would incur drug costs. This criterion would bias the results in the direction that was observed for both costs and length of stay. It would also bias the results toward corticosteroids looking protective for mortality and so perhaps the conclusion that there is no difference in mortality is biased and in fact there may be an increased risk associated with corticosteroid exposure.

2. The exclusion criteria are also confusing in understanding how a no corticosteroid group was defined. If those with no corticosteroid use in the first 7 days of the admission and those that used for less than three days are excluded, who makes up the 'unexposed' group? I am unable to determine the patients that were included as unexposed in the analysis given these exclusion criteria. It would be helpful to more fully describe exactly how each of the exposure groups was determined. This is true of the corticosteroid groups also. It appears that a threshold was used for differentiating the high and low dose groups (pg 7, lines 145-146), but was this on any day during the hospitalization or is it the average corticosteroid dose? In understanding how to interpret the results it is important to understand the details of how the groups were defined.

3. Propensity scores were used to try and account for differences between groups; however it is not clear why a propensity score was developed for low dose versus high dose and yet comparisons were high dose vs. no corticosteroid and low dose vs. no corticosteroid. In this case the propensity score predicts the likelihood of being high dose compared to low dose and may not at all balance on variables that are confounders between any exposure and no exposure and the outcomes in the study. Was the predicted probability from the regression for low dose vs. high dose applied to the no corticosteroid group? What were the propensity score distributions like in each of the two exposure groups compared to those in the no corticosteroid group? While matching helps to alleviate some of the concerns with non-overlapping propensity score distributions, the approach may not balance on factors associated with use versus no use.

4. It is not clear when the covariates used in the propensity score were measured. Were these measured over the entire duration of the hospitalization? If yes, that is in appropriate as some of those factors may have been a consequence of the exposure and not a prediction of the exposure. In developing the propensity scores, the covariates should only include those that were available or occurred before the exposure. This may be quite challenging for those without an exposure, but again it is not clear how this group was defined.

5. There needs to be an adjusted or accounting of within hospital correlation. As there may be different practice patterns across hospitals, different case mixes, and different outcomes that
may not be a consequence of corticosteroid use it is necessary to account for these across hospital differences. Simply including hospital as a covariate in the propensity score model does not sufficiently account for within hospital correlation. There are a number of approaches that could be used, a couple of examples include matching individuals within hospitals (however this may not be feasible if there is a predominant practice within hospitals) or conducting a hierarchical analysis that accounts for the within hospital correlation.

6. Why is 30-day mortality exclusive of in-hospital mortality? Shouldn't these deaths be counted as deaths in the 30-day analysis? These patients died before the end of 30 days.

7. The study is certainly underpowered for the mortality outcomes. In the matched analysis, there are twice as many deaths in the high dose group as the no corticosteroid group.

MINOR CONCERNS

8. Presentation of the unmatched findings is not particularly helpful as these are likely confounded by disease severity.

Are the methods appropriate and well described?
If not, please specify what is required in your comments to the authors.

No

Does the work include the necessary controls?
If not, please specify which controls are required in your comments to the authors.

No

Are the conclusions drawn adequately supported by the data shown?
If not, please explain in your comments to the authors.

No

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