Author's response to reviews

Title: Clinical outcomes associated with Staphylococcus aureus and Pseudomonas aeruginosa airway infections in adult cystic fibrosis patients

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Author's response to reviews: see over
Montreal, May 13th 2015

Re: Resubmission of MS: 4984292991634794 “Clinical outcomes associated with Staphylococcus aureus and Pseudomonas aeruginosa airway infections in adult cystic fibrosis patients”

Dear Editor to the BMC Pulmonary Medicine,

We would like to thank the editor and reviewers for the insightful and constructive comments. We have extensive revised the manuscript and provided additional results following the reviewer’s comments. The changes are visible in the revised manuscript and we have outlined the responses to the reviewers’ comments and question below. We hope that these changes and answers will be satisfactory.

Thank you for your consideration.

Sincerely,

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Responses to reviewers

Major comments and responses

• The greatest issue is the choice to include CF patients positive to both S.aureus and P. aeruginosa in the group named “PA patients”. Co-infected patients should be excluded from the “PA” group, and the analysis performed again with the new groups. The groupings of the “Pa+SA” and “PA only” groups should be justified.

We recognize that combining patients with both PA+SA and PA only raises questions about whether these groups are similar or not. As suggested by the reviewers R1 and R3, we are presenting results with the PA+SA group separate from the PA only. We also compared the PA only and PA+SA patients and found no significant differences in demographic or clinical parameters. We also repeated our analyses where the PA+SA patients are excluded and show that results and conclusions are similar. We have included these results in Table 6 and as supplemental information (Table S1 to S5), and have revised the manuscript accordingly.

• Did the authors included patients with MRSA in the “SA only” group? If this is the case, authors should comment.

Our cohort did include MRSA patients, which represented 4/84 patients (4.8%). Analysis of the cohort after exclusion of these patients showed similar results. The results and discussion were revised to reflect this.

• Adjusted models should be considered for draw results and conclusion in the abstract.

As suggested, we have revised the conclusions stated in the abstract and discussion.

• Conclusions are too speculative about SA protection.

As suggested, this has been removed.

• Were all sputum specimen collected during the study period considered, or only specimen obtained at routine visits? What was the average number of sputum cultures per year in the 3 groups? How many of the specimen were positive for Staph. aureus or P. aeruginosa? Did the pathogens grow intermittently or persistently? Did the authors aim to quantify the bacterial load?

All sputum samples collected were considered when determining infection status, which includes sample collected during routine visit but also at the time of exacerbation. This is now stated explicitly in the methods. The average number of sputum collected for each group was added to Table 1. The proportion of SA and PA positive samples are now stated in the results. We unfortunately do not have sufficient number of sputum samples per year to accurately define patients being intermittently or persistently infected, using the Leeds definition. We defined an infection if at least 50% of sputum cultures were positive for PA or SA, but recognize that this may include intermittently infected patients. We did not measure quantitative bacterial loads.

• What was the average number of routine visits per year? How often was spirometry performed per year in the 3 groups?

In our clinic, spirometry is performed at each routine clinic visit. For this study, we analyzed and reported the spirometry and CRP results at the baseline visit (defined as the first routine visit during which the patient is in stable clinical state within the study period). In previous analyses, we compared the average spirometry for all routine clinic visits within the study period with the baseline visit measurement, and found no significant differences.
If some patients in the PA group were infected with SCV, would this have changed the findings? Our study may overlook the contribution of SCV and this is mentioned in the discussion. It is difficult to speculate on how our results may be different. This may depend on whether these are SCV/PA co-infected patients, or solely infected with SCV. Based on the Basier 2007 and Wolter 2011 studies, SCV may be associated with more severe lung disease, and thus lead to a SA group with a worse prognosis than what we described in our study.

What was the average number of CRP measurements per year? Were only CRP levels obtained during routine clinical visits analysed?
Only the CRP obtained at baseline visits were analyzed. This is now explicitly specified in the methods.

The authors do not mention whether patients in the Staph.aureus and P.aeruginosa only groups were infected with other pathogens.
One patient with BCC was excluded from the study. Other microorganisms (Aspergillus species and Stenotrophomonas maltophilia) identified in sputum cultures are now reported in Supp. Table S1.

Was PFGE typing performed? Did the patients with neither PA nor SA have negative antipseudomonal antibodies?
Unfortunately not.

The Besier J Clin Micro 2007 reference has been added.

Using the ‘no PA/SA’ group as the reference for the SA and PA groups would be more acceptable and would give a much clearer picture of the disease outcomes of SA vs PA.
As stated by the reviewer, we have used the PA group as a reference group for the purpose of comparison, in order to be able to compare SA and PA. The No SA/PA group does have the highest regression coefficient for FEV1, thus suggesting a trend towards this group has better lung function than the PA group. However, this does not reach statistical significance in light of the small sample size in this group. We have also revised the results to reflect this point. Using the no PA/SA instead of PA as a reference group does not increase our power to detect a significant association between PA and FEV1 due to the small sample in the reference group “No PA/SA”, but would compromise our comparison between PA and SA only groups.

Minor comments and responses:
• The conclusions are too speculative about SA protection.
This has been removed.
• All acronyms are defined.
• All suggested minor revisions have been done.