Author’s response to reviews

Title: MORBIDITY AND MORTALITY RELATED TO PNEUMONIA AND TRACHEOBRONCHITIS IN ICU AFTER LUNG TRANSPLANTATION

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Author’s response to reviews:

To Prof. Nicolini

Handling Editor BMC Pulmonary Medicine

Dear Prof. Nicolini,

Thank you for reviewing our manuscript entitled “MORBIDITY AND MORTALITY RELATED TO PNEUMONIA AND TRACHEOBRONCHITIS IN ICU AFTER LUNG
We hope that our answers have addressed all of the reviewers’ and editor’s concerns and that you will now consider the manuscript suitable for publication in BMC Pulmonary Medicine.

Sincerely,

Dr Sébastien Tanaka and Prof. Philippe Montravers

Technical Comments:

- No email addresses of the authors

The email addresses of the authors have been added on the title page.

Editor Comments:

BMC Pulmonary Medicine operates a policy of open peer review, which means that you will be able to see the names of the reviewers who provided the reports via the online peer review system. We encourage you to also view the reports there, via the action links on the left-hand side of the page, to see the names of the reviewers.

Reviewer reports:

Vikram Balakumar Balakumar, MD (Reviewer 1): Please include all comments for the authors in this box rather than uploading your report as an attachment. Please only upload as attachments annotated versions of manuscripts, graphs, supporting materials or other aspects of your report which cannot be included in a text format.

Please overwrite this text when adding your comments to the authors.

Introduction

- While the authors mention about the incidence of post-LT VAP and the existing knowledge of the high morbidity and mortality with pneumonia, they fail to mention what more knowledge they wish to add by the aim of their study.
We thank the reviewer for his relevant question. As mentioned in the introduction section, several issues in the early management after lung transplantation, including colonization of the bronchial tree and tracheobronchitis, remain unresolved. Patients face the combined risks of delayed treatment and the possible development of pneumonia as well as the risk of overtreatment with the possible emergence of MDR bacteria.

The aim of the present study has been clarified in the introduction section: “The aim of the present study was to compare the characteristics of patients who developed one or more episodes of BRI during the first 28 days after LT in ICU with those who did not. The influence of colonization of the bronchial tree and tracheobronchitis on the development of pneumonia and the role of these entities on the outcome were also evaluated”.

Methods

- Did the study population include adults only or both adults and pediatric patients

Our population only included adult patients. This clarification has been added to the revised version of the manuscript, study population section.

- Under microbiological samples (page 5, line 51-65) can the authors state why they routinely obtain samples specifically, 6 months before transplantation - is that a common institutional practice?

Microbiological samples were routinely obtained during the patient’s hospitalization prior to transplantation. As indicated in the manuscript, patients treated for cystic fibrosis are not managed in our institution. However, several other clinical conditions such as severe COPD, bronchiectasis or even primary fibrosis can be associated with colonization of the bronchial tree, which could be a source of concern in case of MDR bacteria at the time of LT and perioperative antibiotic prophylaxis. However, no specific procedures are applied concerning the timing and collection of colonization samples. The decision depends on the pulmonologist in charge of the patient during the preoperative period, which explains why respiratory colonization samples were performed more than 6 months before transplantation in a large proportion of patients.

When are the pretransplant tracheal bacterial samples obtained?

These samples were collected during routine fiberoptic bronchoscopy performed during the overall clinical assessment or in the case of superinfection requiring specific antibiotic therapy.

- Under Definitions of BRI (page 6, line 29) can the authors state what cutoff they used when they mentioned 'decreased PaO2/FiO2 ratio'?

The at least 30% decrease in PaO2/FiO2 ratio was one of the criteria used to define pneumonia. This point has been added to the revised manuscript.

- Page 7, line 15 - can the authors state how they calculated the primary graft dysfunction score?
Primary graft dysfunction was assessed according to the International Society for Heart and Lung Transplantation (Christie JD et al J Heart Lung Transplant. 2005 Oct; 24(10):1454-9). A reference has been added to the text.

Results

- Page 8, line 39 - To avoid confusion, can the authors remove the percentage in the brackets. When reporting results, it is difficult to follow if the percentages are being reported uniformly. In the previous paragraph, the percentages were in comparison with the overall population while here they are in comparison with a particular subgroup.

As suggested by the reviewer, the percentages have been removed.

Discussion

- In page 11, lines 30-31 The authors cannot assume the reason for low rate of donor BRI from donor colonized micro-organisms based on evidence that is not shown.

We agree with the reviewer’s comment. This sentence has been deleted to avoid confusion.

- Based on figure 1, it's interesting to see that most cases of pneumonia are from species unrelated to donor or recipient colonization - can the authors explain the significance of this finding? Is this seen in other studies in lung transplant cohorts?

Most donors before pneumonectomy receive targeted antibiotic therapy or antibiotic prophylaxis, which could explain the low rate of BRI with a micro-organism cultured from the donor’s samples. In addition, during the immediate postoperative period, antibiotic prophylaxis is tailored to the susceptibility of the donor’s flora, which could also play a role.

As noted by the Reviewer, most episodes of pneumonia were due to species unrelated to the donor’s or recipient’s colonization flora, as also been observed in other studies in lung transplant cohorts. For example, in the study by Riera et al analyzing 170 patients, most cases of pneumonia were totally independent of colonization prior to the graft (Riera et al. European Respiratory Journal 2014). Riera et al observed only 3/20 cases of pneumonia caused by species cultured prior to the graft.

Interestingly, no significant difference in the frequency of pneumonia due to organisms cultured from the host or the donor was observed between single and double lung transplantation (4/20 patients versus 5/14 patients, respectively, p=0.43). This point has been added to the results section.

Although most emerging organisms were not cultured from the host’s respiratory tract, we cannot exclude a host digestive tract origin for these bacteria. The gastric reservoir is a well-known source of contamination, which has led many teams to propose the use of selective
decontamination. As indicated in the methods section, we do not use any selective digestive decontamination.

These comments have been added to the discussion section.

Tables and Figures

- In Table 2, under column Bacterial species involved in pneumonia can the authors express the percentages of each bacteria as an expression of total species (i.e. 51 as a denominator) and not separately for gram positive and gram negative - currently it appears quite confusing to the reader.

As suggested by the reviewer, these changes have been made in Tables 2 and 3.

- In Table 3, the purpose of differentiating the various species between donor and recipients bronchial colonization is not clear. While comparing such a wide range of species in donors and recipients, there is bound to be some statistical significance - what is the clinical significance of this analysis?

The purpose of this table is to describe the ecology in this study, ie donor and recipient colonization.

Statistical analysis highlighted the major differences between these two entities. Donor species are mostly Gram-positive bacteria, while recipient species are mostly Gram-negative bacteria with a large proportion of non-fermenting Gram-negative bacilli.

Overall: excellent job of doing a thorough description of methods of the study and addressing all adequate limitations. However, the authors spend a lot of time describing already well known facts regarding the association between pneumonia and mortality and the clinical challenges of diagnosing pneumonia in this population - they can focus more on describing interesting unique findings in their study that adds value to the field.

We thank the Reviewer for his comment. We have therefore clarified the aim of the study in the introduction section. We assume that the low proportion of BRI with microorganisms cultured from donor samples is an important point for the reader. In addition, the small number of cases of pneumonia caused by microorganisms initially cultured from tracheobronchitis is of major clinical relevance. However, based on our local policy of antibiotic therapy against all episodes of BRI, we cannot conclude on the efficacy of this approach and the protective role of early antibiotic therapy in the development of BRI. This point has been added to the discussion section.

An additional point of interest is the emergence of microorganisms not reported in previous samples, in either colonization or tracheobronchitis samples. This observation suggests the potential importance of the digestive reservoir, an issue addressed by several teams by means of
selective digestive decontamination. This point has been added to the revised version of the manuscript.

Ademola Fawibe (Reviewer 2): General comments: the article has addressed an important aspect of medicine and it is very relevant in spite of its retrospective nature. It is generally well written but there are few issues that need to be addressed as can be found in my comments below.

1. The method section should start with statement stating unambiguously that it is a retrospective study and also specify the exact period covered by the review (months and years eg. September 2006-April 2012).

This point has been added to the methods section.

2. The fact that respiratory colonization samples were taken more than 6 months prior to transplantation might have impacted on the results and so this should be mentioned in the limitations.

In our center, respiratory colonization samples were performed in a large proportion of patients more than 6 months before transplantation, which may be a source of bias. Information about species during the last 6 months in our practice might be interesting, especially to determine the antibiotic prophylaxis during the first 48 hours following transplantation.

These comments have been added to the limitations section.

3. Page 9 paragraph 1 lines 10-12 under results: 2nd and 3rd sentences should be reframed in order to make it clearer to the readers eg Overall, 161 (92%) patients were mechanically ventilated of which 64% had BRI

We have rephrased these sentences: “161 (92%) patients required mechanical ventilation during their ICU stay and 64% of patients were mechanically ventilated at the time of diagnosis of BRI”.

4. Refs: there should be uniformity eg where there are more than 6 authors then the 1st 6 should be listed followed by et al as against the haphazard way the authors listed some 6 and et al while some are more than 6 and then followed by et al.

As suggested by the reviewer, these changes have been made.

5. Tables and Figures:
a. Table 1 page 22: the authors need to look closely and make necessary corrections. For example, under underlying diseases, a total of 70 patients were said to have had Emphysema/COPD but 5 without BRI and 64 with BRI. Where is the remaining 1 patient? Further analysis of this same group of patients showed that 14 patients had pneumonia and 51 had tracheobrochitis only making 65 patients which is higher than the 64 patients reported to have had BRI. Similarly for IPF, a total of 66 patients: 7 without BRI and 58 with BRI making 65 patients leaving 1 patient unaccounted for. However, 9 were said to have had pneumonia and 50 with tracheobrochitis only making 59 patients with remaining unaccounted for. Similar irregularities also affect the others group as well as single lung transplantation.

Thank you for this important comment. We have checked our data and found a number of mistakes:

- 70 patients had emphysema/COPD; 5 without BRI and 65 with BRI.
- 66 patients had IPF, 7 without BRI and 59 with BRI.
- 118 patients were men; 6 without BRI and 112 with BRI.
- No mistake was found concerning type of LT (single or double).

These points have been corrected in Table 1 with new statistical analyses.

b. Authors should indicate significant p values with a sign eg asterisk and interpret it in legend below the Tables. Also abbreviations should be interpreted in legends because the readers should be able to interpret Tables and Figures without referring back to the main article.

We are a bit confused by this remark, as adding asterisks does not correspond to the way the results are presented in the papers recently published in BMC Pulmonary Medicine.

Abbreviations have been modified in the tables in line with the reviewer’s comments.

c. Table 5 should be properly titled not just outcome!

We have modified the title of Table 5.