Author’s response to reviews

Title: The Utility of Endotracheal Aspirate Bacteriology in Identifying Mechanically Ventilated Patients at Risk for Ventilator Associated Pneumonia: a Single-Center Prospective Observational Study

Authors:

Ekaterina Kabak (kabak.ekaterina@gmail.com)

Jana Hudcova (jana.hudcova@lahey.org)

Zoltan Magyarics (zoltan.magyarics@gmail.com; zoltan.magyarics@arsanis.com)

Lukas Stulik (lukas.stulik@arsanis.com)

Marie Goggin (marie.a.goggin@lahey.org)

Valéria Szijártó (valeria.szijarto@gmail.com)

Eszter Nagy (eszter.nagy@evelique.com)

Chris Stevens (aclstevens@gmail.com)

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Author’s response to reviews:

We would like to thank you for considering our manuscript for publication in BMC Infectious Diseases, as well as the reviewers for providing valuable feedback and helping us improve our work.

Before addressing the comments of the reviewers, we would like mention the changes to the list of the authors. The work of Marie Goggin was indispensable for this study; in fact, already at the start of drafting the manuscript the decision of listing her in the “Acknowledgements” section proved to be an especially challenging one, seeing how much she contributed to the study. Marie is a senior technologist in the Lahey Clinic Microbiology Laboratory; for the current study she set up the microbiological methods, consulted us on a number of technical details, partially performed the ETA analysis and oversaw the study in the laboratory. During the process of implementing the changes suggested by the reviewers Marie provided invaluable support with questions related to microbiological analysis, local epidemiology data, and technical details of microbiological analysis. We feel that her contribution was substantial enough to qualify her to be a co-author of this manuscript. All the other co-authors have agreed with this decision. Marie herself has reviewed and approved the submitted version.
Next, we would like to provide the point-by-point responses to the issues raised by the reviewers.

Dear Dr. Dominedo,

Thank you for your review and comments to our manuscript. We have implemented your suggested changes as explained below.

• The authors define the aim of the study. Could the authors state what the hypothesis of the study was and define exclusion criteria?

We hypothesized that patients heavily colonized with pathogenic bacterial species in the trachea were more likely to develop culture-positive VAP during their ICU stay, and that heavier burden of colonization is associated with a higher risk of developing a bacterial VAP. The study hypothesis has been outlined in the lines 79-82.

• Could the authors state the primary outcome of the study? Are there any secondary outcomes?

The primary outcome of the study was the VAP incidence in relation to bacterial airway colonization. Secondary outcomes included the duration of mechanical ventilation, ICU and hospital length of stay, as well as all-cause mortality in patients with and without VAP. We have added the primary and secondary outcomes of the study into the manuscript (lines 82-85).

• Could the authors provide more details regarding the statistical analysis? How are variables reported? How was the level of significance set?

The section on the statistical analysis has been expanded (lines 167-173). The workflow of the statistical analysis has been described, and the level of statistical significance has been outlined.

• Could the authors provide more details about the baseline characteristics of the study population? (Smokers, previous antibiotic use, previous corticosteroids use, comorbidities, severity scores)

We have expanded the Table 1 to include more data on the baseline characteristics of the patients in the study, including most frequent comorbidities (hypertension, diabetes mellitus, asthma, COPD, chronic heart failure, malignancy), smoking history (previous and current smoker), history of alcohol abuse, and antibiotic use in the last 90 days or upon admission (line 198 onwards).
Unfortunately, we could not include the severity scores because of the clinical parameters needed for their calculation have not been recorded for every patient, or were recorded at different time points during the ICU stay. We added a remark on the on lines 193-196.

- What was the rate of MDR pathogens in the three ICU involved in the study?

The MDR rate was not calculated separately for the ICUs at the Lahey Clinic. Instead, a global report on the antibiotic susceptibilities of the bacterial species isolated at the Lahey Clinic was provided at the start of the study. We have added an explanation on that in the lines 103-104, 113-116, and 207-210, and summarized the provided findings in Table S1. The link between provided antibiotic susceptibility rates and our microbiology findings is commented on in the lines 217-219.

- Was SDD administered?

No SDD was administered as part of routine ICU patient care. We have added the statement on that (line 159-160).

- Could the authors provide data regarding empiric antibiotic therapy?

We have provided data on empirical antibiotic therapy approach in the Lahey Hospital and Medical Center ICUs in the lines 160-164.

- Pag. 3 line 66: I suggest correcting the sentence as follows: "In the case of VAP radiological and clinical signs…"

We have corrected the sentence as suggested (line 67).


The reference has been added (line 72).

- Pag. 3 lines 97-98: How were MDR pathogens defined?

Resistance to multiple antibiotic classes, with the conventional microbiological methods and Microscan® panels, and/or detection of ESBL or carbapenemase activity. We have described the criteria and the methods of defining the bacterial multidrug-resistance in Lahey Hospital and Medical Center microbiological laboratory (lines 116-119).

- Pag. 4 line 108: How data were collected?

Direct or collateral history taking, as well as analysis of the previous medical records, were used to collect basic demographic parameters. Diagnostic parameters were collected daily as part of the daily patient rounds, and duration of ICU stay, mechanical ventilation and hospital stay were
recorded at the end of the hospital stay. This has been described in more details in the lines 98-103.

• Pag. 5 line 124: Were other samples collected for VAP diagnosis?

For a selected number of patients BAL and NBAL were performed upon the orders of the treating physician. We did not include this data into the analysis, as they were not carried out routinely, and were not limited to cases of suspected pneumonia. We comment on this in lines 147-152.

• Pag. 6 line 151: I suggest changing the title since the paragraph refers to all pathogens isolated in ETA cultures.

The paragraph name was changed according to the suggestions (line 207).

Dear Dr. Ceccato,

Thank you for your review and comments to our manuscript. We have implemented your suggested changes as explained below.

• The rate of VAP is higher than 35%, this rate would seem similar to rate of VAP in patients heavily colonized by Staph aureus. So, the effect of heavily colonisation would be similar than in patients with none isolation. Please discussed it widely.

This finding was, indeed, unexpected. We mentioned this fact and added an expanded discussion on this phenomenon in the lines 338-360.

• There is a lack of clinical data of patients that would be of interest for the analysis, for instance underlying conditions, antibiotics prescriptions, tracheobronchitis diagnosis, CPIS, or infections other than VAP. Please include it.

We have expanded Table 1 with the clinical data including most frequent accompanying conditions (hypertension, diabetes mellitus, asthma, COPD, chronic heart failure, malignancy) and antibiotic use in the last 90 days or upon admission (line 198 onwards). These findings are commented on in the lines 298-300.

Nosocomial infections other than VAP has not been systematically assessed in this study. This has been outlined in the lines 152-153. CPIS could not be included into the analysis, since the parameters needed for its calculation were recorded at the different times of the study period among the patients, or incompletely. We state it in the lines 193-196. The diagnosis of ventilator-associated tracheobronchitis (VAT) was not assessed in the course of the study. Authors believe
that, in absence of radiological confirmation of pulmonary infiltrate needed for the diagnosis of VAP, diagnosis of VAT is most accurate when confirmed by the treating physician, which, in our case, conflicted with the design of the study. An explanation on that is added in lines 154-157.

- There are several figures difficult to understand because they have two, three or more panels (e.g. fig 2, 3 and 4). Please, simplify them.

Manuscript figures have been separated into seven to reduce the amount of multiple panels.

- In the table 1, the clustered between surgical and medical ICU don’t contribute to results and discussion.

We have addressed the comparison of the patients admitted to the SICU and MICU in the lines 183-191 and 296-302.

Sincerely yours,

Zoltan Magyarics