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AUTHORS' RESPONSE

Name of journal: World Journal of Transplantation
ESPS manuscript NO: 24300
Title: Ventilator associated pneumonia following liver transplantation: etiology, risk factors and outcome
Science editor: Jin-Xin Kong

Dear Dr. Jin-Xin Kong,

Thank you and the Journal's Editorial Board, as well as the expert reviewers, for the helpful critique of our manuscript. My colleagues and I sincerely appreciate the opportunity to revise the manuscript and to answer the comments and criticisms regarding our study.
As request, I have provided the following items with respect to our resubmission:

Reviewer's code: 00504119
Reviewer's country: Brazil
Date sent for review: 2016-01-18 19:29
Date reviewed: 2016-01-20 01:43
COMMENTS TO AUTHORS
Change the reference 5 ; internet communication is unclear
Terlipressine as risk facor needs to be clear because the drug is usual medication for hepatorrenal syndrome and the patients are coinfected or had previous infectious, this matter is not clear

AAS'RESPONSE
Reference 5 has been revised, thank you for your suggestion.
Thank you for remarking the issue about terlipressine usage. As reported in the discussion we highlighted the need for further studies to investigate if the hepatorenal syndrome or its treatment with terlipressin is the effective risk factor for VAP. We introduced the use of the mentioned drug instead on its indications as the clinical and lab parameters are included in other scores. Our intent is to report the statistically significant association. Of course, none of the patients who developed VAP presented signs or symptoms of infection before liver transplantation.

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Reviewer's code: 03012910

Reviewer's country: Greece

Date sent for review: 2016-01-18 19:29

Date reviewed: 2016-02-03 18:24

COMMENTS TO AUTHORS

As VAP is the main acquired infection in ICU and Orthotopic Liver Transplant (OLT)recipients have high risk for life-threatening nosocomial infections, studies, like yours, which establish the icidence, the risk factors and the outcome of this special subpopulation, have a lot of interesting, as data about the infections in OLT patients is still poor. Perhaps, extra data about the susceptibility testing of isolated microbes (for example if the klebsiella pneumoniae isolates were carbapenem resistant or not) and the administered antimicrobial agents and their appropriateness, may give more information about treatment options of VAP in OLT patients

AAS'RESPONSE

Thank you for your appreciation to our study and for pointing out the need for more data on susceptibility testing and antimicrobial agents. However our aim was to determine the incidence and the risk factors to stress the concepts of impact and thus prevention of VAP, more than microbiological issues. Our data on the etiology reflect approximately previous studies in terms of microbial agents and the treatment started with broad spectrum agents then followed the susceptibility testing response. Thus we guess to not add other information in the manuscript, however, if requested, we can provide the data. Thank you for giving us the opportunity to clarify this point.

Reviewer's code: 02907947

Reviewer's country: Italy

Date sent for review: 2016-01-18 19:29

Date reviewed: 2016-01-31 02:19

COMMENTS TO AUTHORS

Major comments

1. In the definition, the authors state that they have considered only episodes occurred within 48-72 hours post-intubation, but also those occurring whitin 48-72 hours post-extubation should be considered as VAP. Did the authors check for the early post-IOT episodes in the medical charts?

AAs': Definitively, the definition used in the manuscript is "*appearing 48-72 hours post intubation and initiation of MV"* **that includes both extubeted or still-intubeted patients. Thank you for pointing this out, just in case the definition was not clear.**

2. The paragraph of statistical analysis should be rewritten. The authors stated two times how they presented continuous variables with two different explanations; while they did not explain which kind of multivariate model was used, with which variables and method
   AAs':done

3. In the description of etiology distribution data about antmicrobial susceptibility/resistance are missing
   AAs': Thank you for giving us the opportunity to clarify this point. We understand the need for data on susceptibility testing and antimicrobial agents. However our aim was to determine the incidence and the risk factors to stress the concepts of impact and thus prevention of VAP, more than microbiological issues. Thus we guess to not add other information in the manuscript, however, if requested, we can provide the data.

4. Why did the authors use the terlipressin variable instead of its indication? This should be clarified in the methods and assessed in the discussion as a limitation of the study
   AAs': Thank you for remarking this issue, as reported in the discussion we highlighted the need for further studies to investigate if the hepatorenal syndrome or its treatment with terlipressin is the effective risk factor for VAP. We introduced the use of the mentioned drug instead on its indications as the clinical and lab parameters are included in other scores. Our intent is to report the statistically significant association.

5. Discussion can be shortened in my opinion, and a paragraph on the limitations of the study (monocentric, low number of pneumonia cases, not inclusion of early post-IOT episodes, missing of some variables i.e. indication for terlipressin etc) should be added
   AAs':done

6. Key message should be rewritten, in the first point "VAP diagnosis follows…can be removed, data about univariate should be presented before those of multivariate, the item on terlipressin use should rephrased

AAs': We guess there is no need for key messages that would result redundant, as the core tip sufficiently highlights the key message of the manuscript.

7. Please change the number 5 reference with that of ATS/IDSA guidelines or CDC criteria for nosocomial infections
   AAs':done

8. Tables 2 and 4 can be joined, in table 3 please provide meaning and/or reference for donor risk calculation, table 5 can be removed, please specify in the methods and in footnote of the last table which variables were inserted in the multivariate model.
   AAs': done, you can find the reference for donor risk index in the Data Collection paragraph of the Methods section.

Minor comments

1. In the abstract please rephrase "VAP diagnosis follows…" in VAP was diagnosed according with clinical and microbiological criteria
   AAs':done

2. Remove logistic after univariate (see major comment)
   AAs':done

3. Please specify throughout the paper if the value of MELD score was that on the day of transplantation (median or mean MELD at transplantation)
   AAs':done

4. Please provide the meaning for abbreviation CTP
   AAs':done

5. Please specify the red cells transfusion refers to the large amount of red cell transfusion throughout the paper
   AAs':done

6. Please provide the meaning for the abbreviation TIPS

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AAs':done

We sincerely appreciate the many helpful comments and criticisms of this study. We have incorporated these suggestions in the revised manuscript. My co-authors and I believe that the revised manuscript represents a significant improvement over the original submission to the Journal. Please let us know if any additional changes are required for final acceptance and future publication of this manuscript in World Journal of Transplantation.

Best regards,

Dr. Antonio Siniscalchi