To
Dr. Ying Dou
Science Editor, Editorial Office
Baishideng Publishing Group Inc

Sir,

Thank you for your kind invitation to contribute an Observational Study to *World Journal of Cardiology*.
I have the pleasure to send to your attention the manuscript revised according to the reviewers' and Science Editor comments as well as updated according to the Guidelines and Requirements for Manuscript Revision: Observational Study.

Title: Incidence and Risk Factors for Potentially Suboptimal Serum Concentrations of Vancomycin during Cardiac Surgery

Authors: Paolo Cotogni, Cristina Barbero and Mauro Rinaldi

Name of Journal: *World Journal of C**ardiology***

Manuscript NO: 40797

Answer to Science Editor
The manuscript has been modified according to the suggestions of reviewers and the Science Editor as well as the format has been revised. The corrections are marked in red in this revised edition.

Reviewer's code: 03650328
1. In the Abstract Conclusion, mention the subgroups that the authors have identified as being at risk for suboptimal vancomycin levels. I would also include the result that infusion duration did not correlate with frequency of suboptimal levels.
R. As suggested by the reviewer, we have added in the Abstract Conclusion the details regarding risk factors for suboptimal vancomycin levels and we have included the result that infusion duration did not correlate with frequency of suboptimal levels. Specifically, we have changed the Abstract Conclusion in the following way: 'Results of the present study identified female gender, BMI >25, and creatinine clearance above 70 mL/min as risk factors for suboptimal vancomycin serum concentration during cardiac surgery; no relationship was found between infusion duration and vancomycin level under 10mg/L.'

2. Are the headings for Table 1 correct? In the Abstract, it is stated that the Cmax and AUC were higher in the patients with no level <10 mg/L.
R. We thank the reviewer; we have corrected Table 1 (new Table 2) headings.

3. Given that the number of outcomes (3 SSIs) is too small for statistical comparison, can you estimate the number of patients required for a future study to determine the impact of subtherapeutic vancomycin levels on frequency of SSIs (i.e. will this require a multi-centre study)?

R. We agree with the reviewer that the number of patients to consider having significant results is a topic of paramount importance. However, the number of SSI detected during the study period is very low (2 in the group of patients with vancomycin level constantly above 10 mg/L and 1 in the group of patients with at least 1 level under 10 mg/L). According to our results, we would need 4634 patients to have a 80% chance of detecting, as significant at the 5% level, a decrease in the incidence of SSI from 2% in the control group to 1% in the experimental group. Considering only these 3 patients with SSI it is difficult to get a reliable value of sample size, therefore we decided not to include these considerations in the manuscript.

4. Since the 10 mg/L level was chosen arbitrarily, please report the frequency of all vancomycin levels measured (10, 20, 30 and 40 mg/L) for the cohort.
R. As suggested by the reviewer, we have reported the frequency of all vancomycin levels measured. Specifically, we added the following sentence in the Results section: 'In 443 cases out of 1682 serum samples, vancomycin level was lower than 10 mg/L, in 821 cases vancomycin level was between 10 and 20 mg/L, in 192 cases vancomycin level was between 20 and 30 mg/L, in 73 cases vancomycin level was between 30 and 40 mg/L, in 50 cases vancomycin level was between 40 and 50 mg/L, and in 103 cases vancomycin level was higher than 50 mg/L.'

5. Why was >70 years chosen as the cut-off for age at surgery?
R. The biomedical statistician has chosen the median value (i.e. 70) as the cut-off for age.

6. Similarly, what is the justification for CrCl >70?
R. Similarly, the biomedical statistician has chosen the median value (i.e. 70) as the cut-off for CrCl.

7. Define what you mean by 'fluid balance' and infusion 'stopped vs. non-stopped' in Table 2.
R. 'Fluid balance' refers to the equilibrium between the amount of water administered to the patient and the amount of urine output and blood loss during the surgical procedure. We distinguished patients in 2 subgroups according to the amount of fluids administered during the surgical procedure (more or less than 2000 mL).
Infusion 'stopped vs. non-stopped' refers to cases where the vancomycin infusion was stopped by the anesthesiologist before the end of the vancomycin infusion.

8. Is the timing of the low level(s) more important than the frequency? Was this examined?
R. Thank you for the good question. The answer is no. This issue was already examined in one our previous publication (see reference n. 13).

9. For Figure 2, in the legend, can you please include what the target time was.
R. As suggested by the reviewer, we have added in the legend of the figure 2 the target time. Specifically, 'The target time for the duration of vancomycin infusion is 60 minutes.'

10. In the Abstract, I think it is worth mentioning, in addition to the number who had at least 1 subtherapeutic level, that 54 patients had >=5 subtherapeutic levels since this is likely more relevant for the development of resistance than just having 1-2 low levels.

R. As suggested by the reviewer, we have added the following sentence in the Abstract (Result section) and in the main text (Result section): 'Fifty-four out of 236 patients (22.9%) had at least 5 serum samples with vancomycin level lower than 10 mg/L'.

Reviewer's code: 00227341
I suggest some changes:
- it could be useful to introduce a table on the population characteristics as the reference article is not available for everyone on pubmed
R. As suggested by the reviewer, we have added a new table regarding patients' characteristics (Table 1).

- page 7, line 18 please specify the acronym SSI
R. Done.

- page 8 line 14 MRSA o MSSA?
R. We have specified that is a methicillin-sensitive *Staphylococcus aureus* (MSSA).

- page 8, line 28 : I would suggest inserting two ROC charts in reference to what is written "Vancomycin PK parameters were estimated and compared between above versus under 10 mg/L patient groups (Table 1): Cmax and area under the concentration-time (AUC) curve were significantly higher in the patients with no vancomycin level under 10 mg/L, while the apparent total body clearance (Cl) and the apparent volume of distribution during the terminal phase (Vd) were significantly higher in the patients with at least 1 episode of vancomycin concentration under 10 mg/L."
R. Thank you for this comment. We used ROC curve analysis trying to identify a relationship between duration of drug infusion and the occurrence of vancomycin concentrations under 10 mg/L. However, we couldn't find any relationship and therefore we did not add the relative figures.
Instead, the comparison between the 2 groups (above vs. under 10 mg/L) was performed through Fisher's exact test for categorical variables and Mann-Whitney test for continuous ones and results regarding Cmax, area under the concentration-time (AUC) curve, apparent total body clearance (Cl), and the apparent volume of distribution during the terminal phase (Vd) are reported in Table 2.

I thank you for considering this manuscript for publication in your journal.

Sincerely,

Paolo Cotogni, MD, MSc (Corresponding author)
Department of Anesthesia, Intensive Care and Emergency
Molinette Hospital, University of Turin
Via Giovanni Giolitti, 9
10126 Turin, Italy
Mobile: +393387018496
E-mail: paolo.cotogni@unito.it

Turin, 13 August 2018