Author's response to reviews

Title: Empiric guideline-recommended weight-based vancomycin dosing and mortality in methicillin-resistant Staphylococcus aureus bacteremia: a retrospective cohort study

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Author's response to reviews: see over
Reviewer: Albert Lessing

Thank you for your review and compliments you bestowed upon our work. Below is our response to one of your two clinical observations.

1. Deep infection caused by bone comprised only 1.2% of the patients studied: We were also initially surprised by this finding. However, most cases of osteomyelitis are only transiently bacteremic, which may be responsible for the very low rate of bone infections in our study population.

Reviewer: Dale Fisher

Thank you for your review of our manuscript. We have attempted to address your concerns as outlined below.

1. The study goes too far by implying the potential dangers of “excessive” dosing: We respectfully disagree. We are simply stating that this study failed to provide evidence that guideline-recommended, weight-based dosing improves survival. Given this result, clinicians should carefully monitor vancomycin trough concentrations to minimize the risk of nephrotoxicity since there was a statistically significant relationship between nephrotoxicity and death in this study.

Methods

2. Why did the authors allow lower doses for the first dose in patients with kidney impairment: We acknowledge that the prescribing information states that all patients with mild or moderate renal insufficiency should receive a 15 mg/kg loading dose. However, the study institutions do not follow this practice as evidence by 85% of all patients receiving vancomycin 1 g Q12H. Therefore, we chose to evaluate the regimens based on maintenance dosing.

3. Charlson Comoribidity Index can be measured at any time. No need for emphasis of collection time: We have removed the emphasis from the methods.

4. What is meant by “initial” hospital stay: This has been changed to index hospital stay to provide better clarity to the reader (page 6).

5. Nephrotoxicity could be due to other things and shouldn’t be assumed to be due to vancomycin. In addition, there is no breakdown of nephrotoxicity by dosing: We share the reviewer’s enthusiasm, but this manuscript’s primary aim is to determine whether guideline-recommended, weight-based dosing is associated with mortality. We used a standard definition of nephrotoxicity that has most commonly been used in studies evaluating vancomycin and nephrotoxicity, but this measure cannot explain the reason for nephrotoxicity.

6. The first sentence of the statistical analysis section is unnecessary, particularly regarding extensive clinical experience: This sentence has been deleted as suggested.
Results

7. Table 1 state that non-survivors were more likely to have adjustment for renal impairment. Why is this? It seems to suggest that these patients may have taken longer to reach adequate trough concentrations: Non-survivors are more likely to have a greater severity of illness (as determined by Pitt bacteremia score and ICU admission) and lower CrCl, so it is likely that patients receiving dose adjustments are more likely to die due to their increased severity of illness. We agree that time to therapeutic trough is a potential issue and have added this limitation to the discussion.

8. Also, high vancomycin troughs being associated with mortality is illogical: Vancomycin trough concentrations ≥ 15 mcg/ml were associated with mortality in the univariate, but not the multivariate analysis. Therefore, the associated finding of increased mortality and vancomycin trough concentrations ≥ 15 mcg/ml in the univariate analysis were likely confounded by other factors.

9. It is not clear when the vancomycin trough concentrations were taken: The vancomycin trough concentrations were obtained according to the local standard of practice at each hospital. Our failure to collect the information in a fashion to include time to target trough concentration has been added as a limitation in the discussion section.

10. The implications of the conclusions are dangerous: Please see our previous reply above (comment 1).

11. The limitations of the work are clearly stated: Thank you.

Writing

12. Change reference to this being the first study to first published study: Changed. Thank you for the suggestion.

13. The first sentence in the methods uses “identified” twice and “hospital” 4 times: This sentence has been revised. Thank you for the suggestion.