Reviewer’s report

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

Version: 3 Date: 5 January 2013

Reviewer: Douglas Ball

Reviewer’s report:

Although responses have been provided to all points raised by reviewers, in some cases explanations have been made in the cover letter but no change/addition made to the manuscript as had been intended. These explanations are considered necessary to assist readers in understanding and appraising the study. Please therefore address the following by making changes/additions to the manuscript:

1. Include information on the sample size calculation. Also give additional parameters used i.e. detectable difference, power, calculated size.

2. Include the following from the cover letter in the section describing bias (some editing of text will be required to avoid repetition): "To address potential confounding, we conducted stratified analysis on outcomes considered to potentially affect the primary outcome. Biologically plausible factors that demonstrated confounding were included in the multivariable model. We have also minimized the risk of clustering by utilizing a mixed-effect model and using hospital site as the random effect.

3. Previously had been asked to "Provide a breakdown/flowchart of subject selection and address why relatively few of the 'total population' were included and how this influences interpretation of the results". No flow chart is provided and the influence has not been adequately addressed. The information on the automated screening and lack of records on reasons for exclusion should be included in the manuscript. In addition, more is needed since the use of automated screening explains the process but not the effect which must be addressed. It is recognised that the authors have added a statement relating to lack of external validity late in the discussion but this needs more clarity.

4. Include information on number of patients from each hospital and event rates in the text. Explicitly address the issue of clustering and inter-hospital differences and how this was addressed as a paragraph/set of sentences in the Discussion.

5. Clearly state in the methods that only the first/initial vancomycin trough level was used in analysis.

6. Give information on how vancomycin TDM was conducted at the hospitals eg. lack of routine vancomycin monitoring service rather based on "vancomycin
trough concentrations were obtained as clinically indicated as determined by each
prescribing physician", in the text of methods where describing hospitals. Were the patients with available vancomycin levels likely to be more complex cases than those without (and therefore excluded)? Mention in paragraph on bias in Discussion.

7. The date / timeline for the introduction of weight-based dosing in guidelines is not given in the text and the frequent use of the term "guideline-recommended, weight-based vancomycin dosing" and other phrases e.g. "Vancomycin was dosed according to guidelines in 33.6% of patients" suggests to readers that the study is examining the effects of following the guidelines when in fact they are examining past dosing as per new/current guidelines. Although it may be obvious to the authors, they should make it clear for readers (i) when the guidelines were issued, and (ii) that the retrospective study examines the effect where past dosing has been in line with the new/current guidelines. At times it may be useful to use phrases such as 'weight-based vancomycin dosing as recommended in the new guidelines' rather than the oft repeated "guideline-recommended, weight-based vancomycin dosing" at times in the text.

8. The fact that each study institution could have used different vancomycin assays as part of their clinical standard practice must be stated in the text as potential limitation in the discussion.

9. Provide more in the discussion on obesity/weight issues raised by reviewers i.e. that obese patients could receive higher absolute doses/quantities giving rise to association (as per response to reviewers).

10. Include the response to the question "Why were patients with renal dysunction and/or prior MRSA infection excluded" in the text of the manuscript.

**Level of interest:** An article of limited interest

**Quality of written English:** Acceptable

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**

I declare that I have no competing interests