Reviewer's report

Title: Effect of vancomycin serum trough levels on outcomes in patients with nosocomial pneumonia due to Staphylococcus aureus: a retrospective, post hoc, subgroup analysis of the Phase 3 ATTAIN studies

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Reviewer: Natasha Holmes

Reviewer's report:

The manuscript by Barriere and colleagues describes vancomycin serum trough levels in patients with nosocomial S. aureus pneumonia and explores the relationship between trough levels and clinical outcomes. This is relevant to everyday clinicians because there is increasing use of higher vancomycin doses to improve PK/PD measures but this may be at the expense of increased toxicity without the added benefit of improved clinical outcomes. Their findings about increased nephrotoxicity with higher vancomycin troughs are similar to those published by van Hal et al. in their systematic review and meta-analysis of vancomycin nephrotoxicity with troughs between 15-20 mg/L (AAC 2013:734). This manuscript adds to the existing literature by also evaluating vancomycin troughs and clinical outcomes in a prospectively collected clinical trial population.

As indicated in their methods, this is a retrospective post-hoc sub-group analysis of a trial population so statistical conclusions should be viewed with some caution. It is also noted that in the original ATTAIN trial population, the presence of S. aureus from a respiratory specimen in ICU or ventilated patients may not necessarily indicate nosocomial pneumonia; new CXR changes do not always represent evolving infection and respiratory samples may have been contaminated from S. aureus oropharyngeal colonization.

The authors have acknowledged many of the limitations of their analysis, notably the higher proportion of patients with pre-existing acute renal failure in the high trough group (and therefore a pre-existing problem increased the likelihood of higher trough levels and potential nephrotoxicity), and the higher proportion of patients with multilobar pneumonia in the high trough group (and therefore presumably were sicker and were treated more aggressively). The trend for increased mortality in the sub-group where acute renal failure or recent vancomycin exposure were excluded is only based upon a very small number of patients (a sub-group within the sub-group analysis).

Nevertheless these clinical data were collected rigorously in a clinical trial setting and these findings support the need for further prospective studies.

Major compulsory revisions

None.
Minor essential revisions
1. Line 40: insert word ‘events’ after “Renal adverse…”.
2. Line 99: it is not clear at which timepoint ‘median vancomycin trough level’ was calculated. Was this the median level over the entire course of vancomycin treatment? Did this include levels obtained prior to steady state in this calculation?
3. Line 108-109: there are no definitions or references for ‘acute renal failure’, ‘chronic renal failure’, ‘renal impairment’ or ‘renal insufficiency’. Were these decided at each study site by a trial investigator? Which criteria were used?

Discretionary revisions
4. Line 99: were there differences in median trough levels or clinical demographics in those patients who had shorter treatment courses (eg. 7 days) compared with those who had longer treatment courses (eg. 21 days), eg. were the patients who were treated with vancomycin for 21 days sicker or had more bacteremia?
5. Line 108-109: in patients with pre-existing acute renal failure, how was a renal adverse event defined? How was ‘chronic renal failure’ used to describe a renal adverse event with only a short exposure to vancomycin (7-21 days of treatment)?

Level of interest: An article of importance in its field

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.