Author's response to reviews

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

Authors:

Ronald G Hall II (ronald.hall@ttuhsc.edu)
Kathleen A Hazlewood (khazlewo@uwyo.edu)
Sara D Brouse (sara.brouse@uky.edu)
Chris A Giuliano (ek2397@wayne.edu)
Krystal K Haase (krystal.haase@ttuhsc.edu)
Christopher R Frei (freic@uthscsa.edu)
Nicolas A Forcade (nforcade8@gmail.com)
Todd Bell (Todd.Bell@ttuhsc.edu)
Roger J Bedimo (roger.bedimo@va.gov)
Carlos A Alvarez (carlos.alvarez@ttuhsc.edu)

Version: 3 Date: 2 November 2012

Author's response to reviews: see over
To the Editor and Reviewers,

Editorial comments

1. Please refer to the STROBE checklist for reporting cohort studies and ensure that all criteria have been addressed. In particular, please provide a basis for:
   a. Sample size: We estimated our sample size based on an estimated event rate of 26.5%. We estimated this event rate by averaging the highest (42%) and lowest (11%) event rates of previous work when developing this study. We had pre-specified that eight variables would be included in the multivariable model. Therefore, the ninety predicted events were sufficient to power the multivariable analysis conducted.
   b. Expand on data sources: All data were manually extracted from the patient’s medical record.
   c. Analytic methods for vancomycin assays: All laboratory data, including by vancomycin drug concentrations, were analyzed by the standard of practice methods utilized at each study institution.
   d. Measures to reduce bias/confounding: We recognize that a retrospective cohort is subject to selection bias and confounding. We utilized a well codified inclusion/exclusion procedure to help minimize the impact of these factors. This procedure included patients with MRSA bacteremia who had received vancomycin for at least 48 hours. 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.

2. 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: We utilized automated screening of patients based on the inclusion/exclusion criteria and did not record the reason for exclusion.

3. Describe how many patients were derived from each hospital and a subanalysis with descriptive incidence and risk at each facility:
   a. Hospital 1: 156 patients, 56% nephrotoxicity rate
   b. Hospital 2: 81 patients, 11% nephrotoxicity rate
   c. Hospital 3: 100 patients, 33% nephrotoxicity rate

We recognized that clustering was likely occurring given the different rates of events at each study institution. We addressed the potential for clustering through the use of a mixed-effect model.

4. As led in in the Introduction, the focus/concern relates to whether higher trough concentrations of vancomycin lead to nephrotoxicity. If guidelines for weight-based dosing are not being followed but vancomycin trough levels are similar then this is an important finding that will influence the conclusion. Review the data with this in mind and comment in the Discussion: The vancomycin troughs concentrations were not similar (p = 0.03) between the guideline-recommended dosing
group (median 12.3 mcg/ml; IQR 8.3, 17.5) and the lower dosing group (median 10.1 mcg/ml; IQR 7.1, 14.9). We have now included this data in the results and apologize if not including this information gave the appearance that the vancomycin trough concentrations were similar between the two groups.

5. **Given the extended lengths of hospital stay, presumably multiple trough concentrations were taken for most patients. Which trough concentration was used? What variability was there? How does this relate to following the guidelines? Provide some measure of vancomycin trough concentrations in the univariate analyses - did those who received the guideline recommendations have higher/lower trough levels (at least most of the time)?** We only utilized the initial vancomycin trough concentration since this investigation was focused on the impact of empiric guideline-recommended dosing. We recognize that a relationship exists between vancomycin troughs and nephrotoxicity (regardless of the direction of the relationship) and that clinicians will need to alter therapy to ensure vancomycin troughs remain below 20 mcg/ml. We have added information regarding the median and interquartile range of vancomycin trough concentrations to the manuscript text within the results section.

6. **In the paragraph addressing bias in the Discussion, give an indication of the direction of bias and potential effect on results/conclusion. A special focus on weight is required given it was identified as a risk factor and yet differed between cohorts at baseline. Also address potential differences in care, patient load, etc. at the three hospitals:**

The fact that heavier patients were less likely to receive guideline recommended dosing could have confounded the effect of guideline-recommended dosing on nephrotoxicity and been a potential reason for failing to observe a difference between the two groups. This risk was minimized by the inclusion of weight (≥ 100kg) in the multivariable analysis.

Our use of all vancomycin drug concentrations labeled as “trough” could have produced inaccurate results in some patients if the samples were not documented correctly in the medical record. This non-differential misclassification bias would be expected to be the same in both groups and should have a minimal effect on the relationship between vancomycin trough concentrations and nephrotoxicity. If an effect were to be observed, this bias would lessen the ability to determine the association between vancomycin trough concentrations and nephrotoxicity. The fact that a statistically significant relationship was observed lessens the possibility of this bias being a major factor in our analysis.

We recognize there are differences within the three study hospitals and have now included event rates for each of the study institutions. We have attempted to address the clustering issue from an analytical standpoint by the use of a mixed-effect model. Our data were not granular enough to answer process-specific questions regarding the reasons for these differences.

7. **Discuss/describe similarities/differences in local/facility guidelines that were being used at each hospital (including when they were introduced/updated) and how this might impact on uptake of the consensus guidelines. [International readers may not be familiar with the use of the guidelines of interest in this setting and some explanation/description is required]:** While each of the study hospitals has clinical pharmacists that are responsible for the monitoring of patients on vancomycin, none of the institutions utilized a formal pharmacy-driven vancomycin monitoring service. Our data
were not granular enough to answer process-specific questions regarding the reasons for these differences.

8. **Comment on the low adherence to guidelines and speculate why this was the case in this cohort study. Was this similar to the 'total'/excluded population?:** This is a retrospective classification of patients as to whether they received guideline-recommended dosing from 2002-2008. The vancomycin guideline was published in 2009 and the fact that many drug information sources recommended vancomycin 1 gram every 12 hours is why the use of weight-based dosing was so low. We would expect this to be similar to other hospitals for this time period.

9. **The conclusion is that there was no significant difference in nephrotoxicity therefore the guidelines can be used. One could equally say that since there is no difference, there is no need to use guidelines (assuming equal efficacy outcomes). Rather just monitor trough concentrations. Perhaps the wording needs to be rephrased to more directly address the objective:** The vancomycin guideline recommends the use of actual body weight-based dosing to help increase the likelihood of achieving a vancomycin trough concentration of 15 mcg/ml. The vancomycin guideline states that a vancomycin trough concentration of 15 mcg/ml increases the likelihood of favorable clinical outcomes in patients with MRSA infections. Since actual body weight has been shown as the best predictor of vancomycin pharmacokinetics, the guideline uses the pharmacokinetic data to optimize the likelihood of achieving a trough of ≥ 15 mcg/ml for all patients.

10. **Address the issue of power to detect a difference/sample size in the Discussion/conclusion and how reliable the result is given the wide confidence interval. Comment on 'worst case' that guideline based dosing could increase odds of nephrotoxicity by 3 times (multivariate analysis):** We recognize that our confidence intervals could be considered wide due to a small sample size and potential lack of power. However, our cohort study represents one of the largest sample sizes to our knowledge compared to other studies that have examined this issue. Jefferes et al in Clinical Therapeutics (2007) observed a 95% CI of 1.02-7.74 for vancomycin trough ≥ 15 mcg/ml. Lodise et al reported a 1.7-11.8 95% CI in Antimicrobial Agents Chemotherapy (2008).

Charles Nhachi

**COMMENTS**

1. **The authors introduce some ambiguity by interchanging rates and incidence. This should be clarified:** We have changed all mentions of nephrotoxicity to rates.

2. **The reason for waiving informed consent should be stated immediately after the statement of such waiver:** We have added this information.

3. **The actual retrospective cohort study is never described and defined, and therefore it is difficult to analyze the soundness of the data. The criteria for the number of patients from each hospital is not stated or supported:** We are confused by this comment. The design section outlines the study period, the population being evaluated (patients receiving vancomycin for MRSA bacteremia), and the dependent variable (nephrotoxicity). The study institutions are identified in the setting subsection. Our inclusion/exclusion criteria are outlined in the patients subsection. The dependent variable is defined in the definitions subsection. The independent variables considered for inclusion in the multivariable mixed-effects model are included in the statistical analysis subsection.
convenience sample was utilized for each study institution to achieve the targeted number of patients who developed nephrotoxicity to power the multivariable analysis conducted.

4. The authors fail to clearly expatiate and state the great limitations of a retrospective study: We added the following information to the limitations paragraph of the discussion to expand on the weaknesses of retrospective studies. “Retrospective studies may have differences between the comparison groups in regards to measured and unmeasured confounders. A multivariable mixed-effects model was utilized to minimize the impact of the differences in measured confounders.”

MINOR COMMENTS

1. In the results section:
   a. Who are the other patients?: The definition of other patients has been clarified in the results section. Five of these patients did not have race/ethnicity data and seven were recorded as “other” on the data collection form with no details provided.
   b. How are most patients?: This sentence was revised to “The most common dosing frequencies administered were once (11.3%) or twice daily (86.3%).

2. Are the findings risk factors OR conditions associated with nephrotoxicity? If they are risk factors, how are they evaluated?: They are risk factors which were evaluated in the multivariable mixed-effects model.

Federico Pea

1. Neither duration of treatment, nor stratification of nephrotoxicity risk in relation to length of treatment were analyzed. This needs attention: We are unsure of the source of this criticism since duration of vancomycin therapy was significantly associated with nephrotoxicity in the multivariable model (Table 3).

2. The vancomycin dose range for each group must be specified more than the minimum threshold: Table 1 specifies the median dose for each group as well as the 25th and 75th percentile. The values for the guideline-recommended, weight-based group were 32 mg/kg/day (29, 36) versus 21 mg/kg/day (17, 26) for the lower dose group with a p-value of <0.001.

3. Did each study institution use the same vancomycin assay?: Each study institution used the assay used as part of clinical standard practice as this was a retrospective study.

4. The differences in weight and baseline CLCr may represent major biases in the analysis: Our manuscript already acknowledged that the differences in weight may have made our results subject to a selection bias. We attempted to minimize the impact of this bias through the use of multivariable mixed-effects model. We respectfully disagree with the conclusion that the differences in CLCr would represent a major bias as weight and age were significantly associated with nephrotoxicity in the multivariable model. Baseline serum creatinine was not associated with nephrotoxicity in the univariable analysis and therefore was not included in the multivariable analysis. Therefore, all of the factors evaluated in the estimation of creatinine clearance were evaluated.
5. It is unclear how the authors chose the cutpoint for some covariates (e.g. age > 52 years; weight > 100 kg): We stated in the methods that “Dichotomization of continuous variables was achieved by recursive partitioning to determine significant cut-points.” This method was used to determine the cutpoint of > 52 years. We used previous literature, including reference 24, to justify using a cutpoint of > 100 kg.

6. It would be more appropriate to assess BMI than TBW, given that vancomycin is a hydrophilic compound: We respectfully disagree with this comment. The literature regarding vancomycin pharmacokinetics in obese persons has found TBW to be the best covariate associated with Vd and Cl. Furthermore, the vancomycin guidelines recommend the dosing of vancomycin be based on TBW.

7. What does “none of the institutions used formal vancomycin TDM” mean? Please explain when TDM was performed after starting therapy and how often it was repeated in each patient: Clinical pharmacists are available to monitor vancomycin trough concentrations at each institution. However, pharmacy is not automatically consulted to manage vancomycin for all patients. That is what we intended the statement “none of the institutions used formal vancomycin TDM” to mean. Vancomycin trough concentrations were obtained as clinically indicated as determined by each prescribing physician.

Minor essential revision
Data regarding infection source (Table 2) may be summarized in the text: Infection source data were moved to the 1st paragraph of the results section.

George Sakoulas

1. The authors did not observe an increase in nephrotoxicity with weight-based dosing, but observed an increase in obesity. Could the authors clarify if this is simply a reflection of grams/day risk?: We carefully considered the possibility of this hypothesis as we were intrigued by this possibility. Ultimately, 86% of our patient population received vancomycin 1 gram every 12 hours. Therefore, few patients received higher dosing. Second, the data by Lodise et al suggesting that 4 grams/day increases the risk of nephrotoxicity included only a handful of patients weighing > 100kg in the 4 grams/day group. Therefore, most of the patients received ≥ 40 mg/kg/day, which may represent the effect of vancomycin overdosing instead of an adverse event at clinically recommended doses.

2. Restructure the background to state that clinical failures with higher MIC’s preceded the creep data: Restructured as suggested

3. Why were patients with renal dysunction and/or prior MRSA infection excluded?: Patients with a CrCl below 30 ml/min were excluded because these patients were considered more likely to require a dosing frequency adjustment to less than once daily dosing and our measure of vancomycin dosing intensity was mg/kg/day. Prior MRSA infections were excluded due to the likely prior receipt of vancomycin therapy.
4. Minor comments
   a. Change policymakers to experts in the field (line 4, background): Done
   b. Change skin/muscle to soft tissue in the 3rd line of results in the abstract and in the text: Done