Reviewer's report

Title: Clinical outcomes and molecular typing of heterogenous vancomycin-intermediate Staphylococcus aureus bacteremia in patients in intensive care units

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Reviewer: Kerry LaPlante

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REVIEWER'S REPORT

Comments to Author(s): The information below constitutes my objective and unbiased review of the manuscript titled “Clinical outcomes and molecular typing of heterogenous vancomycin-intermediate Staphylococcus aureus bacteremia in patients in intensive care units” (BMC-ID 4720391841573669) for publication consideration in BMC Infectious Diseases. Comments are as follows:

General Comment: Overall interesting retrospective study focused in hVISA bacteremia patients in ICUs. However, the manuscript needs major revisions to make it acceptable as there is a lack of detail, numerous spelling/grammatical errors, and incorrect use of words throughout (association, cause, risk factors, predictors, confounding). Further, without proper statistical methods (multivariate logistic regression) to assess for independent predictors the use of the words “risk factors” and “predictors” in this study is inappropriate. The study appears to be purely descriptive and I caution the authors on how they present and interpret the results.

Major Compulsory Revisions

Abstract:
1. Line 5: The use of the word “bacteremia” is not correct, the source of infection is irrelevant as hVISA can appear in any type of isolate (tissue, sputum, etc).
2. Methods: specify molecular typing and outcomes assessed
3. Results: lines 16 -18 cannot make this statement using descriptive statistics (X2 or Fishers exact test). Page 3 line 20 and page 4 this statement cannot be made without appropriate statistical analysis.

Introduction:
1. Page 5, line 4: Consider using “blood” or “circulatory system” instead of “bacteremia”. May also consider deleting this sentence and replacing it with a statement that depicts why it is so concerning.
2. Page 5, line 10: Would consider re-wording this statement to “However, recent attention has focused on the emergence of isolates with decreased vancomycin susceptibility.” You mentioned “poor clinical outcomes” here but do not specify until later in the background. Therefore recommend to mention it later.
3. Page 5, lines 11 – 14: Would consider breaking up and clarifying this sentence. Please also cite this sentence. Consider deleting the word “bacteremia” in “…has been considered a phenotype of MRSA bacteremia…” as the source of infection is not technically a phenotype and including the word “bacteremia” is irrelevant.

4. Page 5, lines 15: Consider deleting the word “isolate” after “vancomycin susceptible S. aureus”

5. Page 5, lines 16 – 18: Consider changing to “…. Frequently occur in isolates with a minimum inhibitory concentration (MIC) within the susceptible range (# 2 mg/L by E-test).”

6. Page 6, lines 5 – 6: Consider deleting this sentence as it is not relevant to your study and you have already mentioned the prevalence.

7. Page 6, lines 6 – 10: Consider making this statement into the start of a new paragraph and rewording to “Infections caused by hVISA have been associated with vancomycin treatment failure, persistent bacteremia, and prolonged hospital length of stay.[cite] However, the impact of hVISA bacteremia on mortality has yet to be determined.” Also consider adding a brief statement on these studies and their limitations as well as any data on hVISA in patient’s in the ICU.

8. Page 6, lines 9 – 16: Consider removing this information from background and placing it in your discussion.

9. Page 6, line 17: please specify “risk factors” or define in methods section. Page 11, line 12 -14 states “risk factors for mortality” but is not described in statistical analysis (see comments for that section). This would be another study aim.

10. Page 6, lines 17 – 19: In abstract you mentioned what appears to be a secondary aim comparing survivor and non-survivor groups but it is not mentioned here.

Methods:

Study design and patients
1. Page 8, line 3: Consider providing more information on the type of medical center (how many beds, number and types of ICUs).

2. Page 8, line 4: Please clarify if it was all patients “admitted” to the ICU or in the ICU at the time of the MRSA isolate? How did you define bloodstream infection?

3. Page 8, line 7: “only the data of the first episode was analyzed” do you mean the first isolate? How did you define recurrent and persistent bacteremia?

4. General: were patients that had other infections caused by other organisms at the time of MRSA bacteremia included? Please comment.

Clinical data
1. Page 8, line 10: Using the word “all” is confusing throughout this manuscript as it can have several implications. Consider avoiding the word “all” unless it is defined (i.e. all patients included in the study, all patients in the hVISA group,
etc). For this line consider stating “Data collection from patient medical records included: “

2. Page 8, lines 10 – 14: Do you mean Charlson comorbidity index? Please explain how you identified the primary site of infection, was it by assessment of other MRSA-positive cultures at the time of the MRSA blood culture or by medical notes in chart? Why choose the previous one month for vancomycin exposure? Other studies have done 3 - 6 months previous exposure. For receipt of chemotherapy or immunosuppressive therapy, was a certain dose chosen as the threshold of immunosuppression? What was it? Was there a time period of these treatments-- previous 1 month or was it longer? Please specify “other” immunosuppressive therapy in parenthesis. For “drugs used in this episode” do you mean concomitant antibiotics used? Please specify “status at discharge (alive? Deceased? Persistently infected?).

3. Page 8, lines 14 – 19: Please clarify “in-hospital mortality after MRSA bacteremia”. Length of hospital stay, does this include ICU length of stay (LOS), LOS before positive culture and/or after positive culture? Page 10, line 12 -14 you mention other types of LOS that were not defined in your methods section. Please include the definitions in methods section.

4. Please include how non-survivor and survivor groups were defined.

5. General comment: Did you collect time to clearance of bacteremia between the hVISA and VSSA groups, vancomycin treatment failure, how the MRSA bacteremia was treated or time to appropriate therapy? Or history of MRSA infection?

Microbiological and molecular methods
1. Page 9, line 9. This is generally a short methods section. Specific detail on certain tests would be helpful. For example, how was agr dysfunction defined? How was a reduction of delta-hemolysin defined?
2. How long were the isolates stored for before being tested? The can affect the expression of the hVISA phenotype.

Statistical analysis
1. Please state the type of analysis (logistic regression?) used to identify independent predictors “risk factors” of in-hospital mortality (?) while adjusting for confounding variables.
2. If logistic regression was not used – the terms “predictors” and “risk factors” throughout the manuscript are incorrectly used and the results of this study are purely descriptive. Please advise as this will need to be adjusted in the manuscript.

Results:
1. Page 10, lines 2 – 3: A large number of patients were excluded, but the exclusion criteria are not strict. Were the 69 excluded patients children or had multiple pathogens isolated? Please breakdown reasons for exclusion and the number for each (example: < 18 yo (n=3), etc)
2. Page 10, lines 3 – 5: Consider combining these two sentences: “Of the 48 isolates, 14 (29.2%) harbored the hVISA phenotype.” Do not need to mention the method as it is already stated in the methods section.

3. Page 10, line 10: A large number of patients in the hVISA group could not locate the origin of the infection. This has been previously found to be a risk factor for mortality, and as such is a possible confounder in this study. Was this considered in your statistically analysis? Please comment?

4. Page 10, line 12: The hVISA group had a longer stay in the hospital prior to culture. The MLST results show that these isolates are genetically similar, but there were 2 different SCCmec types. Is it possible that these isolates are clones, and spread patient to patient within the hospital?

5. Page 10, lines 12 – 17: LOS was evaluated in multiple ways but not defined entirely in methods section (LOS in hospital, LOS in ICU, LOS prior to bacteremia (+ MRSA blood culture), LOS after bacteremia onset). Please define in methods section.

6. Page 11: Where are the results for the broth microdilution MICs? Do they correlate well to the Etest?

7. Page 11, lines 2 – 4: Please clarify this statement.

8. Page 11, line 9: Please comment on how you defined hospital-acquired infection and include in methods.

9. Page 11, line 12: This mortality rate is very high, for both hVISA and VSSA. Other sources cite 20-30%. However, other factors associated are not discussed. For example, what antibiotics did these patients receive? Is there a vancomycin dosing protocol in the institution? Were vancomycin troughs taken, and were they in the target range?

10. Page 11, line 12 – 16. Please include odds ratios and 95% confidence intervals for the hVISA phenotype, SOFA score, receipt of hemodialysis and CVA and which covariates were included in your (logistic?) model? If a multivariate logistic regression was not used an example of the interpretation of the results are as follows: patients in the non-survivor group had significantly higher SOFA score, presence of hVISA, and receipt of hemodialysis.


Discussion:

1. General comment:

2. Page 12, line 5 - 11: Consider combining these statements, they are repetitive.

3. Page 12, lines 11 – 17: Please clarify statement, not sure what point is trying to be made here. Please comment how this is relevant to your study as it was not previously stated that glycopeptide treatment failure was assessed herein.

4. Page 13, lines 7 – 9: Please rephrase this statement. The use of the word “will” implies that this has been proven would consider substituting with “may”. Unclear on how “virulence factors” is related as the previous studies mentioned
are about ST type and clinical outcomes.

5. Page 13, lines 10 – 12 : Please reference this statement

6. Page 13, lines 12 – 17: Please rephrase and include more detail on the studies that are being referenced (what outcomes did they evaluate). Please comment on how “the SCCmec type did not produce any adverse outcomes” in your study. This was not included in the results or methods/statistical analysis.

7. Page 14, lines 5 – 7: “The agr dysfunction did not cause persistent bacteremia in our report” Persistent bacteremia was not previously mentioned in the methods or results of this manuscript. Further, due to the study design causation cannot be assessed, therefore the use of the word “cause” is inappropriately applied. Please comment and include in methods and results how this was defined and evaluated.

8. Page 14, lines 8 – 9: Besides small sample size, the purpose of this study was not to evaluate agr dysfunction on mortality. Would consider deleting this statement.

9. Page 14, lines 11 -17: Please clarify the relevance of these studies, unsure what point is being made here.

10. Page 14, lines 19: The term “confounding” is not used properly in this sentence.

11. Page 15, line 3: However there was no difference MRSA attributable mortality between hVISA and VSSA can you comment on this.

12. Page 15, lines 5 – 6: Please specify “incomplete for some factors”.

13. Page 15, lines 8 – 9: Please comment on why the number of enrolled cases was not expanded

14. General comment: other limitations include single center, how long were the isolates stored for before they were tested? Prolonged storage can lead to loss of the hVISA phenotype, is it possible that some may have been missed? If the source of infection was not removed, this may have also confounded the results. Variables that were not collected (i.e. time to appropriate therapy) may also have impacted the results.

15. General comment: would focus on any data that described hVISA bacteremia in patients in addition to those in the ICU and compare it to the findings of this study. Consider referring to Casapao and colleagues (Antimicrob Agents Chemother. 2013 Jun 24) conducted a retrospective multicenter cohort study titled “Clinical outcomes in patients with heterogeneous vancomycin-intermediate Staphylococcus aureus (hVISA) bloodstream infection.

Conclusions:
1. As previously stated the use of the word “predictors” is not appropriate.

Tables:
1. Hemodialysis, shock after infection, and adequate antibiotic treatment is included in table 3 but not in table 1. Please comment why this was not included in table 1 and add the definition of these variables in the methods section under
clinical data.
2. Prior vancomycin therapy is included in table 1 but not in table 3. Please comment
3. Spell out CRP in table 1 and 2
4. Please change Charlson score to Charlson comorbidity score in tables 1 and
5. Table 2. Were the isolates with agr dysfunction associated to a certain SCCmec type or agr subgroup?

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Not suitable for publication unless extensively edited

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

Declaration of competing interests:
no