Author's response to reviews

Title: Community-associated Methicillin-resistant Staphylococcus aureus Bacteremia and Endocarditis among HIV Patients: a cohort study

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Author's response to reviews: see over
Dear Ms. Rajabi,

Thank you for considering our manuscript for publication. The reviewers' comments and suggestions were greatly appreciated and have significantly improved this manuscript. This letter responds to all of the reviewers' comments and we have revised the manuscript accordingly.

Editors Comments:

1. The aims of the study in the Abstract and the Introduction are stated quite differently. In the Abstract, the objectives are reported as follows: 1) To assess the prevalence of USA300 community-associated methicillin-resistant Staphylococcus aureus (CA-MRSA) infections among HIV-infected patients with S. aureus bloodstream infections, 2) To determine risk factors for infective endocarditis among HIV-infected patients with S. aureus bloodstream infections, and 3) To compare in-hospital mortality between HIV-infected patients with CA-MRSA and non-CA-MRSA bloodstream infections.

However, in the Introduction, the authors state that the "study aimed to describe the prevalence of USA300 CA-MRSA among HIV-infected patients with MRSA bacteremia and endocarditis." Further, in the second sentence of the Methods (Study population), the authors write that "This was a retrospective cohort study of all adult (age >18) HIV-infected patients with MRSA bacteremia admitted to the University of Maryland Medical Center."

The latter two sentences do not appear to be correct based on the analyses and results presented. This has also caused confusion among the reviewers.

These statements must be clarified. Overall, the aims in the Abstract and Introduction should be stated more clearly. The authors should consider numbering the aims as above.

Response: We agree that these statements are confusing. We have the revised the stated aims in both the Abstract and the Introduction to be consistent with each other and the analyses performed. The sentences in the both the Abstract and Introduction now read,

“We aimed to 1) assess the prevalence of USA300 community-associated methicillin-resistant Staphylococcus aureus (CA-MRSA) among HIV-infected patients with S. aureus bloodstream infections, 2) and determine risk factors for infective endocarditis and in-hospital mortality among patients in this population.

Furthermore, the statement in the Methods has been revised and now reads,
“This was a retrospective cohort study of all adult (age ≥18) HIV-infected patients with S. aureus blood stream infections admitted to the University of Maryland Medical Center (UMMC) between January 1, 2003 and December 31, 2005.”

2) Abstract (Methods): The following statement in the Methods of the Abstract is very vague and needs to be clarified: "Statistical analysis utilized descriptive analyses and logistic regression to calculate odds ratios (ORs) and 95% confidence intervals (CIs)." It is no clear as stated what the outcome of the logistic regression is and what groups are being compared.

The authors should consider re-stating the sentence as follows: "Risk factors for S. aureus-associated infective endocarditis were determined using logistic regression." The hypothesized risk factors for S. aureus-associated infective endocarditis should be stated in the Abstract and Introduction.

Response: We have revised the Abstract (Methods) as suggested by the reviewer. The section now reads, “Risk factors for S. aureus-associated infective endocarditis and mortality were determined using logistic regression to calculate odds ratios (OR) and 95% confidence intervals (CI). Potential risk factors included demographic variables, comorbid illnesses, and intravenous drug use.”

3) Abstract (Results): Please include both the raw number of patients identified with infective endocarditis and cumulative incidence of deaths in addition to the percentages (rather than only reporting the percentages).

Response: We have revised the sentence in the Abstract (Results) to read, “Sixty-three patients (48%) developed endocarditis and 10 patients (8%) died in the hospital on the index admission.”

4) Abstract (Conclusions): There is some confusion between the terms prevalence and incidence and this should be clarified. The authors note in the Results that the "prevalence" of endocarditis is 8% but then state that CA-MRSA is associated with an increased “incidence” of endocarditis.

Response: We agree that this is confusing. We have revised the sentences to clarify that we had prevalent cases of endocarditis.

5) Methods (Study population): The authors should clearly state how patients were identified and selected for this study.

Response: All patients with Staphylococcus bacteremia within the time period were identified using Safety Surveillort® epidemiological software. These were then cross referenced with the central data repository for HIV infection. We have corrected this in methods. Figure 1 shows progression of selection of patients.

6) Methods (Data Collection): A number of variables were evaluated as characteristics of the study population in Table 1, including hepatitis C, diabetes mellitus, coronary artery disease, hypertension, and end-stage renal disease. However, the authors do not state in the methods section exactly how these variables were defined. These definitions must be included to aid interpretation of the study results.

Response: We have updated the definitions as we used. Hepatitis C was defined as having serologic test positive for antibody, diabetes mellitus was any patient receiving insulin or anti-glycemic medication on outpatient basis, hypertension was any patient receiving antihypertensive therapy on outpatient basis, coronary artery disease was defined as any prior myocardial infarction, interventional procedure or surgery. End stage kidney disease was defined as per National Kidney Foundation guidelines as stage 4 or 5 kidney disease including need for renal replacement therapy.
7) Methods (Analysis): The statistical analysis section is short, not detailed, and described using generalities. For example, the authors state that "Student's t-tests, chi-square, Fisher's exact, and Wilcoxon rank sum tests were used for descriptive analyses to assess bivariable differences between groups." The groups evaluated or compared should be specified.

Risk factors being evaluated should be detailed for each analysis. As currently written, the analysis section does not provide a cogent outline of the analyses conducted. This section should be clarified.

Response: We agree with the reviewer and have expanded this section to clarify the methods used. The beginning of the statistical analysis section now reads, “Student’s t-tests, chi-square, Fisher’s exact, and Wilcoxon rank sum tests were used to identify differences between patients with and without CA-MRSA and between those who and did and did not develop endocarditis or die on the index admission. All variables that were statistically significant (α=0.1) in the bivariable analyses were included in the initial (full) multivariable logistic regression model.

The authors conducted a logistic regression analysis to evaluate risk factors for in-house mortality and present results in Table 3. They should justify why a survival analysis utilizing Cox proportional hazards regression was not performed.

Response: The authors considered using survival analysis utilizing Cox proportional hazards regression rather than logistic regression for risk factor analysis for in-hospital mortality. However, we opted to use logistic regression because many of the potential risk factors, including our primary exposure of interest CA-MRSA bacteremia may have occurred prior to hospital admission, and as such we did not feel it was appropriate to use time to event analysis.

8) Results: The low prevalence of antiretroviral therapy use is indeed concerning, as raised by one of the reviewers. It is possible that if only inpatient records were evaluated that hospital teams might not have prescribed for these medications either because they did not know the regimens or because patients were too sick to take oral medications. The authors should clarify why such a small proportion of these subjects received antiretroviral therapy.

Response: This unfortunately is due to the population that is being seen, most are hard core drug users and poor followup and compliance. Many studies from Baltimore over last 20 years continue to show low antiretroviral use in the intravenous drug using population. I have included this in the discussion with references. We have included the median CD4 count was 56 and mean VL 225,000 in this cohort. We had access to all regimens for these patients as all patients seen within dedicated HIV clinic. The clinic has strong substance abuse help, psychiatry and many providers for care, but failure to attend clinics and non compliance is high. We have included this sad observation in the discussion.

Reviewer: Kyle Popovich

Reviewer's report:

The objective of this retrospective study was to examine the prevalence of CA-MRSA, defined genotypically, among a group of HIV patients with S. aureus bloodstream infections as well as to identify risk factors for endocarditis and mortality. Major findings were that CA-MRSA was a significant risk factor for the development of endocarditis versus non-CA-MRSA.

Major Comments:

1. In the results section, the authors should state the mean or median CD4 count to help the reader understand the population being studied better. Was viral load collected on patients?
Response: We have included this. As per Q8, median CD4 was 56 (range 2-916) and mean VL was 225,000 (range 0 to 750,000 copies) and median VL 75,000. We have added to methods that viral load had to be within 6 weeks either side of the admission.

Also, I am surprised by the really low number of individuals receiving ARVs (30%). The authors may want to comment on this as this low percentage may limit the generalizability of findings.

Response: Please see reply to Q8. This is an inner city population as described in the methods and likely reflects what is seen in other inner city hospitals with large HIV populations and drug users. Despite this our findings are consistent with other studies.

2. Did the authors capture the proportion of infections that presented #72hrs into hospitalization versus >72hours into hospitalization. Since CA-MRSA was defined genotypically, it would be interesting to see how many were community-associated vs nosocomial by epidemiologic definitions, especially as CA-MRSA has been reported as a cause of hospital-onset bloodstream infections.

Response: All bacteremias were from admission blood cultures, within 72 hours of admission. Thankyou and we will add definition and results

3. Did the authors capture bacteremia duration? I would be curious to see if there was a difference for CA-MRSA vs non-CA-MRSA.

Response: We went back and reviewed the bacteremia duration. Ca-MRSA had mean 1.85 days vs non-CA-MRSA of 1.45 days, p value 0.43. We have included this in the results. There was no significant difference. Interestingly, in reviewing extra papers as suggested by Reviewer 2, none have described duration of bacteremia. Although not significant, will add to paper.

4. Since it is now 2011, why was the study from 2003 to 2005? I am curious if data was collected beyond 2005 and if not why? The current study period obviously represents a time when CA-MRSA infections were increasing at several sites nationally. I was curious if the high numbers of bloodstream infections due to CA-MRSA among the population they studied persisted beyond 2005? Also, did the authors look to see if CA-MRSA cases were evenly distributed over the study period or if they increased over a particular time period?

Response: This project has been ongoing for a while with different people involved. The time period was the initial approved study and we have included references showing that CA-MRSA rates have been constant from 2002-2008. We feel it remains relevant as incorporates data on endocarditis rarely reported, still encompasses a time period where high rates of CA-MRSA are seen and defines a population that appears to survive better despite lack of ART therapy.

5. Did the authors evaluate for embolic/metastatic complications of endocarditis such as septic emboli, etc.? Since they found that CA-MRSA caused more endocarditis and these strains are thought to perhaps be more virulent, I would be curious if they noticed a difference in endocarditis complications?

Response: Thankyou for this comment. Overall septic pulmonary emboli were common in both groups. 11 vs 6. What stands out are the numbers of abscesses in the Ca-MRSA group. Of the 53 PVL positive group, 7 had lung abscess of empyema, 5 had pyomyositis, including psoas and other spinal muscle
abscesses, 2 with renal abscesses another 2 had brain abscess while 1 had a pericardial empyema. The non-CA-MRSA had more osteomyelitis 4 vs 1 and 1 epidural abscess. We have included this in the results and comments section

6. Since patients were eligible for enrollment for every new admission (vs. a time cut-off prior to re-enrollment), how many repeats were there in their population? If patients were re-enrolled, was it for the same episode of bacteremia/endocarditis or for a new episode?

Response: there were 7 repeat patients from the 131 patients. None were re-enrolled for the same bacteremia/endocarditis. All repeat patients were new episodes as all occurred after 90 days from initial event.

7. Given the authors conclusion, I think that the topic of USA300 virulence should be addressed in the discussion section.

Response: Will note that in the population described our data on the virulence of CA-MRSA is different to previous reports. We will note the comparisons between our data and the Taiwanese data, that this is the first description in HIV population with most having poor T cell functioning and that the formation of abscesses has not been described.

8. It appears that male gender was negatively associated with endocarditis. Do the authors have an explanation for this? Were there particular community exposures or risk factors seen less frequently among males to account for this?

Response: We can not explain this. We suspect they may present earlier than women in our population, as many of the women have history of exchanging sex for drugs and so may present later in their illness. As this is speculative, we do not want to include in paper

Reviewer: David Rimland

Reviewer's report:

Major Compulsory Revisions

1. The definition of community-associated MRSA is problematic. Most studies originally used an epidemiologic definition, excluding cases with health-care associated factors. Some have used the PFGE types, with USA 300 being the most common. Most, but not all, of these cases have the type 4 mec gene and produce PVL. Defining the cases here as USA 300 with a specific spa type, and positive for both ACME and PVL restricts the definition. It would be more meaningful to present the data with either the epidemiologic definition or simply USA 300 vs. others (Methods, para. 4)

Response: Your comment is correct, however we wanted to define the invasive PVL producing very specifically to show that the previously lack of demonstration of endocarditis may have been due to the broader definition and as you state not have PVL producing strains. We hope this helps address our specificity of definition.

2. It is unfortunate that these are relatively old data (2003-2005). There has been a great deal of change in the epidemiology of MRSA in the last several years.
Response: See Q4 reviewer 1. There has been very little on this disease in HIV infected patients and documentation of endocarditis adds to the literature.

3. Since the median length of stay was only 7 days, the in-hospital mortality of 8% is not too significant. Are there any data on the 30 or 60 day mortality?

Response: Our data is similar to other studies including Kempker that used in-hospital mortality.

4. Did every case of endocarditis have either a TTE or TEE? (Methods, para. 2)

Response: Yes, every case of endocarditis had either TTE or TEE or both. Where patients had both procedures we have included the data to show the extra valvular lesions detected by TEE.

Minor Essential Revisions

1. Abstract- Conclusions: CA-MRSA was not associated with an increased “incidence” of endocarditis. There was simply a greater prevalence of endocarditis among those with bacteremia.

Response: Corrected as requested.

2. Methods, para. 3- How far apart could episodes of bacteremia be to represent a separate episode? Simply using a separate hospitalization does not mean a separate episode, especially since the median LOS was only 7 days.

Response: All repeat cases were > 90 days between episodes.

3. Results, para. 1- What AIDS definition was used? OIs and or CD4 <200?

Response: Will add to definitions. AIDS was CD4 count <200 and/or presence of OI.

4. Results, para. 2- The lack of other independently associated variables could well be due to the relatively small numbers. The confidence intervals are quite wide.

Response: Our 63 cases of endocarditis out of 87 CA-MRSA bacteremia is the largest ever reported for CA-MRSA bacteremia. From reviewing the extra papers suggested, it is possible that these centers were not looking hard enough. As our center sees over 100 cases of endocarditis a year, aggressive documentation of presence of vegetation or not is important in patient disposition, as placement is difficult with active drug usage. Also, Of suggested literature Wang in CID had 3/30 endocarditis (no definitions), Bakowski 0/60, Beeston 0/30, SY Chen 8/111 (7 years of data), Robinson 8/103 (no definitions) and JT Wang had 21 endocarditis cases overall but do not comment on endocarditis with CA-MRSA in table. Kempker in Atlanta has closest data with 19 AIDS patients with USA300 bacteremia and 40 endocarditis cases in the USA 300 group. They do not comment of HIV and USA300 endocarditis, but show strong relationship with HIV status and bacteremia.

5. Table 1- I would change the title to “Characteristics of Patients with MRSA Bacteremia”

Response: Changed

6. Table 1- For several variables (male sex, ART, etc.), indicate that the number in parentheses represent the %.
Response: Already in table (n(%))

7. Table 1- What proportion of the ESRD patients were on dialysis? This is a critical variable for development of bacteremia.

Response; All were receiving HD and will change this parameter to reflect this in methods