Author's response to reviews

Title: Development and validation of a bedside risk score for MRSA among patients hospitalized with complicated skin and skin structure infections

Authors:

Marya D Zilberberg (mzilberb@schoolph.umass.edu)
Paresh Chaudhari (Paresh.Chadhari@us.astellas.com)
Brian H Nathanson (brian.h.nathanson@att.net)
Rebecca S Campbell (becky.campbell@cerner.com)
Matthew F Emons (matt.emons@cerner.com)
Suzanne Fiske (suzanne.fiske@cerner.com)
Harlen D Hays (harlan.hayes@cerner.com)
Andrew F Shorr (Andrew.Shorr@gmail.com)

Version: 2 Date: 4 April 2012

Author's response to reviews: see over
Dear Editorial Board of BMC Infectious Diseases,

We are resubmitting our revised manuscript for consideration for publication in your journal entitled “Development and validation of a bedside risk score for MRSA among patients hospitalized with complicated skin and skin structure infections.” We believe that we have adequately addressed all of the reviewers’ concerns.

We appreciate the reviewers’ diligent attention to our study and their help in improving our paper.

We are looking forward to further comments and decisions.

Respectfully,

Marya Zilberberg, MD, MPH, FCCP

Reviewer: Frank Lowy

1. The nature of the hospitals contributing to the database should be more fully described. It is not clear whether they are representative of US hospitals or more accurately reflect a subset – perhaps more community-based institutions. This would create some selection bias in the nature of the cSSSI admitted to hospital and might explain some of the more confusing variables that appeared to be different between the two groups.
   AU: In Table 1 we listed the available hospital characteristics. Notably over 98% of the patients were in urban hospitals, and approximately 60% in each group were teaching institutions.

2. Isolates are described as non-MRSA. Typically they are listed as MSSA. Is there a reason for the use of the term non-MRSA?
   AU: Non-MRSA group includes MSSA and other organisms. Since the object was to identify MRSA as opposed to all others, this is how the organism data were divided.

3. The results are a bit counter intuitive with some factors that are usually identified with MRSA infections being more commonly associated with the non-MRSA infections. This includes such variables as admission from a noncritical care facility, immunosuppression, ESRD, recent admission, etc. All of these have been associated with an increased risk of MRSA infections, perhaps
not cSSSI but the authors should comment on this observation. In addition the length of stay for the non-MRSA infections was also longer than for the MRSA infections. This again raises the question of the nature of the study population.

AU: We appreciate the reviewer’s request to discuss this further. We have now added the following to the 3rd paragraph in the Discussion section on page 11: “Although this differs from other reports that found 2/3 of all MRSA cSSSI to have underlying HCA risk factors, the discrepancy is likely due more to the lower prevalence of HCA overall in the current study rather than to fundamental microbiologic differences. That is the prior study noted ~75% prevalence of HCA in the cohort of 717 patients admitted with a cSSI, while in the current analysis it was only 35%. Given that the previous result came from a single-center analysis, the current data are more generalizable.”

4. The vast majority of cSSI are not admitted to hospital so this group appears to be a select subset of patients with these infections who warrant admission. Among these are patients with polymicrobial infections, not generally included in this type of analysis. How many of these were there?

It is true that our data are not generalizable to those patients with a cSSI who do not require admission. The focus of our analysis was to identify patients with MRSA. For this reason we did not focus our discussion on presenting the microbiology of other infections. Even in a polymicrobial setting, a MRSA was considered to be pathogenic in cSSI hospitalization. To clarify our selection of cases, we added the following at the bottom of page 4:

“The positive index culture had to contain at least one organism that was not considered to be a skin contaminant. Cultures of organisms considered to be skin contaminants (Corynebacterium/diphtheroids, Staphylococcus epidermidis or other coagulase-negative Staphylococcus sp., Propionibacterium, Streptococcus viridians, Aerococcus spp, Bacillus spp [except B. anthracis]) were excluded from the cohort.”

5. It is difficult to imagine when this beside score would be used. Perhaps the authors can elaborate on this. In most hospital settings the patient is assessed in the emergency department, any collection drained, empiric antibiotics initiated and the patient is sent to the floor. Patients are empirically treated based on knowledge of the antimicrobial susceptibility of the isolates in the community. If necessary therapy is adjusted once the antimicrobial susceptibility of the isolate becomes available. What percent error rate would the authors find acceptable to apply their scorecard in the ED? Most physicians would likely prefer to cover for both MSSA and MRSA especially in those patients with infections serious enough to warrant hospitalization and then adjust therapy.

AU: We appreciate the reviewer’s thoughtful question. Our study really serves as a way of exploring how to develop tools that better assess the pre-test probability of a particular resistant organism. We do not claim that this is the optimal scoring tool, but merely say that we need better tools, and this was an attempt at developing one. As for the threshold, this is less a function of the score than the
end-user, and, although a broad-based discussion of this is necessary, it is outside the scope of the current study.

6. An additional concern regarding this type of analysis, also noted by the authors, is the lack of strain typing. A recognized feature of epidemic clones such as USA300 is the propensity for these strains to lose the SCCmec element while retaining virulence. The risks for a cSSSI infection would likely remain the same but the antibiotic susceptibility would differ.
AU: we agree with the reviewer.

Reviewer: Robert Daum

1. In the Introduction, in the first sentence, the authors correctly point out that MRSA rates have been rising in recent years. They also point out that the CDC has suggested that the rise may be abating. Apples and oranges, however. The CDC is commenting on healthcare-associated infections that are clearly abating. Community associated MRSA incidence was on the rise during the study period.
AU: Thank you for this comment – we have added clarification: “Although rates of serious infections with pathogens such as methicillin-resistant Staphylococcus aureus (MRSA) have been rising over recent years, there is encouraging news from the Centers for Disease Control and Prevention (CDC) indicating that this rise may be abating for healthcare-associated pathogens, though not for community-acquired ones.”

2. The sentence, "Much of the emerging resistance..." in the Introduction, is incorrect with respect to CA MRSA.
AU: It is our understanding that the fundamental driver of resistance is use of antibiotics in general. When used indiscriminately, as they have been shown to be over the past few decades, the inevitable result is selecting for bacterial clones that are not susceptible to these agents.

3. Please provide a definition of complicated skin and skin structure infections (cSSSI).
AU: Please, see “Cohort Selection” section on page 4 – we apologize that instead of referring to Appendix A, we erroneously referred the reader to Table 1. We have now corrected this error.

4. In the Introduction, second line, second paragraph, were only patients with cellulitis hospitalized?
AU: Cellulitis was one of the infections examined. We have inserted the words “for example” in the sentence in question to clarify that we are not confining our investigation to cellulitis. Also, see above comment for the definition.

5. On page 4, re cohort selection, it is stated that admission to the hospital had a
primary diagnosis from Table 1. I presume some of the patients were admitted with a primary diagnosis of cSSSI but this is not discernible from Table 1. Were patients excluded or included who had comorbidities?

AU: Again, we apologize for the error – we should have referred the reader to Appendix A, rather than to Table 1. We have now corrected this mistake. Patients with comorbidities were not excluded.

6. The authors should provide a rationale for extending the score gathering period to the "first 24 hours" of hospitalization. This would seem to negate the value of a simple bedside test that is applicable on admission. If this is incorrect, please explain in the Discussion.

AU: We have added the following rationale for this on page 6:
“The rationale for the 24-hour window was that inappropriately targeted empiric antimicrobial coverage within this time frame is associated with worsened outcomes.”

7. On page 7, the term, "non-MRSA," is introduced. This group is very important because they provide the controls for the MRSA group. However, they are not characterized at all. Please indicate what bacteria infected the non-MRSA patients. In this regard, also please explain what is meant by the term, "medical service," and the term, "comorbidity burden," both of which can be found under "patient characteristics," on page 7.

AU: because our aim was to distinguish MRSA cases from all others, we grouped the cohort into “MRSA” and “non-MRSA,” the latter including all pathogens other than MRSA. We do not present the actual pathogen distribution in that group again because our current aim is merely to distinguish those with MRSA from those with non-MRSA. “Medical service” refers to non-surgical admissions, while the “comorbidity burden,” along with all other baseline characteristics, is described in Table 1, to which we refer in the text.

8. The authors should indicate how they arrived at the scoring system for the age item. It seems peculiar.

AU: When modeling age, we first graphed the variable (after creating categories by decade) across a series of infection types (see Figure 1) as an exploratory analysis.

Figure 1: CSSSI Type by Age
We then repeated this analysis on MRSA patients only and superimposed the graph on the prevalence of each age group (see Figure 2).

Figure 2: MRSA and Age Prevalence by Age Group
This analysis suggested to us to model age as a categorical variable with several categories (similar in intent and structure to using spline functions) and based on our multivariate results, we weighted the age categories to reflect their relationship to outcome as we describe in the Methods Section. One characteristic that may be atypical to the reviewer was an “increase” in weight for the patients aged 30 to 39. This was evident in the data before adjustment and remained true in the multivariate modeling (and our MRSA Score reflects this).

9. On page 8, the first line, please explain the randomization scheme that you used.

AU: Our software package used to analyze the data (Stata/SE 10.1 for Windows) has built in random number generating capabilities. We created a random variable in the dataset that followed a uniform distribution and had values between 0 and 1 and sorted (ie, “shuffled”) this variable. Thus, each patient was “assigned” a random
value. To create an 80% Development Set, we then grouped patients with a random value \(< .80\) into one group and the remaining patients became the Validation Set. A reference for this procedure is:


10. On page 9, the opening paragraph of the Discussion, discusses MRSA as if it were one thing. Since it simply an antibiotic susceptibility pattern of certain Staphylococcus aureus strains, please modify this language.

AU: We appreciate the reviewer’s concern. For the current study we merely focused on all MRSA as a group, and for this reason are carrying this simple grouping through the Discussion section.

11. Page 9, second paragraph, the term, "the escalating penetration of resistant organisms into what appeared to be community-acquired infections," is obscure and this language should be modified.

AU: Thank you, we agree and have reworded in the following way:

“Over the last decade, the increasing frequency of resistant organisms among persons presenting with infections from the community prompted a re-evaluation of the populations at risk for harboring such pathogens.”

12. Page 11, please give the reader some feeling for how much variation there was among the 60 hospitals that are the subject for this study.

AU: Table 1 lists Hospital Characteristics. Are there other parameters that you are interested in seeing added to this table?