Author's response to reviews

Title: Epidemiology of Community-Onset Staphylococcus aureus Infections in Pediatric Patients: An Experience at Children's Hospital in Central Illinois

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Version: 2 Date: 29 April 2009

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To the Editor

BioMed Central Infectious Diseases

Re: Submission of the revised manuscript

Dear Editor:

Thank you for your interest in considering our paper. We are grateful to the reviewers for the critical and constructive comments. Below is our detailed response to the reviewers’ comments on a point by point basis, as suggested.
Referee 1

Compulsory revisions:

1) While I believe that the authors do fulfill their stated objective to assist local clinicians with antibiotic selection, it is not readily apparent whether this paper will be of interest to clinicians working at other institutions. In other words, what general principles or lessons learned can be applied elsewhere? What limitations of the existing literature does this paper address? I recommend that the authors revise the introduction and discussion with emphasis along these lines.

Response: The introduction and discussion have been revised to address these points.

Minor essential revisions:

1) If a large proportion of cases are MRSA and that virtually all anti-MRSA agents are active against MSSA, is the recommendation that both an MRSA and MSSA agents be used in combination supported by the available data?

Response: The problem, and a point made in this paper, is that not all anti-MRSA agents are equally effective against MSSA. We cited general studies showing that vancomycin is inferior to nafcillin for the treatment of invasive MSSA infections. Therefore, as stated in the paper, we recommend nafcillin plus vancomycin as empiric therapy in patients with suspected invasive staphylococcal infections. At our hospital, we also discourage the empiric use of linezolid or daptomycin to minimize the development of antibiotic resistance.
2) Given that 199 patients were included, percents could be consistently reported without decimals.

Response: The numbers have been revised as suggested.

3) The authors chose a definition for invasive disease that is different than what I believe is most widely accepted-namely that invasive disease is defined solely by the isolation of *S. aureus* from a normally sterile body site. Pneumonia is usually only considered invasive if blood cultures or another site such as pleural fluid is positive. The observation that a patient had a positive culture from a gallbladder was not considered invasive is odd. Similarly the three patients with positive blood cultures. Some added details in the discussion would be nice detailing the choice of definitions and exclusion of these patients. Perhaps the authors could just classify patient as SSTI and non-SSTI.

Response:

- We actually used a definition in agreement with the reviewer, and we have reorganized the section on “Definitions” to clarify this. A diagnosis of staphylococcal pneumonia was made if the patient had radiographic abnormalities compatible with pneumonia and the blood or pleural fluid culture was positive for *S. aureus*. Patients who had radiographic abnormalities compatible with pneumonia and *S. aureus* isolated only from sputum or endotracheal aspirates were excluded.

- The patient undergoing elective cholecystectomy with a positive culture from the gallbladder and the three patients who had single positive blood cultures were excluded because they never had signs of infections and were never treated with antibiotics.
As pointed out by a referee, we agree that an alternative way to classify the patients was SSTI and non-SSTI. However, essentially all of our “non-SSTIs” were “invasive” and are better characterized by that term.

4) The addition of denominator data (ie per hospital admissions) to figure 1 would help to interpret changes.

Response: Data has been added to the figure 1.

5) The second paragraph of the discussion is confusing-our data highlights important regional differences…yet…not different than other regions of United States.

Response: The text has been revised to improve clarity.

6) Reporting a systematic search to identify other studies of the same topic would go a long way to convince reader of the novelty (or not) of this study.

Response: As suggested, we have cited additional studies of regional epidemiology of S. aureus infection. Discussion has been added to address this point.

7) Much of data in Table 1 is mentioned in text and footnotes; would prefer to see the data tabulated only if feasible.

Response: When all data are tabulated in one table, it is confusing to the reader. Thus, data in the original table 1 are broken into 2 separate tables.

8) Table 2 could be deleted without consequence.
Response: Table 2 (which is a table 3 in a revised manuscript) can be deleted as suggested. However, we believe that a table can give a clear picture of MDR phenotype among MRSA isolates for interested readers; therefore, we would like to ask to keep this table in the supplementary material as an additional file, if possible.

**Referee 2**

Compulsory revisions:

1) *The authors state that if MRSA is suspected, then nafcillin plus anti-MRSA treatment is important. Other than potentially endocarditis where vanco has had some difficulties, do the authors care to state what the advantage of nafcillin would be? Why not use single treatment with an anti-MRSA agent?*

Response: We agree with the referee that, if possible, single treatment which is active against both MSSA and MRSA should be considered as an empirical therapy in patients with staphylococcal infections. As pointed out by the referee, (and noted above, referee1, item1) vancomycin is inferior to nafcillin for the treatment of invasive MSSA infections including bacteremia and endocarditis. Clindamycin is active against many MSSA and MRSA isolates. However, based on our surveillance for antimicrobial resistance among *S. aureus*, the percentage of MSSA isolates that are resistant to clindamycin has been 20-25%.

As suggested, the paper has been revised and additional details have been provided regarding the reason why nafcillin in combination with vancomycin is suggested in patients with suspected invasive staphylococcal infections.
2) *On page 6, the authors define infections of the skin and give some examples and then state that these are all uncomplicated. The FDA definition may agree in part with this, but not if the has SSTI sufficient to result in hospitalization. I would guess that authors mainly hospitalized complicated SSTI in this series?*

Response: We agree with the referee and the correction has been made.

3) *It would be useful to have the susceptibilities in a table. The authors have attempted to define resistance as MDR. I think they should just show the data.*

Response: Among MRSA isolates, D-test was not routinely documented in the hospital database during 2005-2006 (in contrast to MSSA for which all D-test results were documented). Because of lack of these data, MDR phenotype is used for analytical purposes. MDR is defined as resistance to three or more non-β-lactam antimicrobial agents. Therefore, even if the D-test was not known, this will not impact the result of MDR or non-MDR phenotype. There were only 2 MRSA isolates for which the phenotype could not be determined because they were susceptible to clindamycin but resistant to only erythromycin and tetracycline.

Additionally, table 2 was deleted as suggested by the referee 1. However, we would like to display the table of susceptibilities data (table 4 in a revised manuscript) in supplementary material as additional file if the referee 2 suggests to do so.

4) *We agree with the referee’s comment that “There does however appear to be a modest trend toward increasing invasive infections in the MRSA populations”.*

Response: This suggest has been added in the discussion.