Author's response to reviews

Title: Description and Validation of a Spectrum Score Method to Measure Antimicrobial De-escalation In Healthcare Associated Pneumonia from Electronic Medical Records Data

Authors:

Karl Madaras-Kelly (kmk@pharmacy.isu.edu)
Makoto Jones (Makoto.Jones@hsc.utah.edu)
Richard Remington (Remington@quantified.us)
Christina Caplinger (Christina.Caplinger@va.gov)
Benedikt Huttner (enedikt.huttner@hcuge.ch)
Matthew Samore (Matthew.Samore@hsc.utah.edu)

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Author's response to reviews: see over
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Nathaniel Nazareno  
Journal Editorial Office  
BioMed Central  
236 Gray's Inn Road  
London WC1X 8HB  
United Kingdom

Dear Dr. Nazareno,

Please find attached the revised manuscript entitled “Description and Validation of a Spectrum Score Method to Measure Antimicrobial De-escalation in Healthcare Associated Pneumonia from Electronic Medical Records Data” (MS: 4125275041452189). We are requesting that you consider the manuscript for publication in BMC Infectious Diseases as a Technical Advance article.

Per the editor's request we have addressed each point raised by reviewer #1 and have added the requested ethics statement to the manuscript. In addition, we have considered the comments of reviewer #2 and have made revisions where appropriate.

Please feel free to contact me if you have any questions or concerns about the revised manuscript submission.

Regards,

Karl Madaras-Kelly, PharmD, M.P.H.  
Corresponding author  
and Professor, Pharmacy Practice
Point by point response to Discretionary Revisions suggested by referee #1

A. "The authors might consider merging Steps 1/2 and Steps 3/4 in Figure 1. It would be useful to directly compare the ordinal scale with the susceptibility percentages, and the only difference between Steps 3 and 4 is the addition of the summation (Spectrum Score)."

We have revised Figure 1 to combine the steps as suggested.

B. "As was done in Step 1 of Figure 1, the authors should consider adding the susceptibility percentages to Table 1, in addition to the ordinal scale."

We believe that Table 1 is very complicated as it is written and have opted not to directly add susceptibilities to this table. However, we will add a column to appendix B which provides susceptibilities utilized to create ordinal scores.

C. In Table 1, I would also be interested in seeing the mean susceptibility percentages and standard deviations across the 152 medical centers included in the VA Corporate Data Warehouse. This could alternatively be presented as median and IQR if non-normal in distribution.

We believe that the request is beyond the scope of this particular manuscript and have opted not to include such information. Indeed an entire publication could be dedicated to presenting VA culture and susceptibility data. Several members of the research team are working on other projects that may provide such estimates in other research communications in the future.

Antibiograms may differ by hospital, unit (e.g., ICU, non-ICU), and specimen source (e.g. sputum, wound). It would be good for the authors to comment on a single Spectrum Score applied across all medical centers. This will be important as hospitals consider the need to input their own local susceptibility data when replicating these methods.

Susceptibility estimates were converted to ordinal values and then summed across microbial domains and multi-antimicrobial regimens to minimize differences in susceptibility across facilities. We believe differences in susceptibilities across VA facilities make relatively minor contributions to changes in ordinal values for almost all organism-antimicrobial pairs.

The concept of antimicrobial de-escalation is similar irrespective of local resistance patterns, and while absolute values are used to calculate baseline and day 4 scores, de-escalation was measured by a reduction in score. Differences in de-escalation practice across facilities may be dependent on the degree of baseline broad-spectrum use, which in turn may reflect perception of the need for broad-spectrum coverage based on local susceptibilities; however, such an analysis is beyond the scope of this manuscript and further work will be required to determine if risk adjustment for baseline susceptibility patterns across facilities is useful. We have modified the discussion to address how variability in susceptibility might impact the finding.

D. The authors comment that "antimicrobial stewards view IV to PO conversion favorably when classifying de-escalation events." I agree with this statement; however, I wonder whether it is clinically relevant to highlight the p-value of 0.002 when comparing mean Likert scores for paired vignettes containing IDENTICAL antimicrobials but differing routes of administration. The values of 5.0 and 4.6 seem quite similar in terms of expert opinion on a 7 point scale.
We would agree with the reviewer that it is hard to conceptualize the clinical significance of a half point change in Likert scale for antimicrobial stewards rendering judgments on de-escalation events based on a series of synthesized cases. Nevertheless, all three exercises consistently identified the importance of oral therapy when evaluating de-escalation events. We have reviewed all language relative to the findings regarding differences between IV and PO therapy, and have modified the manuscript language as appropriate.

E. Appendix A is user-friendly for someone with a programming background. Appendix B will have 20k rows. I wonder if the authors might make their code available for others to use as they develop their own institutional Spectrum Score.

We believe that the step-by-step instructions and provision of ordinal spectrum scores for all combinations encountered in the HCAP cohort, would allow other investigators to replicate our work without providing the code. Our code exists and has been tested to meet the specifications described in this manuscript. However, there are three limitations that would need to be addressed before we would feel comfortable sharing the code. First, the code was written in SQL and in a way that met the specific task but was not optimal for SQL. We made the decision not to turn to SAS or other row-based programming approaches due to the peculiarities of the workflow for this project. In this sense, it was not ideal with respect to the coding approach. The second is that while we attempted to use the principles of the common data model approach, in the course of focusing research, there are pieces of code that would need to be rewritten to be portable to other investigators. Finally, while we document our code, we would need to improve the level of documentation in order to be understandable to an uninvolved investigator and have opted to not provide such code at this time.

Referee #2

1. The authors define antibiotic deescalation in the introduction (lines 87-91). However, the validation of their spectrum scoring tool hinges on the role of IV to PO interchange. This topic receives a short evaluation in the limitations section (lines 335-338). Since IV to PO and antibiotic deescalation are unique, discrete issues in antimicrobial stewardship, the authors need to provide more discussion about this inconsistency. Is the spectrum scoring system invalid b/c it relies heavily on the PO conversion adjustment? Is it more broad than just a spectrum scoring system? Should the scoring system be redefined as a stewardship, or best practice, scoring system?

It is important to remember that the estimates for de-escalation were generated from vignettes which may or may not reflect de-escalation practice as measured in patients. The initial 300 vignettes were generated based upon randomly selected patients from the cohort. However, during the three validation exercises some of the antimicrobial regimens in the cases required minor manipulation which may have impacted the de-escalation rate in the vignettes. We have revised the discussion section to clarify this point.

2. Lines 125-126: the authors need to better define how they calculated the percent susceptible for organism/antimicrobial pairs. Did they use only the first isolate per patient? Did they use only the last isolate per patient? Did they take ALL isolates regardless of who they came from? If the latter is true, then there is a major flaw in the spectrum scoring system since the % susceptible is biased with multiple isolates from a single infection AND is likely biased from continued antibiotic exposure resulting in a higher rate of antibiotic resistance. Since the scoring system is meant to identify only new infections in hospitalized patients, I would suggest the authors use a first isolate per patient method.

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In an effort not to duplicate the text in our first ICHE publication, some details were left of the manuscript under consideration that was included in the ICHE publication. “Percent susceptibility was calculated for individual antibiotic-organism pairs for each organism domain utilizing 1 isolate per patient per year.” We have added this to the text.

3. The authors should discuss the limitations of their study to patients admitted with HCAP. Based on the manuscript as written, it appears as though the spectrum score can only be applied to patients with infection on hospital day 0. What happens if the patient develops HCAP on hospital day +10 or +30? What if multiple infections occur? CAUTI? CLABSIs? What if the patient develops C.difficile infection during their stay? The limitations must address these common scenarios. If the scoring system does not/cannot address these situations, that is ok, there is still value in the authors’ work and findings; however, it is not clear that these scenarios were excluded or included?

It is true that the method was designed to evaluate de-escalation in patients being admitted from the community with HCAP with the intent on evaluating de-escalation practice across facilities. More than 85% of patients admitted to VA hospitals are started on antimicrobials within the first 2 days of hospitalization; therefore, this was the targeted population. All patients who met HCAP criteria, were started on antimicrobials within 24 hours and who remained on antimicrobials for 3 days were included, irrespective of other diagnoses. It is possible that a portion of patients may have developed subsequent infections and these cases may represent “escalations” of therapy.

Conceptually, there is no reason why a similar method could not be applied to cases were treatment was started after day 2 of hospitalization, as long as scores were re-evaluated several days later. We believe that the text clearly states the time-course of treatment and infections treated.

4. The title of this paper should reflect antimicrobial de-escalation in healthcare associated pneumonia

We have changed the title to reflect this suggestion.

5. Line 82: change to <<recommend that hospital-based programs practice

Have corrected

6. Line 83: stewardship should not be capitalized

Have corrected

7. Line 114-115: change <<regimen’s degrees of microbial spectrum>> to <<microbial spectrum of the regimen>>

Have corrected

8. Line 118: delete <<al>>

Have corrected

9. Line 152-158: This list is essentially the ESKAPE pathogens (E. coli instead of Enterobacter) Enterococcus faecium rarely, if ever, causes pneumonia, why is this weighted more heavily? Would not weight E. faecium in a pneumonia study.

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We can understand the referee’s puzzlement with the inclusion of Enterococci in the score and MDR weighting scheme. It is important to remember that the selection and weighting of pathogens was based on the opinions of antimicrobial stewards obtained through the Delphi process. We would agree that this is an unlikely pathogen in pneumonia; however, the context of the Delphi panel was focused on inclusion of microorganisms in the score and weighting to address MDR potential. We thought it proper to include Enterococcus for that reason.

10. Line 163: Add a comma after <<species>>

Have corrected

11. Line 167: Antibiotic susceptibilities are not independent variables. This needs to be elaborated upon as a limitation. Since the investigators have the raw microbiology data, they can create a cross-table antibiogram which analyzes the actual resistance rates. Granted, the assignment of ordinal values to the quartiles is unlikely to change values drastically, this should be addressed as a limitation.

We have already commented on the limits of utilizing microbial susceptibility data and the need for additional references in the discussion and feel that additional discussion is not needed.

12. Line 181: Authors define skip days but I do not understand how they were used in the calculation. Based on Figure 1, I assume they projected the use of vancomycin q48 to daily score calculation; however, this is not clear based on the sentence. I believe this is simply a difficult concept to convey and would ask they authors explain further by re-writing. Consider building the skip day calculation into Figure 2.

We would agree that the concept of skip days is difficult to convey, however, have chosen not to address skip days in the figure. The step by step appendices provides further guidance for those wishing to replicate the work including skip days.

13. Line 196: List years of experience per steward as the mean could be highly skewed with only 3 people (i.e. 3 people with ~15 years of experience or one person with 42 years of experience and 2 people with 1 year) OR report as mean and range.

Have corrected

14. Line 206: Insert <<and>> after <<cases>>

Have corrected

15. Line 223: Same comment as for line 196

Have corrected

16. Line 239-240: please describe the bug/drug pairings which required investigator opinion

This is already available in Table 1

17. Line 285: Table 2 is Figure 3??? I do not see a Table 2 and do not see a Figure 3 referenced elsewhere in the manuscript

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Documents are available online

18. Line 317: No apostrophe in <<tetracycline’s >>

Have corrected

19. Lines 324-327: This seems highly dependent on what information the clinicians actually have at days 2 and 4 and what technologies, initiatives, and stewardship practices they have in place. Authors should mention and address the role of MALDI-TOF, procalcitonin, and other rapid diagnostics in the limitations of the day 2 and 4 assignment.

We addressed this limitation in the previous spectrum score manuscript.

20. Line 334: Replace <<stewards>> with <<stewardship>>

Have corrected

21. Line 335: Rewording of <<Finally, in the final>>

Have reworded

22. Line 335: insert comma after <<exercise>>

Have corrected

23. Line 357: Need to include other disease states

Have addressed in line 358

24. Line 362: remove improper space after <<conversion>>

Have corrected

25. Line 363: replace <<pneumonia patients>> with <<patients with healthcare-associated pneumonia>>

Have corrected

1. Lines 320-321: Was this true for the other older drugs? Did the investigators look at this a confounder?

Have opted not to address

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