Author's response to reviews

Title: Data correction pre-processing for electronically stored blood culture results: implications on microbial spectrum and empiric antibiotic therapy

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Author's response to reviews: see over
Authors” reply to reviewers’ comments

MS: 1480184030241465 - Data correction pre-processing for electronically stored blood culture results: Implications on microbiological spectrum and empiric antibiotic therapy

Reviewer 1

C1. On page three (3), third line from the bottom, the authors reference a publication by S. Richter et.al. regarding “Minimizing the workup of blood culture contamination”, (J Clin Microbiol 2002; 40: 2437-2444). In the preceding paragraph the authors address the impact of blood culture results and reporting with regard to the (empiric) treatment options for patients. However, this reference is a focused study of evaluating BC for possible contaminants and suggestions to then minimize the workup of certain organisms in BC based on their laboratory algorithm. During the following paragraph the authors discuss BC contamination in more detail. I suspect that reference 4 has been misplaced and should have been noted within the following paragraph.

The respected reviewer is totally correct. We have corrected the placement for reference 4 to the correct location.

C2. Figure 1 describes a “flowchart” for the raw data method (RDM). As this method is well explained within the Methods section of the text, I believe that this figure does not add any substantial information or contribution to better understanding this particular data assessment method. I suggest eliminating figure 1 from the manuscript.

We followed the respected reviewer’s advice and have omitted figure 1.

C3. The authors describe within the results and discussion sections the impact of all three data assessment methods on the evaluation of BC contamination. These data are presented well and the tables are fully conclusive. However, table 1 includes an analysis of frequency of organisms encountered in all BCs included in this study. Table 1 mentions 333 “other organisms”. The manuscript does not further specify what other organisms were encountered (page 10 under results). I suggest that the text should mention what other organisms (e.g. descriptive grouping) were seen.

We have added a respective paragraph which gives further information about the other 333 microorganisms yielded from BCs to the manuscript’s result section.

C4. On page 8, the authors describe the duplicate free and the contaminants free methods (DFM, CFM). Please describe in more detail the criteria for the DFM, as similar antimicrobial susceptibilities, even with the disclaimer of 85% similarity, do not conclusively proof that those are duplicate isolates. In addition, the authors should discuss the impact of using this method. In many ways, “duplicate isolates” of organisms with different antimicrobial susceptibilities could suggest an emerging change and may warrant notification of physicians. On the other hand, in developing antibiograms, CLSI guideline M 39-A2 sets forth definitive criteria for excluding certain isolates for the purpose of cumulative antimicrobial susceptibility analyses.

The respected reviewer touches here a very difficult and complex issue: how far can two isolates be differentiated based on phenotypic markers alone. Clearly, if two strains differ in their genus or species, than it is very obvious. But even with biochemical properties, if not substantial, it becomes vaguer to firmly state a true difference. Differentiating two strains based on their antibiotic susceptibility is common in clinical practice, but also prone to substantial errors. As the respected reviewer is better aware than we are only differences in
antibiotic susceptibility in major antibiotics, e.g. S. aureus susceptible or resistant to oxacillin or penicillin G, are indicative for strain differences. When we stated that differences of not more than 15% in antibiotic susceptibility were accepted we were considering the practice that a strain re-isolated from a patient was tested to additional antibiotics or previously tested antibiotics were not tested. Hence, the difference we mentioned pertained more to missing or additionally tested compounds. We have added this issue to the text. However, we fully agree with the respected reviewer that in fact, only molecular typing allows distinguishing 2 strains in more details and with higher certainty. Maybe in future, when molecular typing methods become more routine and also accessible by data mining tools, this matter can be taken into further account. However, we do not believe that even more sophisticated methods will change the conclusion of our investigation. We therefore humbly ask the respected reviewer to accept our minor amendments.

C5. On page 8, for the description of the CFM, the authors mention alpha-hemolytic streptococci. I would discourage the use of this term, as it may include some enterococci as well as VGS. Enterococci are considered true pathogens. This issue is further discussed in manuscripts reference 4 (S. Richter et.al. regarding “Minimizing the workup of blood culture contamination”, J Clin Microbiol 2002; 40: 2437-2444).

We agree with the respected reviewer. We have changed and modified the definition to alpha- or non-hemolytic streptococci, exactly according to Richter et al. on page 2241. Additionally, we have inserted the reference there again.

C6. With the regard to the associations of empiric therapy and antimicrobial susceptibilities, the authors must consider that the difference for the CFM method for fusidic acid, while an interesting observation, is not relevant to the topic of this discussion. A revision of the results should either contain data that describe the commonly used antimicrobials for the treatment of blood stream infections (BSI) in the authors’ institution, or should reflect a true antibiogram considering the approved antimicrobials for the treatment of BSI. This information is available in the M100 S19 Clinical and Laboratory Standards Institute (CLSI) manual for performance standards of antimicrobial susceptibility testing. Similar standards are published by the European Society for Microbiology and Infectious Diseases. In this regards, the evaluation of antimicrobials such as fusidic acid, fosfomycin, and trimethoprim adds little information to the issues discussed in this manuscript.

We have followed the respected reviewer’s comment and have added this issue to the discussion section of our manuscript.

C7. In addition to the revisions in figures 4 and 5, I suggest to include the following reference to the discussion of the data: Munson et al. Journal of Clinical Microbiology 2003; 41: 495-497. This publication describes the fact that very little changes occur in the antimicrobial management at the time when antimicrobial susceptibility results are available to physicians. This would add an interesting point of discussion to this manuscript and further underscore the importance of antibiograms in the empiric choice of antimicrobials. I suggest that the authors expand on this issue in their discussion of the data.

We thank the respected reviewer for pointing out this important reference. We have incorporated the issue and the reference into the introduction section of our manuscript, where we have started similar thought about the matter.
C8. Table 2: In the comparison of RDM vs. CFM as well as DFM vs. CFM the p-value for S. epidermidis shows “>0.0001”. I believe that this should read “<0.0001” as this means statistically significant.
We have corrected the mistake and thank the reviewer for pointing it out to us.

C9. Page 3, line 7: please correct to “….testing results, pharmacokinetics of the drug…”
Corrected accordingly now.

C10. Page 3, line 10: please correct to “…Contrarily, in clinical settings, microbiological…”
Corrected accordingly now.

C11. Page 6, line 11: please eliminate “an” before administration tools
Corrected accordingly now.

C12. Page 6, line 16: correct “b)” to “c)”
Corrected accordingly now.

C13. Page 7, line 4-15: please reword these sentences, as to better reflect which methods are compared in what manner. Also, line 7 reads at present time “…tree separate queries…”. I believe that this should read as “three”.

C14. Page 7, line 18: please correct the sentence to better reflect the way antimicrobial susceptibilities were assessed: e.g. “…. and antimicrobial susceptibilities, using interpretive criteria (susceptible, intermediate, resistant) as defined by CLSI’. One can reference the M100 S19 at this point.

C15. Page 12, line 21: please add the word “true” before bacteremia.
The word “true” was added accordingly.
Reviewer 2

C1. Figure 2: "no" missing on arrow leading to "do not count" box on flow diagram.
We thank the respected reviewer for pointing out this mistake. We have corrected the previous figure 2 (after omitting the previous figure 1 now the new figure 1, see C8.) accordingly.

C2. Figure 3: Significant Error: the flowchart logic for possible skin contaminants does not indicate that at least one duplicate positive culture of the same organism was necessary within 5 days for the isolate to be considered an episode; it shows only that subsequent positive cultures of the same organism are not counted as a new episode. Follow the logic currently diagrammed for, say, a coagulase-negative staph on a new patient: positive culture -> possible skin contaminant? -(y)-> same patient -(n)-> count as episode
The respected reviewer is absolutely correct. We have modified the flowchart accordingly.

C3. Pages 7-8: consider placing references to figures 1, 2, and 3 within each description, rather than at the beginning of the section.
We thank the respected reviewer for this valuable comment, which makes the content easier to follow for the reader. We have followed the reviewer’s advice accordingly.

C4. Page 8: clarify whether all coagulase-negative staphylococci were considered "the same microorganism" for the purposes of the DFM and CFM, or were they ever speciated and considered separately at the species level.
No, the respected reviewer is absolutely correct. Coagulase-negative staphylococci were considered “the same microorganisms” only at the species level. If, e.g., one Staphylococcus warneri and one S. haemolyticus isolate was yielded within 48 hours from the same patient, this was counted as two independent episodes. We have added this information to the manuscript.

C5. Pages 8-9 (and figures 2 and 3): In your description of the DFM and CFM you count the same organism w/i 14 days as part of the same episode. How did you handle persistently positive cultures, e.g. organism A was present on day 0, day 10, and day 20 - was the day 20 culture counted as a new episode since it was >14 days from the first isolate, or was it not counted since it was w/i 14 days of the 2nd isolate? This would be an uncommon event, and I don’t think it would change the results either way you did it. But I couldn’t tell which way from your manuscript - please consider clarifying.
Also, for the CFM, if a coagulase-negative staph were cultured on day 0 and again on day 3, then the day 0 culture would be counted as an episode. If coagulase staph were again cultured on days 7 and 10, would that be a new episode (since the day 7 culture is >5 days from the day 0)? Figure 3 would seem to indicate so, but shouldn’t the 14 day rule for duplicates still apply? In other words, to confirm a common skin contaminant, a second culture w/i 5 days just as for non common skin contaminants? I'm not suggesting that you should re-analyze, but please clarify.
We counted a new duplicate isolate 14 days (2 days) backward from the last positive culture with the same organism. In the above example, organism A would have counted only once, as the isolate on day 20 was only 10 days after the isolate yielded on days 10. We have looked into our data, and indeed, such a situation occurred only in 6 patients, 3 times with S. epidermidis, 2 times with S. aureus, and one time with Pseudomonas aeruginosa, respectively. We have addressed this matter in the method section of the manuscript.
C6. Page 9: you refer to the "National Committee for Clinical Laboratory Standards (NCCLS)"; this has been the Clinical and Laboratory Standards Institute "CLSI" since 2005; although it was still NCCLS at the time of your data collection, perhaps you should clarify.

The respected reviewer has a valid point. The correct current name of the Institute together with a brief explanation on the previous name is included in the text now.

C7. Figure 1: this rule is so simple I'm not sure this figure adds much. Consider removing.

We fully agree with the respected reviewer. We have omitted figure 1 now completely.