Author's response to reviews

Title: Appropriate Initial Antibiotic Therapy in Hospitalized Patients with Gram-Negative Infections: Systematic Review and Meta-Analysis

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Version: 3 Date: 25 June 2015

Author's response to reviews: see over
June 23, 2015

Dear Editor-in-Chief,

We are pleased to submit our revised manuscript “Appropriate Initial Antibiotic Therapy in Hospitalized Patients with Gram-Negative Infections: Systematic Review and Meta-Analysis” for your consideration. We have addressed reviewers’ comments and this cover letter includes line by line response to reviewer’s comments. This manuscript represents an evidence review of contemporary literature that we performed at the Tufts Center for Clinical Evidence Synthesis. All authors have read and approved the submission of the manuscript. The manuscript has not been published elsewhere, and it is not currently under consideration for publication by another journal.

We appreciate your consideration of this submission to BMC Infectious Diseases. Thank you very much for your time.

Sincerely,

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Reviewer's report and responses
Title: Appropriate Initial Antibiotic Therapy in Hospitalized Patients with Gram-Negative Infections: Systematic Review and Meta-Analysis
Version: 2 Date: 30 April 2015
Reviewer: Benjamin Rogers

Reviewer's report:
Thank you for inviting me to review this work. The study is a systematic review and meta-analysis of studies reporting outcomes related to initial/empiric antimicrobial therapy for Gram-negative infections. I commend the authors on the effort of such a large literature search and extensive review of full-text papers. The paper is well written. I think this is a worthwhile exercise, however there are some limitations to what is presented.

Response: Thank you.

Major
1) On the whole it is somewhat difficult to assess the validity of this exercise as quite limited data is provided about the studies included within the analysis. Whilst summaries are provided within Table 1 and the text several factors that are crucial are not readily assessable. (Supplementary table 1, where this information might sit, is very light-on for details) Key factors include the severity of illness and actual definition of appropriate therapy including the time-delay allowed. Firstly, the impact of inappropriate therapy is going to be greatest in patients with septic shock. Second, the impact of delay (at least in septic shock) is in hours not days. The first window used is 48 hours in the subgroup analysis. Likewise mortality within each study is not provided. This must vary greatly between studies depending on the type of infection studied.

Response: We have added these key factors including the severity of illness, actual definition of appropriate therapy, and mortality rate in the new Table 1. We have conducted additional analyses using ≤24 hour window for timeliness of appropriate therapy (Table 2).

2) In regard to the adjusted analysis my comment is somewhat similar. Very little data is provided about how the studies derived adjusted mortality, so it is difficult to understand the validity of this result. On the whole I think it is going to be very difficult to derive a valid result looking at adjusted results, as there is so much uncertainty about how to adjust for pre-existing conditions in such studies. Certainly more data needs to be presented if we are to take this result as meaningful.

Response: We have added a column on multivariable adjusted covariates in the new Table 1. While there is no consensus on what variables to adjust for in multivariate analyses, we believe when authors performed multivariable adjusted analyses for the outcome of mortality, they have appropriately considered severity of illness in their population to adjust in the analyses.
Minor
3) In regard to the economic analysis, again I think this is a worthwhile exercise, especially for indicators such as LOS. However, attempting to combine the dollar value cost is somewhat difficult due to the widely varied cost of care. The inclusion of studies that used resistant/susceptible as the stratification is also problematic as these are heterogeneous groups of appropriate and inappropriate therapy.

Response: We agree with your suggestions that the economic data comes from a heterogeneous group of studies. Given the paucity of data for the economic outcomes evaluating the timeliness of appropriate antibiotic therapy, we felt it was worthwhile to present any available comparative data.

4) Specific comments.
I find the acronyms confusing as they are quite similar and too long. As the whole analysis is referring to initial antimicrobial therapy, possibly they could simply be IT (Inappropriate therapy) and AT (Appropriate therapy), or something along these lines?

Response: We have modified the acronyms to Appropriate Antibiotic therapy (AAT) and to Inappropriate antibiotic therapy (IAT) throughout the text section.

Line 100 – Just a small point but I do not think this is a good description of gram-negative resistance, as much is not by mutation but my acquisition of mobile genetic elements. Possibly it might be more accurate to say ‘via mutation and gene acquisition’.

Response: Thank you, we have edited this (line 118-119).

117 Authors should state if it meets the PRISMA statement rather than saying ‘standard methods’

Response: We have edited this (lines 139-140).

188 – It is unclear if this means administering an antibiotic to which the final isolate was susceptible, or any antibiotic?

Response: Thank you, we have clarified this (lines 212-213).

198 – Weren’t 5 outcomes considered?

Response: Thank you, we have edited (line 222-223).

256 – I presume the authors are now referring only to the studies with direct evidence?

Response: Thank you, we have edited (line 280).
This is a very limited exploration of the limitations! Clinical response – really need to say when treatment failure was measured or it doesn’t make any sense.

**Response:** We have added more to the limitation section (lines 285-303). We have acknowledged that except for one study, none measured when treatment failure was measured (lines 338-339).

Table 1
The pathogens are a little confusingly labelled and not identified by accepted nomenclature e.g. do the authors mean ‘Acinetobacter spp.’? Is it ESBL Klebsiella spp. or all Klebsiella spp?

**Response:** We have corrected this in Table 1.

**Reviewer’s report**
**Title:** Appropriate Initial Antibiotic Therapy in Hospitalized Patients with Gram-Negative Infections: Systematic Review and Meta-Analysis
**Version:** 2
**Date:** 1 April 2015
**Reviewer:** Marya Zilberberg

**Reviewer’s report:**
This is a systematic review and meta-analysis of studies examining the impact of antibiotic treatment timing and choice on the outcomes of hospitalized patients with Gram-negative nosocomial infections. In general, the review was well performed and the meta-analysis is well done. There are a number of questions/concerns that I would like addressed by the investigators.

**Response:** Thank you.

1. In my mind I do not think that the authors made an adequate argument for why this meta-analysis is needed. That is, I can think of a handful of studies that in fact focus on very specific resistant organisms that fail to confirm the importance of IAAT in the setting of a serious infection. The vast majority of studies published I this area leave very little doubt about this. Specifically, some doubt still exists for Acinetobacter, and it might me of interest to isolate the studies that look at that for a sensitivity analysis. Otherwise, the rationale for this review needs to be boosted.

**Response:** In the introduction section, we have added a bit more on the objectives for conducting this review. We have conducted additional sensitivity analyses with and without Acinetobacter studies. We did not find any significant impact with removal of Acinetobacter studies. Additional sensitivity analyses are presented in Table 2.

2. I am having trouble with the rationale for looking at community-acquired infections for the utilization outcomes. I understand that the data are just not there for the nosocomial
infections, but that in and of itself is important. I concede that it may be OK to look at CA infections, but the authors really need to convince me that it is in fact valid given their study aims.

**Response:** Ideally we would have liked to look at resource utilization for nosocomial infections as that has the greatest relevance given our study aims. However, given the paucity of data in that space and the availability of data in the CA space, we felt it was worthwhile to present the latter data.

3. On page 9 the authors summarize the definitions for AAT. They say that timeliness was the #1 criterion, and coverage of cultured organism was #2. To the best of my knowledge, many of the studies require both to be considered AAT. It would make sense to present a sensitivity analysis based on this definition.

**Response:** Thank you; we have edited this as per your suggestion. We have presented additional data according to the timeliness, susceptibility, or both.

4. Given that you have such a rich database of studies, it might be useful to perform separate subgroup analyses based on organism and based on infection source. This might shed light on whether IAAT plays the same role consistently across these conditions.

**Response:** Subgroup analyses based on organism is already presented in Table 2 (previously numbered as Table 1). Additional combination based on organism and infection source is now added to Table 2.

5. One of the limitations is that this work focuses exclusively on culture-positive cases, making it less generalizable to those where cultures grow nothing. One way people have looked at all (culture-positive and negative) infections is by defining “appropriate” as “guideline-concordant.” I am not suggesting that the investigators add this literature here, but please mention something about it in the Discussion.

**Response:** Thank you, we have acknowledged this as a limitation.

6. Discussion can be focused and shortened.

**Response:** Thank you, we have edited the discussion section.