Reviewer's report

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.

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.

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.

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.
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?

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’.

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

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

198 – Weren’t 5 outcomes considered?

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

317 – 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.

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?

**Level of interest:** An article of importance in its field

**Quality of written English:** Acceptable

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**

I declare that I have no competing interests