Reviewer's report

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

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Reviewer: Marya Zilberberg

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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.

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 in this area leave very little doubt about this. Specifically, some doubt still exists for Acinetobacter, and it might be of interest to isolate the studies that look at that for a sensitivity analysis. Otherwise, the rationale for this review needs to be boosted.

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.

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.

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.

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.

6. Discussion can be focused and shortened.