Reviewer’s report

**Title:** Efficacy of Ceftazidime-Avibactam in the Treatment of Infections due to Carbapenem- Resistant Enterobacteriaceae

**Version:** 0  **Date:** 05 Jun 2019

**Reviewer:** Ghady Haidar

**Reviewer's report:**

This article adds to the existing literature by describing outcomes of patients with OXA-48+ CRE. These data confirm what is known about C/A and KPC+ CRE. I agree that data regarding OXA-48+ CRE are limited.

Non-science comments: please refer the MS for syntax and grammatical revisions.

General comments:
The authors should provide the distribution of Carbapenem MICs. OXA-48 is usually a weak carbapenemase. If that is the sole mechanism of Carbapenem resistance, I would not expect the MICs to be markedly elevated. This should be in a table alongside the PCR results.

Abstract: OXA-48 is not mentioned until the conclusion. Please revise. In addition, whether or not rates of CRE are rising is debatable (complex issue based on country, city, hospital etc).

Background:
-Please see above re: whether CRE are actually increasing. I would remove this statement given the above complexities
-FDA and other governmental agency approval is really only relevant for getting the drug on the market. CAZ-AVI has been around for 4 years, and its niche is CRE. Please revise this section: instead of focusing on the FSA labels etc, please describe how CAZ-AVI has emerged as the frontline agent for KPC+ CRE infections give superior efficacy and less toxicity compared to historic salvage regimens (can cite Shields et al, AAC 2017, van Duin et al, CID 2018, Tumbarello et al, CID 2019). There is no need to discuss these studies at length however.

Methods:
-What breakpoints for CRE are the authors relying on?
-How were "clinically established infections" defined?
-For the primary outcome: in cases of pneumonia, did the authors repeat cultures (BAL/sputum)?
-How long were patients on therapy for to be included? Any dose? 48-72 hours?
-How were cases/controls matched?
-So the CAZ-AVI cohort was treated between 12/2017 and 8/2018, while the non-C/A cohort was treated between Jan 2017 and August 2018? Is this because CAZ-AVI wasn't available at your institution until Dec 2017?
Results:
- The patient characteristics section can be simplified in the text
- What was the other mechanism of resistance? (Line 119). As above, this should be detailed in a table
- Did the authors exclude NDM+ isolates from the analysis? C/A is not active. Please clarify this point: the comparison needs to be OXA-48 vs OXA-48
- The breakdown of antibiotics used may be better suited for a table
- Did any patients in the C/A cohort receive an additional agent?
- What was the duration of therapy?
- Was susceptibility testing against CAZ-AVI done?
- Please list relapse and mortality rates in the text
- In cases of patients who relapsed, did any high-level Carbapenem resistance and/or CAZ-AVI resistance emerge

Discussion/conclusion:
I would recommended revising the discussion and making it about:
- We are doing better in managing CRE
- Prior data have focused on KPC
- This focused on OXA-48 and thus confirms that CAZ-AVI should be used for infections caused by these pathogens
- Precision medicine

I realize that the p value was 0.14, but 80% success in C/A vs 53% success in the others is clinically significant. It's very difficult to show statistical significance with extremely small numbers (esp in retrospective studies), but this should not dissuade us from using this drug, nor should it make us conclude that CAZ-AVI is "as good" as salvage regimens for OXA+ CRE. The prior data overwhelming demonstrate that it is better.

The paradigm of CRE management has changed. Things are not as bleak as they were 5 years ago, as we currently have 4 agents on the market (CAZ-AVI, mero-vabor, which have emerged as the drugs of choice for CRE infections, as well as plazomicin and cravacycline). It is clearly superior to and safer than old salvage regimens (see the references I cited before).

There are at least 4 more agents on the horizon: cefiderocol (2019), imi-relebactam (no OXA-48 activity, 2019), IV fosfomycin (2019 in the USA), and aztreonam-avibactam. The discussion should acknowledge this: in settings where CAZ-AVI and mero-vabor are available, these drugs should be give for CRE infections, not old salvage regimens. However, the "niches" where each will be superior have yet to be defined; for instance, the presence of OXA-48 would be a situation where one would use C/A and not M/V. There is really no need to discuss the merits of combination therapy for KPC+ CRE in 2019.

The authors should also highlight the importance of understanding the genotype of the CRE: with the plethora of agents already available or on the horizon, the genotype of the organism will be instrumental in determining what the optimal antibiotic for the offending pathogen is. Mero-vabor and imi-relebactam for example would not be expected to have a role in treating OXA-48+ infections, in contrast to CAZ-AVI as the authors demonstrate.

Among the future directions, it would be interesting to see how OXA-mediated resistance to CAZ-AVI
will emerge.

Are the methods appropriate and well described?
If not, please specify what is required in your comments to the authors.

Yes

Does the work include the necessary controls?
If not, please specify which controls are required in your comments to the authors.

Yes

Are the conclusions drawn adequately supported by the data shown?
If not, please explain in your comments to the authors.

Yes

Are you able to assess any statistics in the manuscript or would you recommend an additional statistical review?
If an additional statistical review is recommended, please specify what aspects require further assessment in your comments to the editors.

I am able to assess the statistics

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