Reviewer’s report

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

Version: 0 Date: 20 Jun 2019

Reviewer: Kevin Escandón-Vargas

Reviewer's report:

Unfortunately, there are several language issues, including phrasing and grammatical errors throughout the manuscript. Please ensure that you have thoroughly checked your manuscript for any other language errors. I recommend asking a NATIVE English speaking colleague to help you copyedit the paper. If this is not possible, you may need to use a professional language editing service. Use of an editing service is neither a requirement nor a guarantee of acceptance for publication.

Please include the email addresses for all authors on the title page. The corresponding author should still be indicated.

Change the title: you will know my detailed reasons by reading my comments below. Avoid "effectiveness", consider just treatment or use. Not all patients had OXA-48, but one cohort group received CAZ/AVI compared to the other. Consider just CRE, not OXA-48.

Background

- Lines 45-47: CRE is likely on the rise, but CRE varies geographically. Likewise, the different mechanisms of resistance (hydrolases and others) vary geographically. References cited are insufficient and outdated given the more recent evidence published about CRE or CPE. Please update, verify, and adequately support your claims. Please read:

- Lines 48-49: Reference 4 is inappropriate, they just studied the outcomes of VIM-positive/negative K. pneumoniae BSIs, that's very specific and unrelated to your article and claims. Moreover, the following part is not correct: "bacteremia being the most strongly associated risk factor". The well-known article by Falagas compared all-cause deaths and CRE-attributable deaths between CRE and CSE within the same type of infections. The overall CRE infection and CRE bacteremia were risks factors in these meta-analyses, compared to CSE infection and bacteremia, respectively, NOT COMPARED WITH no bacteremia, so the main risk factor for mortality is carbapenem resistance or carbapenemase production (as shown in https://www.ncbi.nlm.nih.gov/pubmed/27104910), which is logically more serious in a BSI than other types of infection. This is a subtle but important difference.
Please amend the sentence and cite more recent evidence also suggesting that the main independent risk factor in CRE vs. CSE is carbapenem resistance (or carbapenemase production) itself:
and

- Lines 54-60: EMA reference is not needed. Please have a look at these articles, rewrite this paragraph, and use top recent evidence about the use of CAZ/AVI.

- Line 55: replace inhibitors with inhibitor.


- Line 59-60: this sentence is not adequately written.

- Line 60: The first letter of "Gram-" should not be capitalized unless you start a sentence or write "Gram stain". It is "gram-negative", not "Gram-negative". See https://wwwnc.cdc.gov/eid/page/preferred-usage. Please correct throughout the manuscript.

- Line 62: replace "Bacilli" with "bacilli" and don't use italics. This is not a genus, species or family to use that style.

- Line 63: replace "pneumoniae" with "pneumoniae". Also make this correction in your abstract (line 27; both in the text and the submission system), line 127, and expansion of abbreviation KPC (not KPCs) in the abbreviation list.

- Line 65: read, discuss, and cite the recently published narrative review on CRE in Saudi Arabia (https://www.ncbi.nlm.nih.gov/pubmed/31060974). Be brief/introductory in Background; discuss your results using that evidence in your discussion.

Methods

- Line 78: specify the wards or the hospital section where the patients were chosen from. Did the exposed and non-exposed come from the same pool of patients? Were there any excluded patients or was a CRE infection the only inclusion criteria used? On what basis did the patients receive CAZ/AVI or other antibiotics? Did you collect any info on why, for example, a patient with an OXA-48 CRE received CAZ/AVI whereas another patient with OXA-48 CRE was treated with combination therapy?

- Line 81: rephrase for clarity: "We compared patients with CRE infections who received CAZ-AVI with those who received other agents."

- Line 87: replace "of" with "with".

- Line 92: replace "KPCs" with "KPC".

- Line 94: Abbreviation CRE already in use.
- Line 99: You should write beta-lactamase genes as follows: "bla (in italics), class in subscript (no italics), no spaces in between.

- Line 105: change "T-test" to "Student t test" (t italicized)

- Line 105: merge the text; there is unnecessary space on this page.

- Line 105: be consistent with your style (use only one style). Choose between "p-value", "P value", and "p value"; always the P should be italicized. Also correct Table 1 and Table 2. In results, only use "P" (italicized), delete the word "value".

Results

- Line 110: change "by" to "with".

- Line 110: why did you exclude children? You should include them to increase the sample a bit; otherwise, state adults in your inclusion criteria.

- Line 109: Dates are discordant. Exposed group (Dec 2017-Aug 2018) Non-exposed group (Jan 2017-Aug 2018) Methods (general? Jan 2017-Jun 2018) Since this is an observational cohort study, selection period of exposure (CRE infection - treatment with CAZ/AVI) and non-exposure (CRE infection - treatment with other antibiotics) should ideally be the same. Otherwise, a justifiable reason should be declared. The general date should include the others.

- Line 111: Make clear if matching was really performed or whether you mistakenly meant "matching" for the standard procedure of choosing a non-exposed group, which is not called matching (also lines 155, 157). Matching is a strategy to select controls/unexposed subjects that in certain important features are identical to cases/exposed subjects, in order to adjust for some variable distributions at the design stage. It is most frequently performed in case-control studies. In the case you had matched unexposed to exposed subjects, details should be stated. A serious concern in such a case is a reduced efficiency (power) partly because of a reduction in the number of study patients. I don't think you'd have wanted that.

- Line 118: replace "(n=8, 80%)" with "(8/10, 80%)".

- Line 120: replace "(n=19, 68%)" with "(19/28, 68%)".

- Line 125: Use the abbreviation already stated in Line 58 or delete it (HAP), be consistent.

- Line 126: merge the text; there is unnecessary space on this page.

- Line 127: Statistically speaking, there is no such a P value of 1.00. Replace it with ">0.99". You can see https://www.myresearcheditor.com/report-p-values-apa-ama.html Also, correct Tables 1 and 2.

- Line 129: the First letter of antibiotic names are not capitalized except for starting a sentence or in the
Discussion

- Lines 145: This first sentence is not right. This is neither a clinical trial nor a prospective cohort comparing treatment options for a valid number of infection cases due to OXA-48-producing Enterobacteriaceae. Rephrase.

Have in mind that if you want to mention that you have shown clinical remission in the majority of patients with CRE infections in your hospital caused by OXA-48-producing organisms, you should present in the text (maybe also in Table) how many patients achieved this outcome among those who had been isolated an OXA-48-producing organism. What we know, as to how the manuscript stands, is that 8/10 among CAZ/AVI had OXA-48 vs. 20/28 among non-CAZ/AVI had OXA-48, and that 8/10 among CAZ/AVI achieved clinical remission whereas 15/28 among non-CAZ/AVI did it.

- Lines 146-147: Amend this sentence. You cannot know if the mortality was due to the comorbidities unless you perform contingency tables for mortality and at least examine P values after comparing the group with and without comorbidities or the mean/median Charlson index depending on the distribution. That analysis would allow you "a likely inference" but this info is not presented; more precise conclusions would be allowed if you had performed a univariable risk factor analysis obtaining ORs, and a multivariable analysis adjusting for confusion (obtaining adjusted ORs). I understand, however, that your scarce sample size would not allow performing this type of analyses with enough statistical power. Further, consider the inappropriateness of your conclusion if you remember that having a CRE (alone) is an independent risk factor for death. And that's a fact shown by several studies with hundreds of patients, of course with a different aim and design than yours.

- Line 147: merge the text; there is unnecessary space on this page.

- Line 148: Include here the 2019 review on CRE in Saudi Arabia, and update your discussion.

- Line 149: "In our cohort, 80% of tested isolates were OXA 48 positive, and 20% were NDM positive." This is incorrect. Based on your results, you had 28/38 (74%) with OXA-48 and 7/38 (18%) with NDM (note that 1 had a coproducer organism), and there are 4/28 with an unknown resistance mechanism. At this point, I ask you to include in Results a table including all the patients, with the type of bacteria, the MICs for antibiotics, the molecular screening of the resistance mechanism, and the treatment. If you see it's extensive, include it as a Supplementary table (see our guidelines).
As you found a predominance of OXA-48, discuss its epidemiology in contrast to your results, therapeutic implications, etc. Consider using https://www.ncbi.nlm.nih.gov/pubmed/31060974 and https://www.ncbi.nlm.nih.gov/pubmed/28990132

"This was obvious" What was obvious? On the contrary, it seems as if you had analyzed the effect of the type of treatment (combination therapy vs. monotherapy) on mortality and cure. So far, what we know is that 25/28 patients were started on combination therapy and the proportions of those 28 patients who got cured or died. These are separate results that do not tell if combination therapy is more efficacious or not than monotherapy.

I agree with using the word "comparable" since the P value for clinical remission and cure were above 0.05. However, note that combination therapy (or, worst, monotherapy with toxic/likely subtherapeutic agents) are not "the current specific regimen" for managing CRE. At least, not in several countries where novel B-lactam/B-lactamase inhibitor combinations are available and are the gold standard. If, otherwise, this pertains to the situation in your country, make it clear. Also, I recommend writing a sentence mentioning that the low sample number affects the statistical power of testing, thereby not allowing to reproduce the clear benefits in terms of clinical outcomes when patients with CRE are treated with B-lactam/B-lactamase inhibitors. Elaborate based on some of the recent evidence which I have provided above.

Avoid starting a sentence with numbers; otherwise, spell them out.

This does not read well, get the assistance of an English writer.

It does not make sense that you write a result from your study citing another work. Furthermore, Souza's work is reference 12, and you cited reference 13. You must include and discuss previous results of CRE studies and CAZ/AVI studies in Saudi Arabia.

merge the text; there is unnecessary space on this page.

Again, English is not good when describing your limitations.

Conclusions

you did not discuss your results in terms of the type of infection, so do not conclude about something you did not discuss.

List of Abbreviations: do not use capital letters except for the first letter of the first word when writing out the abbreviations.

merge the text; there is unnecessary space on this page. Change "Declaration" to "Declarations".

verb form "are" is missing.

Some authors work at Pfizer. Besides, this company provided funding and
language assistance. Declare the respective conflicts of interest.

Authors' contributions: avoid wordiness. Summarize these contributions in a paragraph with a few sentences. Put common contributions after contributors.

References: check the journal citation style of our journal. I suggest using an appropriate reference manager to simplify the task.

Table 1

- There are unnecessary details. Use cardiovascular disease and renal disease as general categories for grouping heart failure, IHD, CVA, CKD, ESRD. Note that since there is no significance, this level of detail does not provide value but additional space.
- Replace "N" with "n", use italics.
- Use italics for bacteria.
- Expand E. coli. Delete it as an abbreviation on the footnote.
- Delete this "Continued on next page", "Table 1 continued". Reformat the layout using portrait orientation.

Table 2

- Replace "N" with "n", use italics.
- Add "(\%)
" to the first group column.
- Reformat the layout using portrait orientation.

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.

No

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

**Quality of written English**
Please indicate the quality of language in the manuscript:

Needs some language corrections before being published

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Please complete a declaration of competing interests, considering the following questions:

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None

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