Author’s response to reviews

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

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20 August 2019

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Dear Editors,

We would like to take this opportunity to thank you and the reviewers for helping us further clarify and improve our manuscript (MS# INFD-D-19-01006). We have included a point-by-point response letter and revised manuscript with the changes made tracked. Our responses to your comments are below. We hope that the revisions in the manuscript and our detailed responses will satisfactorily address your concerns.
Editor Comments:

Lines 96 and 260 (both in CRE and CSE abbreviations): write correctly "Enterobacteriaceae" (in italics).
Response: “Enterobacteriaceae” was corrected to italics (line 98 and 299 for both CRE and CSE abbreviations).

Line 103: delete "remain an issue".
Response: “remain an issue” was deleted (line 105).

Lines 107: correct "carabapenemases".
Response: “carabapenemases” was corrected to “carbapenemases” (line 109)

Lines 125 and 159: dates are discordant for the comparative group. November 2017 or 2018?
Response: comparative group included patients between January 2017 and November 2017. We corrected the manuscript and changed “November 2018” to “November 2017” (line 167).

Line 149: replace "data of normal distribution data", which makes no sense, with "normally distributed data".
Response: “data of normal distribution data” was changed to “normally distributed data” (line 153).

Lines 168-172: this is a long sentence without sense. Please rewrite.
Response: Agree. Since the MICs distribution was similar between the two groups, we deleted all details and referred to supplementary tables (line 177)

Line 169: delete "".
Response: deleted (line 177)

Lines 172-173: please change "Details on MICs of carbapenem and CAZ-AVI for both groups are presented in supplementary tables S3 and S4." to "Details on mechanism of carbapenem resistance and
antibiotic MICs for both groups are presented in Supplementary Tables S3 and S4."
Response: "Details on MICs of carbapenem and CAZ-AVI for both groups are presented in supplementary tables S3 and S4." Was changed to "details on mechanism of carbapenem resistance and antibiotic MICs for both groups are presented in Supplementary Tables S1 and S2." (lines 177-179).

Line 260: capitalize initials of CLSI, italicize Klebsiella pneumoniae.
Response: CLSI initials were capitalized. “Klebsiella pneumoniae” changed to italics. (line 299)

Tables 1 and S1
- Use italics for bacteria.
- Since you decided to only use HAP and delete VAP in the text, also please correct tables and their footnotes.
Response: we used italics for bacteria and deleted VAP from tables and their footnotes. (Tables 1 and S1)

Table 2
- Add "(\%)" to the first group column.
Response: (%) added to first group column in Table 2.

Tables S3 and S4
- Use italics for bacteria.
- Correct "Klebisella"
Response: we used italics for bacteria and corrected “klebisella” to “Klebsiella” (Tables S3 and S4).

Table S5
- Correct "sulphamethoxazole"
- Capitalize the first letter of "carbapenem"
Response: “sulphamethoxazole” was corrected to “sulfamethoxazole”. First letter of “carbapenem” were capitalized (Table S5).
Lastly, please review all table mentions in the text, their order should logically be table 1, table 2, and of supplementary tables, tables S1, S2, S3, S4, S5. When making changes, avoid mistakes in table titles, in-text mentions, file labels, and locations.
Also, add a section "Additional files" (after the References/Figure legends) where you list the following information for each additional/supplementary file in the file inventory:
- File name (e.g. Supplementary table 1), titles of supplementary data, or description.
Response: Order of all tables including supplementary tables were changed logically as they appear in the manuscript. Table titles, labels and locations were changed as necessary. We added a section after references (line 440) to list all additional files (Table 1 and 2) and (Supplementary Tables S1, S2, S3, S4, S5).

Ghady Haidar (Reviewer 1): The authors have extensively revised the manuscript and addressed a plethora of comments from both reviewers + the editorial board.

The flow is much, and the quality of the MS has overall improved.

The only major comment is re: the first line of the discussion (line 197), which says "Our study demonstrated similar clinical remission between CAZ-AVI and standard treatment with antibiotics."
This contradicts line 186, which says: "Eight patients (80%) in the CAZ-AVI group achieved clinical remission compared to 15 patients (53.6%) in the comparative group (P=0.14)." This is a clinically meaningful difference. We tend to focus a lot on the importance of p values < 0.05 in medical literature, but this isn't a universal truth (there is an abundance of emerging statistical literature about this). I would rephrase this as follows:
"Even though our small sample size likely precluded our ability to find statistically significant differences, our study demonstrated a clinically significant benefit of CAZ-AVI for the treatment of CRE infections, including those caused by OXA-48 producing organisms, compared to standard therapy."
Response: Thank you. We agree, our data showed that CAZ-AVI was superior numerically and the small sample size precluded our ability to find statistically significant differences. We modified the first paragraph of the discussion as suggested (line 215-218)

Other comments:
Abstract: "A" carbapenemase gene, not "the" (line 70).
(EDITOR: please correct this in the abstract system as well)
Response: corrected (line 70)

Line 146: technically, CRE is defined as ertapenem MIC of >=2 or imi/mero/dori >=4; please make the change
Response: agree. Manuscript was modified accordingly (lines 149-150)

Lines 216-218: I would delete. Not sure what this adds:
"The reported clinical outcomes are similar to our results; however, our cohort population had complexity index of 5.5 compared to 3 in this study, and we think this is a notable feature."
Response: Deleted (line 249)