Author’s response to reviews

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

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Author’s response to reviews:

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BMC Infectious Diseases journal

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 believe that the reviewers’ comments have enhanced and enriched our manuscript. We have included a point-by-point response letter and revised manuscript with the changes highlighted. Our responses to your comments are below.
We hope that the revisions in the manuscript and our detailed responses will satisfactorily address your concerns. We look forward to hearing from you.

Regards,

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Reviewer reports:

1. Ghady Haidar (Reviewer 1): 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.
Response: Thank you. The manuscript was reviewed and edited by professional English language editing service. All changes are highlighted in the revised manuscript.

2. 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.
Response: We added carbapenem MICs data for both groups alongside the PCR results (supplementary table 3 and 4). We described meropenem and imipenem MIC distribution in the manuscript (lines: 168-173)

3. 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).
Response: Thank you. We modified abstract to include description of the most common identified gene. We agree whether CRE rate is rising is debatable. We modified the abstract accordingly (lines 70-71).

Background:

4. 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 FDA 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.

Response: Thank you for your comment. The first and second paragraph of background were rewritten to reflect the requested changes. All suggested references were added to manuscript.

Methods:

5. -What breakpoints for CRE are the authors relying on?
Response: All confirmed isolates of CRE from culture were tested using Xpert ® Carba-R kit following manufacture recommendation for rapid detection and differentiation of the blaKPC, blaNDM, blaVIM, blaOXA-48, and blaIMP gene sequences linked to carbapenem resistance in gram-negative bacteria. The interpretation of the MIC for both Meropenem and Imipenem is based on the Clinical Laboratory Standards Institute (CLSI) M100-25th Edition (2015):

<table>
<thead>
<tr>
<th>MIC</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 1</td>
<td>Susceptible</td>
</tr>
<tr>
<td>2</td>
<td>Intermediate</td>
</tr>
<tr>
<td>≥ 4</td>
<td>Resistant</td>
</tr>
</tbody>
</table>

Manuscript was adjusted accordingly (lines 144-146)

6. -How were "clinically established infections" defined?
Response: “clinically established infections” defined as infections due to CRE confirmed after being reviewed by infectious diseases specialist. We wanted to use this term to indicate that all isolates included in the study represent true infection rather than colonization.

7. -For the primary outcome: in cases of pneumonia, did the authors repeat cultures (BAL/sputum)?
Response: Because of the retrospective nature of this study. Most patients did not have a repeat culture from BAL/sputum. On the other hand, all patients with bacteremia had subsequent blood cultures which allowed us to analyze clearance of bacteremia between the two groups.

8. -How long were patients on therapy for to be included? Any dose? 48-72 hours?
Response: Patients were included if they received at least 24 hours of therapy (CA-AVI or other CRE targeted therapy). Methods were updated accordingly (line: 120)

9. -How were cases/controls matched?
Response: We did not do matching in our study design or analysis. CAZ-AVI was introduced to our institution in December 2017. Since then CAZ-AVI became the standard of therapy for CRE infections. We compared patients who received CAZ-AVI with the patients with CRE infections who were treated with other agents between Jan 2017 and August 2018. We clarified this in the manuscript (lines: 123-126)

10. -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?
Response: Yes. CAZ-AVI was not available until December 2017.

Results:

11. -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?

Response: “other mechanism of resistance” indicate that none of the five genes were detected by our testing. To clarify this, we modified the manuscript and changed “other mechanism of resistance” to “no carbapenemase gene was detect”. We added supplementary tables (tables S3 and S4) which details all mechanism of resistance in both groups.

We reanalyzed the data after excluding patients with mechanism of resistance other than OXA-48 and added two supplementary tables (Tables S1 and S2). Results remained similar in regards of baseline characteristics (Table S1) and outcomes (Table S2).

Patients in the CAZ-AVI group did not receive additional agents while on CAZ-AVI therapy.

12. -What was the duration of therapy?
Response: unfortunately, data on duration of therapy were not consistently documented.

13. -Was susceptibility testing against CAZ-AVI done?
Response: Yes. We identified 7 out of 10 patients in whom susceptibility test was done for CAZ-AVI. The result of MICs are included in supplementary table S3. We updated the manuscript accordingly (lines: 168-173)

14. -Please list relapse and mortality rates in the text -In cases of patients who relapsed, did any high-level Carbapenem resistance and/or CAZ-A Vi resistance emerge?
Response: Thank you for your comments. Mortality and relapse data were added to the text (lines: 189-190)

Discussion/conclusion:

15. I would recommend 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

Response: Thank you. The discussion was completely re written and all above comments were addressed.

16. 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.
Response: We agree with the reviewer. We acknowledged the limitation of small sample size in the discussion (lines 246-248)

17. 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 eravacycline). It is clearly superior to and safer than old salvage regimens (see the references I cited before).
Response: Thank you. We discussed new options for management of CRE infection in our discussion (lines: 219-234)

18. 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 given 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.

Response: See response to comment #17

19. 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.

Response: Agree. We discussed the importance of molecular testing and limitations of some of the new agents for management of CRE infections (lines 230-239).

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

Response: Agree. We addressed this comments (lines 240-244)

Marta Mora (Reviewer 2): Probably, BMC Infectious Diseases readers would appreciate more data concerning use of CAZ/A VI in clinical practice through the world, as authors show in present manuscript.

1. Globally I would appreciate if authors could clarify methodology, mainly how they selected the two retrospective cohorts (it is not clear control cohort)

Response: Thank you. We did not perform matching in our study design or analysis. CAZ-AVI was introduced in our institution in December 2017. Since then CAZ-AVI became the standard of therapy for CRE infections. We compared patients who received CAZ-AVI with the patients with CRE infections who were treated with other agents between Jan 2017 and August 2018. We clarified this in the manuscript (lines: 123-126).

2. Regarding results, it would be interesting to differentiate empiric and targeted treatment, and clarify time from microbiology sample to empiric treatment and time to targeted therapy.

Response: Thank you for our comment. We agree with the reviewer; however, we did not collect information on empiric therapy. Time from first CRE culture to starting targeted therapy is presented in table 1.

3. In my opinion as not English native, additional work is needed to improve quality of writing

Response: The manuscript was reviewed by nature editing service and all changes were highlighted.

Kevin Escandón, MD MSc (Editor):

1. 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.

Response: The manuscript was reviewed by nature editing service and all changes were highlighted.
2. Please include the email addresses for all authors on the title page. The corresponding author should still be indicated.

Response: Email addresses for all authors were added.

3. 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.

Response: Thank you. Title was changed to “Efficacy of Ceftazidime-Avibactam in the Treatment of Infections due to Carbapenem-Resistant Enterobacteriaceae”

Background

4. 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:

Response: Thank you for your comments. Please also response to reviewer 1- First and second paragraph of background were rewritten. All references were included as appropriate.

5. 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:
https://www.ncbi.nlm.nih.gov/pubmed/28950924 and

Response: Agree with the editor. We adjusted the manuscript accordingly (lines 98-100)

6. 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.
Response: Thank you. EMA reference was removed and the paragraph was rewritten accordingly (lines 101-110). All above requested references were added.

Response: inhibitors was replaced with inhibitor.

Response: This sentence was removed. First and second paragraph were rewritten.

9. Line 59-60: this sentence is not adequately written.
Response: This sentence was removed.

10. 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.
Response: Thank you. Agree, changes were done.

11. Line 62: replace "Bacilli" with "bacilli" and don't use italics. This is not a genus, species or family to use that style.
Response: Thank you. Agree, changes were done.

12. 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.
Response: “pneumonia” was changed to “pneumoniae” and “KPCs” was changed to “KPC”

Response: Thank you. We included data from this review in background briefly and discussed again in the discussion (lines 111-113 and 235-236).

Methods

14. 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?
Response: Please see response to reviewer #1 comment# 9. Several parts were rewritten/added to methods section to clarify inclusion/exclusion of patients (lines 118-126).

15. Line 81: rephrase for clarity: "We compared patients with CRE infections who received CAZ- AVI with those who received other agents."
Response: Thank you. We rephrased the sentence in the manuscript (lines 123-126)

16. Line 87: replace "of" with "with".
Response: Thank you. Revised. (line 132)

17. Line 94: Abbreviation CRE already in use.
Response: Thank you. Revised.

18. Line 99: You should write beta-lactamase genes as follows: bla (in italics), class in subscript (no italics), no spaces in between.
Response: Thank you. Revised.

19. Line 105: change "T-test" to "Student t test" (t italicized)
Response: Thank you. Revised.

20. Line 105: merge the text; there is unnecessary space on this page.
Response: Thank you. Revised.

21. 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".
Response: Thank you. We revised the manuscript. Use of P value now is consistent throughout the manuscript.

Results

22. Line 110: change "by" to "with".
Response: Revised. Thanks.

23. Line 110: why did you exclude children? You should include them to increase the sample a bit; otherwise, state adults in your inclusion criteria.
Response: Thank you. Pediatric infectious diseases are under different service in our hospital. Also, there was no molecular testing done on pediatric patients. We included adult patients only. We clarified this point in the manuscript. (line 120)

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.
Response: Thank you. We screened CRE cultures between (Jan 2017-August 2018). CAZ-AVI became available and the standard for treatment of CRE infections in December 2017. Exposed group (Dec 2017-Aug 2018). Non-exposed group (Jan 2017-November 2018). we corrected this in methods (lines 123-126)

25. 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.
Response: Thank you. We agree with you that we mistakenly included “matching”. We replaced “matching” with “comparative group”.

26. Line 118: replace ",(n=8, 80%)" with "(8/10, 80%)".
Response: Thank you. Revised.

27. Line 120: replace ",(n=19, 68%)" with "(19/28, 68%)".
Response: Thank you. Revised.

28. Line 125: Use the abbreviation already stated in Line 58 or delete it (HAP), be consistent.
Response: Thank you. To be consistent we used the term “HAP” only in the manuscript and removed “VAP”

29. Line 126: merge the text; there is unnecessary space on this page.
Response: Thank you. Revised.

30. 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.
Response: Thank you. Manuscript revised accordingly.

31. Line 129: the First letter of antibiotic names are not capitalized except for starting a sentence or in the case of brand names. For example, correct "Colistin" throughout the manuscript.
Response: Thank you. Manuscript revised accordingly.

32. Line 130: Do not use brand names. Replace "Bactrim" with "trimethoprim/sulfamethoxazole".
Response: Thank you. Manuscript revised accordingly.

33. Line 129-131: Instead of "21 (75%)" in the text, you should write "(21, 75%)". Apply this change to all the following cases. This is a matter of style, common scientific language.
Response: Thank you. Manuscript revised accordingly.

34. Lines 133-138: Present the most frequent/relevant findings in the text; if necessary, create a Table for mentioning all.
Response: we created a table and included all combinations. supplementary (table 5)

35. Lines 140: I want to be sure that you used the appropriate tests for the comparison of categorical variables between the 2 groups. This is important for getting the right P values. Please tell me the variables for which you used chi-square and Fisher exact test. Do not include this info in the manuscript.
Response: chi-square and Fisher exact test was used to compare the following categorical variables (Gender, Diabetes mellitus, Hypertension, Cardiovascular disease, Renal disease, Malignancy, Transplant, HIV, CRE bacteremia, CLABSI, HAP/ VAP, eUTI, cIAI, SSTI, Klebsiella pneumoniae, E. coli, Clinical remission, Clinical cure without relapse or death within 30 days, 30 days all-cause mortality, Attributable mortality to CRE, 30 days relapse of the same isolate
Discussion

36. 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.
   Response: Thank you. We have re-analyze the data and included only patients with OXA-48 in both group (supplementary tables 3 and 4) we clarified this point in the results (lines 179-180 and 192-193)

37. 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.
   Response: Agree. Discussion was rewritten as recommended (lines 200-203)

38. Line 147: merge the text; there is unnecessary space on this page.
   Response: Thank you. Revised.

   Response: Thank you. Revised.

40. 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).
   Response: Thank you. We added supplementary tables S3 and S4 to include all requested data.

   Response: Done. The manuscript revised accordingly (lines 235-239)

42. Line 155: "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.
Response: Agree. This statement was removed

43. Lines 157-161: 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.
Response: Methods were adjusted to clarify why we used CAZ-AVI vs other combinations (see response to reviewer# 1 comment #9). Discussion was rewritten to highlight the limitation of sample size (lines 246-248)

44. Line 164: Avoid starting a sentence with numbers; otherwise, spell them out.
Response: Revised.

45. Lines 164-166: This does not read well, get the assistance of an English writer.
Response: Done.

46. Line 166: 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/A VI studies in Saudi Arabia.
Response: Discussion was revised accordingly.

47. Line 168: merge the text; there is unnecessary space on this page.
Response: Done.

48. Again, English is not good when describing your limitations.
Response: Done.

Conclusions

49. Lines 170-173: you did not discuss your results in terms of the type of infection, so do not conclude about something you did not discuss.
Response: Agree. We revised conclusions (lines 250-255)
50. List of Abbreviations: do not use capital letters except for the first letter of the first word when writing out the abbreviations.
Response: Thank you. Manuscript revised accordingly.

51. Line 182: merge the text; there is unnecessary space on this page. Change "Declaration" to "Declarations".
Response: Thank you. Manuscript revised accordingly.

52. Availability of data: verb form "are" is missing.
Response: Thank you. Manuscript revised accordingly.

53. Competing interests: Some authors work at Pfizer. Besides, this company provided funding and language assistance. Declare the respective conflicts of interest.
Response: Thank you. Manuscript revised accordingly.

54. Authors' contributions: avoid wordiness. Summarize these contributions in a paragraph with a few sentences. Put common contributions after contributors.
Response: Thank you. Manuscript revised accordingly.

55. References: check the journal citation style of our journal. I suggest using an appropriate reference manager to simplify the task.
Response: We updated references- add new references and deleted some reference as per response above. We used end note for referencing as per the journal style.

56. 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.
Response: Thank you. All points were addressed.

57. Table 2
- Replace "N" with "n", use italics.
- Add "(%)" to the first group column.
- Reformat the layout using portrait orientation.
Response: Thank you. All points were addressed.