Author's response to reviews

**Title:** Ertapenem versus piperacillin/tazobactam for the treatment of complicated infections: a meta-analysis of randomized controlled trials

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**Author's response to reviews:** see over
Dear editors:
Thank you for arranging a timely review for our manuscript. We have carefully evaluated the reviewers’ critical comments and thoughtful suggestions, responded to these suggestions point-by-point, and revised the manuscript accordingly. With regard to the reviewers’ comments and suggestions, we wish to reply as following enclosure.

Yours sincerely,

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To the main concern about the paper of Reviewer #2

**Major Compulsory Revisions**

1. *Ideally, the contents of the tables should have been included in the meta-analysis figures and not in separate tables.*

   Thanks for the reviewer’s suggestions and we have adjusted the contents of the meta-analysis figures and tables. Currently, the contents of tables of the first submitted manuscript have been included in the meta-analysis figures of the revised manuscript.

2. *Page 8: Please check that the word “thrombocytosis” is correct as “thrombocytopenia” is probably what is meant.*

   Thanks for the carefulness of the reviewer. While, we think “thrombocytosis” is correct. About this question we will explain as following. In our analysis, the trial performed by Roy *et al* [1] and Graham *et al* [2] reported the incidence of thrombocytosis during ertapenem and piperacillin/tazobactam therapy. Roy reported the incidence of thrombocytosis during parenteral therapy 10.0% of patients in the ertapenem group and 11.2% of patients in the piperacillin/tazobactam group, and Graham reported 3.2% and 1.7% respectively. The pooled subgroup analysis of three clinical trials also reported thrombocytosis was one of the common drug-related laboratory adverse (6% in the ertapenem group, 10% in the piperacillin-tazobactam group) [3]. Only the trial performed by Solomkin *et al* [4] in our study reported one patients in the ertapenem group discontinued therapy because of thrombocytopenia. So we think the word “thrombocytosis” in Page 8 is correct.

   **Reference:**
   
   
   
   

3. *The last sentence of the conclusion in the abstract section is not a conclusion of what is presented. This sentence must be deleted as this is not concordant with IDSA guidelines.*
Thanks for the reviewer’s comment and we have realized this problem. We have deleted the last sentence of the conclusion in the abstract section and revised our conclusion.

4. The second sentence in the conclusion section (“The present evidence”) must be modified to “The present evidence suggests that the clinical use of ertapenem is associated with decreased emergence of antimicrobial resistance and lower costs.”

Thanks for the revision of the reviewer. We have modified the second sentence in the conclusion section of the first submitted manuscript (“The present evidence”) to “The present evidence suggests that the clinical use of ertapenem is associated with decreased emergence of antimicrobial resistance and lower costs.”

5. The manuscript needs extensive linguistic/typographic editing. I cite some of the modifications needed:

   page 2, line 1: “Ertapenem” instead of “ertapenem”
   page 2, line 3 “and” instead of “or”
   page 2, line 6 “good” instead of “well”

   Please leave one space after the dot after the second sentence in the results section of the abstract.

   Page 3, line 5: Please delete the word “casual”,
   Page 3, lines 6-7: Please change font size,
   Page 3, line 8: please delete “et al”,
   Page 3, last two lines of the second paragraph: Please change font size,
   Page 3, third paragraph: please change font size in lines 3, 4, 7, 8, 9,
   Page 4, last line of the fourth paragraph: Please change “contact” to “contacted”,
   page 5, third paragraph: Please replace “infection” to “infection”,
   Page 5 fourth paragraph: please leave a space before the word assessed,
   page 6: the sentence “Except …6 hours”: has to be modified,
   page 8, sixth paragraph: Please modify “effect” to “effects” and “was” to “were”

Thanks for the revision of the reviewer. We are so sorry for making so many grammar and spelling errors. We have revised our manuscript by native English speaker.

6. Please delete in the first paragraph of the discussion: “although the success…. (Table 2, Figure 2)”.

   We have realized this problem and deleted the sentence “although the success…. (Table 2, Figure 2).

7. While the approach of the authors to review together different types of infection (APIs, cSSSIs and cAIIs) is to be respected, this should not be based on a methodological principle to increase the statistical power. In addition the syntax (“meta-analysis…did not conduct an additional analysis”) needs improvement.
Please delete the last line of the third paragraph, page 9: “This additional analysis...power.” Please also delete the second sentence: “But...tazobactam” Please add after the “recommended antimicrobial regimens” a parenthesis: (piperacillin/tazobactam, ceftriaxone plus metronidazole and ticarcillin/clavulanic acid).

Please modify the sentence “So...meta-analysis” to “The focus of our meta-analysis was to compare the effectiveness and tolerance of ertapenem with piperacillin/tazobactam, a well-established therapeutic agent, in patients with complicated infections”. Then please move the third paragraph after this modified sentence.

Thanks for the reviewer’s suggestions. We have known that reviewing together different types of infections (APIs, cSSSIs and cIAIs) should not be based on a methodological principle to increase the statistical power. We have revised the section of our manuscript according to the reviewer’s suggestions.

8. Page 9, line 4 in the third paragraph: Please delete “et al “(the authors propably mean etc.)

Thanks for the carefulness of the reviewer. We have deleted “et al” in line 4, page 9 of the first submitted manuscript.

9. Page 9, first line of the fourth paragraph: Please delete ”is”

Thanks for the carefulness of the reviewer. We have deleted “is” in first line of the fourth paragraph, page 9 of the first submitted manuscript.

10. Page 9, third line of the fourth paragraph: Please delete “causal”

Thanks for the carefulness of the reviewer. We have deleted “causal” in third line of the fourth paragraph, page 9 of the first submitted manuscript.

11. Page 9: change the font size of staphylococcus in the third paragraph

Thanks for the carefulness of the reviewer. We have changed the font size of “staphylococcus” in the third paragraph, page 9 of the first submitted manuscript.

12. The last sentence of the conclusion needs probably modification to “However, there is rather limited evidence for the effectiveness of ertapenem compared to piperacillin/tazobactam, in patients with severe complicated infections caused by one or more pathogens.”

Thanks for the revision of the reviewer. We have modified the last sentence of the conclusion to “However, there is rather limited evidence for the effectiveness of ertapenem compared to piperacillin/tazobactam, in patients with severe complicated infections caused by one or more pathogens.”

13. Page 9: Please specify the study with the reference following directly the word “study”

Thanks for the suggestion of the reviewer. We have added the reference following directly the word “study” in Page 9.
14. Please modify the sentence “Notably….(Figure 2,3).” To “Notably, in our meta-analysis ertapenem had a comparable effectiveness (Figure 2, 3), to piperacillin/tazobactam an agent possessing antienterococcal and good antipseudomonal activity”.

Thanks for the revision of the reviewer. We have modified the sentence “Notably…. (Figure 2, 3).” to “Notably, in our meta-analysis ertapenem had a comparable effectiveness (Figure 2, 3), to piperacillin/tazobactam an agent possessing antienterococcal and good antipseudomonal activity”, in page 9.
To the main concern about the paper of Reviewer #1

Major comments:

1. **Data sources:** the authors should better detail the methods for the papers search. The data reported in this section are generic. They should also report if the papers contained in the references section of the papers found in the databases were also considered for the meta-analysis.

   Thanks for the reviewer’s comment. In fact, we did hand search of all reference lists from the relevant articles and reviews for additional eligible studies. We have described this research strategy in our first submitted manuscript (“References from relevant articles, including review papers, were also reviewed.”). Furthermore, we also consulted experts in the field.

   In a word, we did an extensive paper search for our meta-analysis. We are so sorry that we did not describe our search strategy well, and we have revised the section in our manuscript.

2. **The outcomes considered seem to be surrogates.** The mortality is a “hard” end-point. But, as reported by the authors, three studied have excluded severe infections and this represent a drawback of the meta-analysis. Thus, no conclusions on the efficacy of Ertapenem can be drawn.

   Thanks for the reviewer’s comment. We also know mortality is a “hard” end-point. So we added mortality meta-analysis in our manuscript (Fig1C in our manuscript). The result indicated that there was no difference between ertapenem and piperacillin/tazobactam group, getting similar findings with meta-analysis of the other outcomes in our study.

   As the reviewer said, one limitation of our meta-analysis and the three included RCTs was the inability to assess the effect of ertapenem on severe infection. But we know, a high APACHE II score is predictive of a poor outcome in the treatment of intra-abdominal infections [1]. Therefore, in clinical controlled trials, patients should be stratified prior to randomization on the basis of disease severity using APACHE II scores (high scores vs. low scores). But it is very difficult to accrue sufficient numbers of patients with APACHE II scores >30 to provide a meaningful comparison of response rate differences among severely ill patients. Furthermore, intra-abdominal infection with APACHE II > 30 is often a rapidly or terminal illness which is usually excluded by clinical trials. So it is reasonable for excluding severe infections with APACHE II scores >30 in included trials of our meta-analysis. All of the three included clinical trials have declared that there is rather limited evidence for the effectiveness of ertapenem compared to piperacillin/tazobactam, in patients with severe complicated infections caused by one or more pathogens. Our conclusion is based on the present evidence. We also declared that our conclusion should be cautiously interpreted on severe infections,
and is limited to the patients with mild to moderate complicated infections APACHE II scores <30).

Reference:


Minor commence

1. The authors should better specify what laboratory adverse effects were considered (I presume the liver enzymes as reported in the discussion section).

Thanks for the reviewer’s suggestion. We have better specify what laboratory adverse effects were considered in page 8, “drug related adverse effects ”section of our revised manuscript.