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### ARTICLE DETAILS

<table>
<thead>
<tr>
<th>TITLE (PROVISIONAL)</th>
<th>Efficacy and safety of ceftazidime-avibactam versus polymyxins in the treatment of carbapenem-resistant Enterobacteriaceae infection: a systematic review and meta-analysis</th>
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<td>AUTHORS</td>
<td>Yang, Ping; Li, yinyan; Wang, Xiaojuan; Chen, Na; Lu, Xiaoyang</td>
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### VERSION 1 – REVIEW

| REVIEWER               | Guimaraes, Thais  
|------------------------| Universidade de Sao Paulo Faculdade de Medicina Hospital das Clinicas, Infectious diseases Department |
| REVIEW RETURNED        | 23-Jan-2023                                           |
| GENERAL COMMENTS       | It is an interesting meta-analysis on a very important topic that is the comparison of CAZ-AVI with polymyxins for the treatment of carbapenem-resistant bacteria. Although the topic is very pertinent, I have some considerations to make: 1) in the abstract in line1 is described "last line of defense in China" , I think the phrase would look better as the last therapeutic option and it is not only in China, but worldwide 2) In the introduction, line 17 of page 3 states that for CRPA there is also no other treatment. What about ceftazidime-tazobactam ? CAZ-AVI is a medicine for the treatment of CRE, as avibactam can inhibit type A carbapenemases common in Enterobateriales. This carbapenemase is not common in Pseudomonas especies and aviabactam in this stage would be inhibiting AmpC-type enzymes 3) line 1 page 5 lack EMA reference 4) line 21 page 4 of the methods as well as in the entire article refer to "Enteroterobacterales" and not "Enterobacteriaceae" 5) As I said in item 2, CAZ-AVI is not a drug to treat carbapenem-resistant Pseudomonas, and only one study included in this meta-analysis was conducted with Pseudomonas (CRPA). I strongly suggest removing this study and focusing the meta-analysis on CRE treatment 6) Again line 14 of page 15 it's not just in China 7) line 1 of page 16, add FDA reference 8) reference 17 is incomplete |

| REVIEWER               | Gu, Zhi-Chun  
|------------------------| Renji Hospital, School of Medicine, Shanghai Jiaotong University, Department of Pharmacy |
| REVIEW RETURNED        | 27-Jan-2023                                           |
| GENERAL COMMENTS       | The manuscript undertakes a meta-analysis to explore the efficacy and safety profile to compare CAZ-AVI with polymyxins in the treatment of CRO. It showed that CAZ-AVI treatment holds a dominant position on efficacy and safety relative to polymyxins in |
carbapenem-resistant Gram-negative bacterial infections. The topic is novel and of importance for patients with infection. However, several comments and questions should be addressed firstly.

1. Introduction section: The authors indicated that there was still no better treatment to deal with CRO except ceftazidime-avibactam (CAZ-AVI) or polymyxins based regimen in China. It is suggested that the authors should declare why other drugs are not mentioned, for example, tigecycline?

2. Study selection section: “Eligible studies included all available published studies that compared CAZ-AVI with polymyxins for the treatment of CRO infections in adult patients (> 18 years), CAZ-AVI or polymyxins-based combined administration scheme were allowed.” The types of bacteria and diseases were not limited in the inclusion and exclusion criteria. Does that affect the conclusion? This should be added in the discussion.

3. Table 1. Characteristics of the included studies section: In baseline characteristics table, drugs of combination regimens could be mentioned briefly.

4. 3.3.1 Mortality section, page13, line1: The format of “I2” should be noted.

5. 3.3.4. Nephrotoxicity section, page 14, line 1: The format of “95% CI 0.29–0.69” should be unified with others.

6. Discussion section, page 14, line7: “Our meta-analysis found that polymyxins-containing regimes was associated with increased risk of mortality, clinical failure and nephrotoxicity.” This statement is ambiguous. Polymyxins, as a therapeutic drug, shouldn’t increase the mortality of patients. Maybe the author wants to say it’s not as good as CAZ-AVI, but it’s better to say it another way.

7. Discussion section, page 14, line19: “Both combined and single drug regimens were included in our meta-analysis.” Is there any difference between polymyxins combination therapy and single drug regimen? Does it affect the results of this study? This should be further discussed.

8. Discussion section, page 15, line14: “Until now, CAZ-AVI and polymyxins containing regimes have been highly recommended as the frontline agents in the treatment of multidrug-resistant Gram-negative bacterial infections in China.” The data collected in this study was international. It is suggested that don’t just say China, say other countries, too.

9. Discussion section, page 16, line15: “This review had some limitations that should be acknowledged. First, 14 studies only recruited 1407 patients, the sample size was small. Second, most studies did not provide antimicrobial resistance or enzyme production information, changes in the pathogens resistance of antibiotic exposure were not available in all included studies.” The failure to perform subgroup analyses of diseases and strains is also a limitation, which is recommended to be supplemented.

10. Discussion section: The development of other novel drugs that can be applied to CRO infection could be briefly mentioned.
instead of just CR-Enterobacteriales. The methods are sound and the PRISMA checklist is included.

My only major comment relates to the inclusion of conference abstracts in the analyses. As these are not subject to the same rigor of review as publications and there is a lack of complete data available to evaluate methodologies and outcomes (as stated by the authors in the manuscript, methodology was not included for one of these abstracts) the authors may consider removing these from all analyses. It is also unclear if these abstracts were identified via the stated search terms, though with both being presented at IDWeek (abstracts are published in an OFID supplement) I imagine this is the case. The other issue that this brings up is that only one conference is being searched for abstracts while others are not, leading to an incomplete search of conference abstracts. Overall, I believe the paper would be stronger without inclusion of these data.

The authors can also consider highlighting the limitations of some of the included studies and their effect on generalizability. For example, only one study evaluated CR-PSA, and therefore therefore it may be more appropriate to identify this as a limitation and caution generalization of these outcomes to all CR-PSA. Similarly, only one study of polymyxin monotherapy was included.

It also may be helpful to identify the polymyxin used (i.e. colistin or polymyxin b) and the dosing reported for these agents, as available. Given the significant differences in PK between these agents, polymyxin b is currently recommended as the primary agent for treatment of invasive infections except UTIs (International Consensus Guidelines for the Optimal Use of the Polymyxins: Endorsed by the American College of Clinical Pharmacy (ACCP), European Society of Clinical Microbiology and Infectious Diseases (ESCMID), Infectious Diseases Society of America (IDSA), International Society for Anti-infective Pharmacology (ISAP), Society of Critical Care Medicine (SCCM), and Society of Infectious Diseases Pharmacists (SIDP)). If possible it may be interesting to compare if differences in effect are seen between comparators, however may not be possible/helpful if the number of studies using one polymyxin or the other are low (it seems most used colistin-based regimens).

Minor: One of the studies are listed as the author first name instead of the last name (ref 6 should be Shields, not Ryan). Please double check references for accuracy.

Page 11 Lines 7-8: The authors should clarify that combination therapy was ALLOWED in these studies, but not required. Most patients appear to have received CAZ-AVI monotherapy in many of these studies. It would be helpful to add the number of patients in each group who received combination therapy to table 1.

Discussion lines 13-14 "In our meta-analysis, a CAZ-AVI-based..." I'm not sure what this sentence means, it reads as if some patients in the CAZ-AVI group were not treated with CAZ-AVI, however I think the authors mean that more patients in each study were treated with CAZ-AVI than polymyxins except the two citations?
Thanks for Dr. Thais Guimaraes’s valuable suggestion, we had revised our manuscript according to your kindly comments. Also, we excluded three studies according to the comments of reviewers 3 and yours, and re-conducted the meta-analysis. We responses to the comments are as follows.

1) In the abstract in line 1 is described "last line of defense in China", I think the phrase would look better as the last therapeutic option and it is not only in China, but worldwide

Thanks for reviewer’s kind suggestion, we had revised ‘last line of defense in China’ to ‘last therapeutic option worldwide’ on page 1, line 22-23.

2) In the introduction, line 17 of page 3 states that for CRPA there is also no other treatment. What about ceftalozane-tazobactam? CAZ-AVI is a medicine for the treatment of CRE, as avibactam can inhibit type A carbapenemases common in Enterobacteriales. This carbapenemase is not common in Pseudomonas species and avibactam in this stage would be inhibiting AmpC-type enzymes

Thanks for reviewer’s kind suggestion. According to your comment, we had excluded the study to compare CAZ-AVI with polymyxins for CRPA. So, the focus of our article is to compare the efficacy and safety of CAZ-AVI and polymyxin in the treatment of CRE infection. Also, we introduced other drugs and limitations to treat CRE infections besides CAZ-AVI or polymyxins in introduction section, on page 3, line 20-page 4, line 6.

3) line 1 page 5 lack EMA reference
Thanks for reviewer’s kind suggestion, the reference was added as reference 10.

4) line 21 page 4 of the methods as well as in the entire article refer to "Enteroterobacterales" and not "Enterobacteriaceae"

Thanks for reviewer’s kind suggestion. However, after our discussion, we thought that ‘Enterobacteriaceae’ had a wider bacteria spectrum, and what we want to compare is the effect of two drugs on ‘Enterobacteriaceae’ but not ‘Enteroterobacterales’. Moreover, in our study, 4 studies compared the effect and safety of two drugs on CRKP. After reviewing related information, we believed that CRKP belongs to ‘Enterobacteriaceae’ but not ‘Enteroterobacterales’. So, after careful consideration, we still thought that ‘Enterobacteriaceae’ was more accurate. Once again, we thanked for the reviewers of their comments and hoped that we can be approved.

5) As I said in item 2, CAZ-AVI is not a drug to treat carbapenem-resistant Pseudomonas, and only one study included in this meta-analysis was conducted with Pseudomonas (CRPA). I strongly suggest removing this study and focusing the meta-analysis on CRE treatment

Thanks for reviewer’s kind suggestion, we had removed this study about CRPA. In addition, the other two conference article were also removed according reviewer 3. Also, the meta-analysis was reconducted. We hoped that our latest results can more reflect the real situation.

6) Again line 14 of page 15 it’s not just in China
Thanks for reviewer’s valuable suggestion. We think the reviewers’ opinions are very professional. But what we wanted to express here is that although there are many new drugs that can be used to treat CRE infections, there are still very limited drugs available in China to treat CRE infections. The only drugs available in China are polymyxins or ceftazidime avibactam. So, we revised this sentence as “Until now, current antimicrobial therapy options for CRE infections are very limited, including polymyxins and novel β-compound preparations of lactamase inhibitors, such as ceftazidime/avibactam, amtreonam/avibactam, meropenem/farobatam and imipenem-cilastatin/rilibatam. However, given the availability of such drugs, CAZ-AVI and polymyxins containing regimes have been highly recommended as the frontline agents in the treatment of multidrug-resistant Gram-negative bacterial infections in China.” on page 11, line 17-23.

7) line 1 of page 16, add FDA reference
Thanks for reviewer’s kind suggestion, the reference was added as reference 32.

8) reference 17 is incomplete
We are sorry for our mistake, reference 17 was updated. In addition, the order of the discussion section had been adjusted, reference 17 was displayed as reference 23 now. In addition, all reference formats have been carefully checked and updated. Thanks for reviewer’s careful suggestion again.

Reviewer: 2

Thanks for Dr. Zhi-Chun Gu’s valuable suggestion, we had revised our manuscript according to your kindly comments. Also, we excluded three studies according to the comments of reviewers 1 and 3 and re-conducted the meta-analysis. We responses to the comments as follows.

1. Introduction section: The authors indicated that there was still no better treatment to deal with CRO except ceftazidime-avibactam (CAZ-AVI) or polymyxins based regimen in China. It is suggested that the authors should declare why other drugs are not mentioned, for example, tigecycline?

Thanks for reviewer’s kind and valuable suggestion, we are sorry about our negligence about tigecycline. We had revised this part on page 3, line 21-page 4, line 4. Also, we had added new antibiotics for the treatment of CRO, on page 4, line 5-6. We hoped these changes can have a better express.

2. Study selection section: “Eligible studies included all available published studies that compared CAZ-AVI with polymyxins for the treatment of CRO infections in adult patients (> 18 years), CAZ-AVI or polymyxins-based combined administration scheme were allowed.” The types of bacteria and diseases were not limited in the inclusion and exclusion criteria. Does that affect the conclusion? This should be added in the discussion.

Thanks for reviewer’s kind and valuable suggestion. We are sorry about our carelessness, and two reasons can be used to explain this phenomenon. One reason was the type and proportion of diseases was not concretely described; the other reason was that the little heterogeneity was found even if we combine all the study. Also, this was referred in discussion section, page 13, line 23-page 14, line 2.

3. Table 1. Characteristics of the included studies section: In baseline characteristics table, drugs of combination regimens could be mentioned briefly.

Thanks for reviewer’s kind and valuable suggestion. We added “drugs of combination regimens” section in Table S1, also the combination regimens were depicted in the notes to TableS1 (Supplementary materials, page 2-4).

4. 3.3.1 Mortality section, page13, line1: The format of “I2” should be noted.

Thanks for reviewer’s kind and valuable suggestion. The format of “I2” was revised as “I2” in 3.3.1 mortality section, on page 10, line 10.

5. 3.3.4. Nephrotoxicity section, page 14, line 1: The format of “95% CI 0.29–0.69” should be unified with others.

Thanks for reviewer’s kind and valuable suggestion. The format of “95% CI 0.29–0.69” was revised as “95% CI of 0.23 to 0.77” in 3.3.4. Nephrotoxicity section, on page 11 line 3.

6. Discussion section, page 14, line7: “Our meta-analysis found that polymyxins-containing regimes was associated with increased risk of mortality, clinical failure and nephrotoxicity.” This statement is ambiguous. Polymyxins, as a therapeutic drug, shouldn’t increase the mortality of patients. Maybe the author wants to say it's not as good as CAZ-AVI, but it's better to say it another way.

Thanks for reviewer’s kind and valuable suggestion. We revised this sentence as ‘Polymyxins-containing regimes had an increased risk of mortality, clinical failure and nephrotoxicity compared with
7. Discussion section, page 14, line 19: “Both combined and single drug regimens were included in our meta-analysis.” Is there any difference between polymyxins combination therapy and single drug regimen? Does it affect the results of this study? This should be further discussed.

Thanks for reviewer’s kind and valuable suggestion. The reasons can be explained as follows: 1) there were both combined and single drug regimens in original studies, as described in notes to table S1 (Supplementary materials, page 2-4); 2) previous meta-analysis demonstrated a similar effect and safety of monotherapy compared with combination therapy, as referred in discussion section, on page 12, line 22-24; 3) the little heterogeneity was found even if we combine both combined and single drug regimens. So, we have reason to believe that this treatment will not have a great impact on the results.

8. Discussion section, page 15, line 14: “Until now, CAZ-AVI and polymyxins containing regimes have been highly recommended as the frontline agents in the treatment of multidrug-resistant Gram-negative bacterial infections in China.” The data collected in this study was international. It is suggested that don’t just say China, say other countries, too.

Thanks for reviewer’s valuable suggestion. We think the reviewers’ opinions are very useful. But what we want to express here is that although there are many new drugs that can be used to treat CRE infection, there are still very limited drugs available in China to treat CRE infection. The only drugs available in China still are polymyxins or ceftazidime avibactam. As we revised to “Until now, current antimicrobial therapy options for CRE infections are very limited, including polymyxins and novel β-compound preparations of lactamase inhibitors, such as ceftazidime/avibactam, amtreonam/avibactam, meropenem/farobatam and imipenem-cilastatin/rilibatam. However, given the availability of such drugs, CAZ-AVI and polymyxins containing regimes have been highly recommended as the frontline agents in the treatment of multidrug-resistant Gram-negative bacterial infections in China.” on page 11, line 17-23.

9. Discussion section, page 16, line 15: “This review had some limitations that should be acknowledged. First, 14 studies only recruited 1407 patients, the sample size was small. Second, most studies did not provide antimicrobial resistance or enzyme production information, changes in the pathogens resistance of antibiotic exposure were not available in all included studies.” The failure to perform subgroup analyses of diseases and strains is also a limitation, which is recommended to be supplemented.

Thanks for reviewer’s kind and valuable suggestion, we are sorry about our carelessness. The failure to perform subgroup analyses of diseases and strains can be explained as follows, one reason was the type and proportion of diseases was not concretely described in original research; the other reason was that the little heterogeneity was found even if we combine all the study. Also, this was referred in discussion-limitation section, page 13, line 23-page 14, line 2.

10. Discussion section: The development of other novel drugs that can be applied to CRO infection could be briefly mentioned.

Thanks for reviewer’s kind and valuable suggestion. We added novel drugs that can be applied to CRO infection, such as amtreonam/avibactam, meropenem/farobatam, imipenem-cilastatin/rilibatam, on page 11, line 19-20.

Reviewer: 3

Thanks for Dr. J. Nicholas O'Donnell’s valuable suggestion, we had revised our manuscript according to your kindly comments. Also, we excluded three studies according to the comments of reviewers 1 and yours, and re-conducted the meta-analysis. We responses to the comments are as follows.
1. My only major comment relates to the inclusion of conference abstracts in the analyses. As these are not subject to the same rigor of review as publications and there is a lack of complete data available to evaluate methodologies and outcomes (as stated by the authors in the manuscript, methodology was not included for one of these abstracts) the authors may consider removing these from all analyses. It is also unclear if these abstracts were identified via the stated search terms, though with both being presented at IDWeek (abstracts are published in an OFID supplement) I imagine this is the case. The other issue that this brings up is that only one conference is being searched for abstracts while others are not, leading to an incomplete search of conference abstracts. Overall, I believe the paper would be stronger without inclusion of these data.

Thanks for reviewer’s kind and valuable suggestion. We are sorry about our inclusion criteria are not strict enough. We had excluded these two conference articles, also, a study about CRPA was also removed (as suggested by reviewer 1) in the new meta-analysis. We believed the new meta-analysis is more representative of the real results.

2. The authors can also consider highlighting the limitations of some of the included studies and their effect on generalizability. For example, only one study evaluated CR-PSA, and therefore it may be more appropriate to identify this as a limitation and caution generalization of these outcomes to all CR-PSA. Similarly, only one study of polymyxin monotherapy was included.

Thanks for reviewer’s kind and valuable suggestion. The study evaluated CR-PSA was removed in the new meta-analysis. Although only one study of polymyxin monotherapy was included, there were both combined and single drug regimens in original studies, as described in notes to table S1 (Supplementary materials, page 2-4). So, this polymyxin monotherapy study was not excluded. In addition, previous meta-analysis demonstrated a similar effect and safety of monotherapy compared with combination therapy, as referred in discussion section, page 12, line 22-24.

3. It also may be helpful to identify the polymyxin used (i.e. colistin or polymyxin b) and the dosing reported for these agents, as available. Given the significant differences in PK between these agents, polymyxin b is currently recommended as the primary agent for treatment of invasive infections except UTIs (International Consensus Guidelines for the Optimal Use of the Polymyxins: Endorsed by the American College of Clinical Pharmacy (ACCP), European Society of Clinical Microbiology and Infectious Diseases (ESCMID), Infectious Diseases Society of America (IDSA), International Society for Anti-infective Pharmacology (ISAP), Society of Critical Care Medicine (SCCM), and Society of Infectious Diseases Pharmacists (SIDP)). If possible it may be interesting to compare if differences in effect are seen between comparators, however may not be possible/helpful if the number of studies using one polymyxin or the other are low (it seems most used colistin-based regimens).

Thanks for reviewer’s kind and valuable suggestion. We acknowledged that the significant differences in PK between colistin and polymyxin b, among our study, six studies used colistin as the control group while four studies used polymyxin B as the control group, and another study included colistin and polymyxin b as the control group. Also, the dosage was not reported in detail. Therefore, further subgroup analysis was not performed for the two drugs as control group. This limitation was also replenished in discussion-limitation section, page 14, line 3- line 6.

4. Minor: One of the studies are listed as the author first name instead of the last name (ref 6 should be Shields, not Ryan). Please double check references for accuracy.

Thanks for reviewer’s kind suggestion and careful check. We have revised the reference format and checked all references.

5. Page 11 Lines 7-8: The authors should clarify that combination therapy was ALLOWED in these studies, but not required. Most patients appear to have received CAZ-AVI monotherapy in many of
these studies. It would be helpful to add the number of patients in each group who received combination therapy to table 1.

Thanks for reviewer’s kind and valuable suggestion. We emphasized “Based on our inclusion criteria, monotherapy or combination therapy were allowed”, on page 7, line 12-15. In addition, we described specific administration protocol of CAZ-AVI in each study in detail, and added the number of patients in each group who received combination therapy in notes to TableS1 (Supplementary materials, page 2-4).

6. Discussion lines 13-14 "In our meta-analysis, a CAZ-AVI-based." I’m not sure what this sentence means, it reads as if some patients in the CAZ-AVI group were not treated with CAZ-AVI, however I think the authors mean that more patients in each study were treated with CAZ-AVI than polymyxins except the two citations?

Thanks for reviewer’s kind and valuable suggestion. We originally intended to express that CAZ-AVI was used alone in two studies, and administrated as combination region in the rest study. However, we removed three studies according to reviewer 1 and 3 and reanalyzed the included studies. We revised this sentence to “Therefore, most of the included literatures were based on the combined administration of ceftazidime avibactam or polymyxin, and the combined administration plan includes other activity antibiotics.” on page 12, line 18-20. Also, the monotherapy or combination monotherapy was carefully depicted in notes to Table S1 (Supplementary materials, page 2-4). We hoped this revision would more clearly express our results.

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**GENERAL COMMENTS**

**REVIEWER** Guimaraes, Thais  
Universidade de Sao Paulo Faculdade de Medicina Hospital das Clinicas, Infectious diseases Department  
**REVIEW RETURNED** 24-Mar-2023

I reviewed the revised manuscript and I think that the authors made all modifications according to my comments. Also and mainly they excluded three studies according to the comments of reviewers 3 and mine, and re-conducted the meta-analysis with interesting results.

**REVIEWER** Gu, Zhi-Chun  
Renji Hospital, School of Medicine, Shanghai Jiaotong University, Department of Pharmacy  
**REVIEW RETURNED** 26-Mar-2023

All the comments have been addressed, now the current version can be considered for publication.

**REVIEWER** O'Donnell, J. Nicholas  
Albany College of Pharmacy  
**REVIEW RETURNED** 20-Mar-2023

The authors have addressed reviewers' comments adequately. Minor English language edits would be helpful in improving the clarity of the manuscript.

In the table, Shield's paper is still listed as "Ryan 2017".

Page 4, line 6- I think the authors are referring to meropenem/vaborbactam and imipenem/cilastatin/relebactam.
Reviewer: 3

Dr. J. Nicholas O'Donnell, Albany College of Pharmacy

Comments to the Author:

The authors have addressed reviewers' comments adequately. Minor English language edits would be helpful in improving the clarity of the manuscript.

In the table, Shield's paper is still listed as "Ryan 2017".
We are very sorry about our negligence, and have revised to ‘Shields 2017’ in table 1 and table S1

Page 4, line 6- I think the authors are referring to meropenem/vaborbactam and imipenem/cilastatin/relebactam.
Thanks for editor’s kind suggestion, and we have revised to ‘meropenem/vaborbactam and imipenem/cilastatin/relebactam’ on page 4, line 6. Also, corresponding modifications have also been made on page 11, line 20.