Author's response to reviews

Title: Daptomycin versus linezolid for treatment of vancomycin-resistant enterococcal bacteremia: systematic review and meta-analysis

Authors:

Yu-Chung Chuang (weischuang@gmail.com)
Jann-Tay Wang (14bcr@yahoo.com.tw)
Hsin-Yi Lin (linh@nccu.edu.tw)
Shan-Chwen Chang (changsc@ntu.edu.tw)

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Author's response to reviews: see over
Dear Editor,

Thank you very much for your kind attention to our paper entitled “Daptomycin versus linezolid for treatment of vancomycin-resistant enterococcal bacteremia: systematic review and meta-analysis” by YC Chuang et al. We also sincerely appreciate your kindly suggestion and consideration of publication in “BMC Infectious Diseases”. We have revised our manuscript according to the comments and suggestions of the reviewers.

What we have done are listed and explained in the following:

**Reviewer 1**

1. Table 1, there are some columns that lack then “%” of cases (last 4 lines)

*Response*

We added the missing “%” in the last 4 lines of table 1.

2. Also in Table 1, possible confounders were cited in the last column, however as it is not stated the numbers we do not know which group is the disadvantaged. It would be interesting to state this data.

*Response*

We added the numbers of the confounders in both groups in Table 1.

3. Discussion section: line 2. Suggest delete the word “previous” from 13
previous studies…

Response

We deleted the word “previous” as suggested. (P. 15 line 2)

4. They should include as limitation the fact that we do not know the diagnosis of bacteremic infection and associated therapies (such as removal of catheters)

Response

Thank you very much for the comments. We add limitations in the discussion section as follows “though all studies reported that there are at least one set of blood culture yielded VRE, however, important information such as the foci of the bacteremic infection and the associated therapy, such as catheter removal or not were not clearly stated” (P. 19 line 1 to line 3, underlined)

Reviewer 2

Major Compulsory Revisions:

1. Figure 2. Manuscript of Mave was published in 2009, not 2007. Also, a ORs authors have referred are actually different from what were written in the original manuscripts. (e.g. According to original paper of Mave et al, aOR is 1.71 [0.56-5.19], not 5.22). Similarly, Mckinnell reported aOR as 2.1 (0.99-4.70), not 4.45. Please check one more time carefully for referring original data.

Response

Thank you very for your comments. The referred paper of Mave et al. (2009) has been
In addition, we have rechecked the original reported aORs. In our article, we use the statistical package, REVIEWER MANAGER. In the package, if the point-estimate and the upper-bound of 95% C.I. are filled, then the lower-bound of 95% C.I. is also determined automatically. We filled the point-estimates and the upper-bound of 95% C.I. according to the data in McKinnell et al. (2011), but the lower-bound of 95% C.I., that are automatically determined in REVIEWER MANAGER, are different from those in McKinnell et al. (2011). The reason of this mismatch could be due to that these values of McKinnell et al. (2011) were rounded off to the first (or second) decimal places, or calculation methods used to estimate 95% C.I. were different among different statistical software. It would be better if the raw data of Mckinnell et al. (2011) could be obtained.

It is also noted that if we filled the point-estimates and the lower-bound of 95% C.I. only, and the upper-bound of 95% C.I. is determined automatically, the results of meta-analysis are similar.

Discretionary Revisions

2. It might be beneficial to mention more on “Confounding by Indication ”(PMID 24982037). Sicker patients were included in the daptomycin groups as compared to linezolid group in the recent studies on VRE bacteremia which authors have referred. It would be quite possible that some residual confoundings exist even after adjusting my multivariate regression in each study.

Response

We agreed that though these studies tried to adjust the confounders by using multivariate
logistic regressions, there are still residual confounding factors. The confounding by indications might result in difficulties in comparing the treatment efficacies in such critical patients in nonrandomized studies. We added the discussion on “confounding by indications” in the discussion section (P. 18 line 16 to P. 19 line 1, underlined)

**Reviewer 3**

This systematic literature review and meta-analysis by Chuang et al., compared the effectiveness of linezolid versus daptomycin at treating vancomycin-resistant enterococci using the outcomes of mortality and microbiologic cure. When they pooled the results of 13 underpowered studies, they found a significant benefit of linezolid over daptomycin in regards to mortality. The systematic literature review and meta-analysis were done according to the PRISMA guidelines and the subset analyses showed interesting distinctions between the different study groups. Overall this is a well done meta-analysis. Only a few changes should be made.

**Response**

We thank the reviewer’s comment. We revised the manuscript as the reviewer suggested.

**MAJOR CHANGES:**

1. Both the background and discussion sections state that confounder were not adjusted for in the meta-analysis by Whang et al., Do the authors mean that Wang did not use adjusted odds ratios when pooling the results? There is a difference. Please clarify.

**Response**

We thank the reviewer’s comment. We revised the manuscript as the reviewer suggested.
The Meta-analysis by Whang et al. didn’t use the adjusted odds ratio when pooling the results.

2. The manuscript needs a better description of why some studies were excluded. For example, how was one study classified as “unacceptable”? Was a cut-point using the SIGN50 criteria chosen a priori? Also, why were “epidemiologic” studies excluded?

Response

The study by Weinstock et al. was classified as unacceptable quality and excluded since that the study didn’t clearly define the outcome and the exposure, which might result in detection bias. (P. 10 line 5 to 8, underlined)

Cut-point using the SIGN50 criteria was chosen a priori. Study quality was assessed using SIGN50, and studies with unacceptable quality were excluded. (P. 8 line 1 to 2, underlined)

Epidemiology studies that didn’t report daptomycin and linezolid treatment outcomes were excluded. Studies that we included were clinical trials or observational studies of the treatment of patients with VRE bacteremia that reported daptomycin and linezolid treatment outcomes simultaneously. (P. 7 line 16 to 19, underlined)

3. The results section needs to be more informative. First, a statement should be made on the quality of the overall studies and measured by SIGN50. Second, there should be a statement on what the individual studies adjusted for (the authors could move lines 16-18 on page 17 of the discussion to the results section to accomplish this).
**Response**

Thanks for the suggestions. We re-write the first part of the result. It reads as

“According to the SIGN50 criteria, none of the 13 studies were classified as high quality. The study by Weinstock et al. was classified as unacceptable quality and excluded since that the study didn’t clearly define the outcome and the exposure, which might result in detection bias. All enrolled studies were classified as acceptable quality with some potential flaws in each study with an associated risk of bias.” (P. 10 line 4 to 9, underlined)

We also moved the line 16-18 on page 17 to the result section as suggested. (P. 11 line 3 to 6, underlined)

**MINOR CHANGES:**

1. The manuscript should be proofread, especially on page 11.

**Response**

We have asked an English native speaker to help proofread the manuscript especially on page 11.

2. Lines 8-9 of the abstract conclusion is too strong of a statement for the type of studies pooled (superior is a strong word). Please modify it to match the conclusions of the manuscript.

**Response**

We revised the abstract conclusion in order to match the conclusions of the manuscript. (P. 4 line 9 to 10, underlined)
3. The abstract and the background states that linezolid is approved for treatment of VRE but
doesn’t state if daptomycin is approved for VRE. Please clarify this.

Response

No, daptomycin is not approved for the treatment of VRE. (P. 3 line 5, and P. 5 line 11
to 12, underlined)

4. It is confusing that the x-axis changes from figures 5A/5B to figure 5C. Please either make
5C its own figure (figure 6) or modify the x-axis of figure 5C.

Response

In order to make the reader not to get confused about the x-axis, we make figure 5C to
figure 6.

5. I don’t understand page 14 lines 16-18. Your analysis with an adjusted OR
from Furuya did show a significant difference. Why do these lines say there was not a
significant difference on reanalysis? Please clarify.

Response

Sorry for the confusion. We have clarified these statements in the discussion section as
follow “It is noted that Furuya et al. reported the adjusted OR in their paper. However, Balli
et al. mis-classified Furuya et al. in the group of unadjusted OR. If this mis-classification is
corrected in the meta-analysis by Balli et al., then daptomycin group did not have higher
mortality when aORs were pooled in their paper. “ (P. 15 line 15 to 19, underlined). Our
analysis with an adjusted OR from Furuya et al. did show a significant difference.
We appreciate those comments and suggestions of the reviewers to improve the quality of our manuscripts. We also thank you very much for kind consideration for possible publication of our paper in “BMC Infectious Diseases”.

Sincerely yours,

Jann-Tay Wang, MD, PhD.

National Taiwan University Hospital, Taipei, Taiwan

E-mail: 14bcr@yahoo.com.tw; Tel: 886-2-23123456 ext 65054

Telfax: 886-2-2397-1412