Author's response to reviews

Title: Effectiveness of Tigecycline-based versus Colistin-based Therapy for Treatment of Pneumonia Caused by Multidrug-Resistant Acinetobacter baumannii in a Critical Setting: A Matched Cohort Analysis

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Version: 2
Date: 31 December 2013

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

Thank you very much for your kind attention to our paper entitled “Effectiveness of Tigecycline versus Colistin for Treatment of Pneumonia Caused by Multidrug-Resistant Acinetobacter baumannii in a Critical Setting: A Matched Cohort 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 editor and the reviewers. We have added a “Competing interests” section, and declared that “the authors declare that they have no competing interests”. What we have done are listed and explained in the following:

**Reviewer 1.**

**Major Compulsory Revisions**

The main objective of this manuscript was to report and compare the clinical outcome of patients with pneumonia due to carbapenem-resistant Acinetobacter spp. treated with tigecycline and colistin. This is an important issue as there are few options to treat these infections. However, the clarity of this manuscript has to improve to be acceptable.

**Response:**

We thank the reviewer for the comments. We will try our best to elucidate the points that may appear to be unclear to readers.
Methods:

1. For the etiological diagnosis of pneumonia, the authors considerate isolates from “blood, bronchoscopic bronchial brushing, lavage or sputum”. Although the reference standard for pneumonia has never been clearly established, it is standard to use quantitative cultures of respiratory specimens. Did the author use quantitative or qualitative cultures? Sputum is generally not recommended and this should be included as limitation or exclude these patients.

Response:

Thank you for the suggestions. Qualitative culture was used through the study (P. 7 line 17, underlined). We agreed that using sputum culture to diagnose the etiology of pneumonia is the limitation. However, there were no standard diagnostic criteria for VAP, even quantitative culture is a unstable method. [1] According to the reviewer’s suggestion, we described the limitation of sputum culture in the “Discussions” section. It now reads, “The majority of the patients were diagnosed using qualitative sputum culture, which might result in over-diagnosis of pneumonia. Hence, the difference of the effectiveness between tigecycline and colistin might be underestimated.” (P. 18 line 4 to 6, underlined)

2. The reference 22 is does not apply for the definition of nephrotoxicity

Response:

The definition of nephrotoxicity was not standardized between the studies.[2] We used the criteria which was modified from Garnacho-Montero et al. [3] We cited the original reference. (P. 9 line 18, underlined)

3. It is not usual to match in cohort studies. Why did the authors choose to do this instead
of including all patients and perform a multivariate analysis for the outcomes?

**Response:**

Propensity score matched study became more popular recently in medical studies. [4] Compared to performed multivariable analysis of original cohort including all patients, both methods should often lead to the same conclusions.[4] However, propensity score matched analysis provides quasi-experimental design, which compared the outcome between two similar groups. [5] (P. 10 line 10 to 11, underlined)

Results:

1. The main result (outcome mortality) is very confusing: Table 4 shows statistically difference among the 2 groups and apparently this is related to 84 patients of each group. However in the text “the excess mortality of tigecycline is significant ONLY among those with MIC > 2 µg/ml”. Please clarify.

**Response:**

In our hospital, there were no susceptibility reports of tigecycline or colistin before treatment. Actually there were no tigecycline interpretation criteria according to CLSI or EUCAST.[6] Both tigecycline and colistin were presumed to be effective empirically. Our aim is to compare the effectiveness of tigecycline compared to colistin in treating MDRAB pneumonia when tigecycline and colistin susceptibilities are unknown. Table 4 showed that if using tigecycline vs. colistin in MDRAB pneumonia, but the susceptibility results of tigecycline and colistin were not available. Tigecycline group had poor outcome. Among patients who were treated with tigecycline, only 22 have isolates available for tigecycline MIC testing. The post-hoc analysis analyzing the mortality showed that the excess mortality of tigecycline is significant among those with MIC >2µg/mL (10/12 vs. 37/84,
P=.01), but not for those with MIC $\leq 2\mu g/mL$ (4/10 vs. 37/84, P=.81). (P. 14 line 14 to 18, underlined)

2. Does the author performed a multivariate analysis for the outcome “Nephrotoxicity”? In the methods “nephrotoxicity” was a defined as primary outcome.

**Response:**

We performed a multivariable analyzed for the outcome “Nephrotoxicity”.

The primary end point was analysis using the risk difference in outcome, which included mortality, and nephrotoxicity, between the colistin group and the tigecycline group. Since the characteristics between two groups were similar, therefore we can compare the primary end-point directly between two groups. [5]

Mortality was further analyzed using multivariate approach to control possible confounding variables (Table 4). We also analyzed the nephrotoxicity considering the same variables used in mortality analysis, however the model didn’t achieve convergence. The excess nephrotoxicity remained significant even after being adjusted by propensity score (adjusted RD 7.4%, 95% C.I. 1.2% – 13.6%, P=.02). (P. 14 line 10 to 12, underlined)

3. What was the time elapsed between Acinetobacter isolation and the beginning of antibiotic treatment (a major determinant of survival following infections) in the two patient groups?

**Response:**

The mean time ($\pm$ sd) elapsed between Acinetobacter isolation and the beginning of antibiotics of tigecycline or colistin group is 1.9 ($\pm$ 1.8) and 2 ($\pm$ 1.5) days, respectively (P = 0.72). (P. 13 line 17 to 19, underlined)
4. What were the colistin doses used?

**Response:**

In patient without renal dysfunction, the mean dose of colistin used was 3.0 (±0.8) mg/Kg/day. (P. 14 line 3 to 4, underlined) The dosing strategy during the study periods was according to standard package insert dosing, typically 2.5 – 5kg/day of colistin base divided over 8 or 12 hours for normal renal function (T.T.Y Biopharm Ltd., Taipei, Taiwan).

5. What were colistin MICs?

**Response:**

The MIC50 and MIC90 of colistin were 1 and 2 µg/mL, respectively. All tested isolates were susceptible to colistin. (P. 14 line 13 to 14, underlined)

6. What were the rates of polymicrobial infections per group?

**Response:**

Since compared to colistin, tigecycline had activity against MRSA and no activity against *P. aeruginosa*. Thus, those with MRSA or *P. aeruginosa* coinfection were not enrolled. In the enrolled population, there were three (one *Chryseobacterium indologenes*, one *Escherichia coli*, and one *Enterobacter aerogenes*) polymicrobial infections in tigecycline and four (one *Chryseobacterium indologenes*, one *Escherichia coli*, one *Enterobacter cloacae*, and one *Klebsiella pneumoniae*) in colistin group (P = 0.71). (P. 13 line 19 to P.14 line 2, underlined)

7. What are the specimens of Acinetobacter isolation?

**Response:**
163 cases had positive sputum cultures of *A. baumannii*, among them 118 sputum samples were from tracheobronchial aspirate. 36 cases had positive bronchoscopic bronchial lavage culture. (P. 13 line 15 to 17, underlined)

8. Table 1 and 3 depicts clinical demographics and outcomes. It would be better to separate.

*Response:*

We separate the clinical demographics and outcomes of table 1 and table 3. Now, the outcomes were described in the “Results” section. (Table 1, Table 3, P. 12 line 14 to 16, P. 14 line 6, and P. 14 line 10, underlined)

Discussion


*Response:*

We discussed recent references [7-9] that demonstrated the association between tigecycline therapy and increased mortality relative to comparators in the “Discussions” section. It now reads, “There were several meta-analysis showed excess overall mortality of tigecycline in the pooled analysis of different infection. The higher mortality might be due to increased superinfections and more adverse events in the tigecycline groups, and an increased risk of death especially among patients with VAP.” (P. 16 line 8 to 11, underlined)
2. Some results of combination therapy appear only at this section and it seems that are results for the entire cohort. This is confusing.

Response:

In the matched cohorts, the case numbers of combination therapy are too small (for example case numbers of colistin with carbapenem combination, and tigecycline with carbapenem combination were both less than ten). Therefore, for the purpose of describing the effect of combination therapy, we described the combination therapy effect among the entire cohort. We moved the descriptions of combination therapy to the “Results” section.

(P. 12 line 16 to 19, underlined)

Conclusion:

1. The authors did not state the conclusions correctly.

Response:

We rephrased the conclusions. Now it reads, “Our data disfavors the use of tigecycline-based treatment in treating MDRAB pneumonia when tigecycline and colistin susceptibilities are unknown, since choosing tigecycline-based treatment might result in higher mortality. The excess mortality of tigecycline-based group may be related to higher MIC of tigecycline (> 2µg/mL).” (P. 19 line 3 to 6, underlined)

REFERENCES

2. Falagas ME, Kasiakou SK: Toxicity of polymyxins: a systematic review of the evidence


Reviewer 2.

Major Compulsory Revisions

1. MICs of both tigecycline and colistin were not determined in enrolled patients before
they were administered with these agents. According to susceptibility test afterward, the susceptibility rate is 50% for tigecycline, while 100% for colistin. And the results of the manuscript demonstrated that excess mortality in tigecycline group was from patients with non-susceptible MDRAB isolates (MIC<2µg/mL). So to compare effectiveness of tigecycline and colistin between both cohorts is problematic. Well matched cohorts in which enrolled patients are susceptible to both tigecycline and colistin or demonstrate comparable susceptibility rates in both groups are needed.

Response:

Thanks for the reviewer’s critical suggestions. Among patients who were treated with tigecycline, only 22 have isolates available for tigecycline MIC testing. If we used the MIC breakpoint (2 µg/mL) for members of the Enterobacteriaceae family according to the Food and Drug Administration definition for tigecycline, only 10 isolates showed susceptibility to tigecycline. The case numbers are too small to establish a well matched cohort in which enrolled patients are susceptible to both tigecycline and colistin.

We agreed that it is best to enrolled patients that are susceptible to both tigecycline and colistin. However, according to CLSI or EUCAST there are no standardized criteria to interpret the susceptibility result of tigecycline against Acinetobacter.[1] In addition, our aim of the current study is to compares the effectiveness and the adverse effects of colistin-based versus tigecycline-based therapy in treating MDRAB pneumonia when tigecycline and colistin susceptibilities are unknown.

Rather than enrolled all susceptible patients in the matched cohort, we agreed that there may be different MIC profile of colistin or tigecycline against A. baumannii, so we do post-hoc analysis to see whether higher MIC or lower MIC of tigecycline affect the clinical outcomes. (P. 12 line 12 to 15, underlined)
2. Now combination treatments including tigecycline and/or colistin are usually prescribed for patients with MDRAB pneumonia for better outcomes as well as elusion of resistance in both agents during therapy. In this study, there are also some patients in both cohorts receiving combination therapy. Although the ratio of patients receiving various combination therapies was comparable, I suggested that patients receiving single agent and those receiving combination therapies should be separated. OR the aim of the study should be changed to compare effectiveness of tigecycline-based therapy and colistin-based therapy.

Response:

We changed the aim of the study to be “compares the effectiveness and the adverse effects of colistin-based versus tigecycline-based therapy in treating MDRAB pneumonia”. (P. 6 line 1 to 3, underlined)

Minor essential Revisions

Broth microdilution method should be used to test MIC of tigecycline.

Response:

We agreed that broth microdilution might be the gold standard to be used to test MIC of tigecycline. However, according to CLSI, both agar dilution and broth microdilution are acceptable for MIC testing of Acinetobacter. Since, the result of broth microdilution might be affected by whether fresh medium used, but agar dilution might not.[2, 3] Thus in our lab, the MIC testing of colistin and tigecycline were uniformly performed using agar dilution. However, limited study showed that the MIC obtained by agar dilution is lower than that obtained by broth dilution techniques.[2] We described the limitation of agar dilution in the limitations. (P. 18 line 14 to 18, underlined)
REFERENCES


We appreciate those comments and suggestions of the editor and reviewer 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”.

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