Author’s response to reviews

Title: Risk factors for mortality in patients with Stenotrophomonas maltophilia bacteremia and clinical impact of quinolone–resistant strains

Authors:

Eun Jin Kim (stone0128@ajou.ac.kr)
Yong Chan Kim (amomj@naver.com)
Jin Young Ahn (COMEBACKTOSEA@yuhs.ac)
Su Jin Jeong (JSJ@yuhs.ac)
Nam Su Ku (SMILEBOY9@yuhs.ac)
Jun Yong Choi (SERAN@yuhs.ac)
Joon-Sup Yeom (JOONSUP.YEOM@yuhs.ac)
Young Goo Song (IMFELL@yuhs.ac)

Version: 1 Date: 23 Jul 2019

Author’s response to reviews:

Dear Editor-in-Chief,

Thank you for your careful review of our manuscript and your helpful comments. We hereby resubmit our manuscript titled “Risk factors for mortality in patients with Stenotrophomonas maltophilia bacteremia and clinical impact of quinolone–resistant strains (Manuscript ID INFD-D-19-00576)” to be considered for publication in BMC Infectious Diseases.

We appreciate your acknowledgement of the importance of our manuscript’s subject and your offer to reconsider our manuscript pending proper revision. We agree with the comments made by the reviewers, and have made the appropriate revisions.

This letter includes our responses to the reviewers. We have thoroughly reviewed their important comments, and highlighted all of the changes using underlined red characters while addressing all of the issues that were raised by the reviewers on a point-by-point basis. Below we have outlined all of our responses to the given comments, and explained all of the changes we made to our paper.
We believe that our revisions have addressed all of the reviewers’ concerns, and hope that our manuscript will now be accepted for publication.

Thank you again for considering our manuscript for publication. We look forward to your reply.

Sincerely,

Su Jin Jeong, M.D., Ph.D.

Department of Internal Medicine

Yonsei University College of Medicine

50-1 Yonsei-ro, Seodaemun-gu, Seoul, Republic of Korea, 120-752

Tel.: +82-2-2228-1986

Fax: +82-2-939-6884

E-mail: JSJ@yuhs.ac

Response to Reviewers

Reviewers’ comments:

Reviewer #1:

1) Overall I thought the manuscript was well written. In the abstract and results section the authors describe empirical FQ use as an independent risk factor for mortality (OR 0.172, indicating protection). The text describes how patients treated empirically with a FQ had lower mortality, and clearly explains why. I would recommend changing the wording in the abstract and in the results to separate out the factors that were truly associated with higher mortality (quinolone resistance, heme malignancy, etc).

Response: Thank you for your thoughtful comments. We have modified the sentence according to your advice.

→ <Result>

→ On multivariate analysis, hypoalbuminemia (odds ratio [OR], 5.090; 95% confidence interval [CI], 1.321 – 19.621; P = 0.018), hematologic malignancy (OR, 35.567; 95% CI, 2.517-502.515; P = 0.008) and quinolone-resistant strains (OR, 7.785; 95% CI, 1.278 – 47.432; P = 0.026) were independent risk factors for mortality. Alternatively, usage of an empirical
regimen with quinolone (OR, 0.172; 95% CI, 0.034 – 0.875; P = 0.034) was an independent protective factor for mortality.

2) As a reader, it seems fairly clear to me that FQ-resistance is somewhat of a surrogate marker for overall disease severity. I did appreciate that the authors drew attention to the significance of catheter retention related to FQ resistance.

Were these the only antibiotics used to treat SM bacteremia at your institution? Did you look at follow up cultures for any development of resistance on therapy?

Response: Prior to this study, we only focused on the use of antibiotics; but in the future, removal of unnecessary CVC will be performed in conjunction with antibiotic treatment. The choice of antibiotics is voluntary, and the use of quinolone and/or TMP-SMX, etc. are all possible. A follow-up culture was used to confirm the negative state, but there was no case in which the resistance development was confirmed.

Reviewer #2: The manuscript is well-written and comprehensive. However, there are some problems to be clarified.

(1) Levofloxacin is not included in the AST panel in early 2000s. Did the authors store all the isolates and re-test the MICs of levofloxacin in this study?

Response: The study used data from 2006, and quinolone sensitivity tests were available for all participating hospitals in 2006.

(2) Polymicrobial bacteremia is a major confounding issue for patients with SM bacteremia. The authors classify it as infection source in table 2 is not adequate. Please separate it as a single category and analyze its effect.

Response: We have modified Table 2 according to your advice. Since we analyzed according to each factor, the statistical results did not change. Then, subgroup analysis was performed in patients with polymicrobial infections. However, there was no significant difference between the two groups regarding death. We added the following sentence in the discussion section as you suggested.

→ <Discussion>

→ The rate of polymicrobial infections in SM bacteremia was high in the previous literature [23] and in this study as well (42.8%). Thus, high polymicrobial infections may be a
confounding factor for appropriate antibiotic use, and this may have affected the mortality risk-factor analysis. Therefore, subgroup analysis was performed in patients with polymicrobial infections. However, there was no significant difference between the two groups regarding mortality (Supplemental table 1).

(3) The definite treatment part is confusing. Only 24.8% of patients receive TMP/SMX. Please discuss it in the discussion part.

Response: The most commonly used antibiotics were fluoroquinolone (31.7%, 40/126) and TMP/SMX. The usage rate of carbapenem was 14% (18/126) and inappropriate treatment was 30% (39/126). Furthermore, the rate of TMP/SMX and/or quinolone use was 56.5%, cephalosporin or/carbapenem approximately 40%. During the study period, it was possible that SM bacteraemia was judged to be insignificant or that pathogen had a weak virulence. In addition, most patients with intensive ICU care (65.9%) or those with malignancy (62.7%) had antibiotics already in use (especially carbapenem or cephalosporin), and it seems that they used quinolone in combination treatment, rather than using TMP / SMX. Also, high polymicrobial infections may be a confounding factor for antibiotic use. This study emphasizes the importance of more appropriate use of antibiotics. We added the following sentence in the discussion section according to your advice.

→ <Discussion>

→ Significantly, the use of empirical or definitive treatment of carbapenem was higher in the mortality group, although it was not significant in the multivariate analysis. This suggests that the possibility of breakthrough infections by SM in patients being treated with carbapenem is due to intrinsically resistant carbapenem and the selection pressure of SM should be considered [30, 31]. Only 24.8% of patients received TMP/SMX. A high proportion of ICU care and polymicrobial infections may have influenced antibiotic selection. Nevertheless, careful use of carbapenem is necessary, and the possibility for breakthrough infections should be considered.

(4) In table 1, the length of stay before bacteremia is not significantly different between survivors and non-survivors. Please be sure it is correct (12 days versus 26 days should be significantly different)

Response: We used Student's t test since our study involved more than 30 cases. Both groups satisfied equidispersion. However, when p value was re-tested by T-test, it was found to be 0.469 with no difference in the mean. IQR results suggest that there is no significant difference between the two groups due to the wide range of variance in non-survivor group. But we agree
your advice, and p value was found to be 0.038 when non-parametric method (Mann-Whitney test) was tested again in univariate analysis after normality test. In multivariate analysis, however, p value was found to be 0.382 (OR 95% CI 0.997-1.001), and it was not significant. We modified Table 1 and the following sentence in the result section.

→ <Result>

→ Univariate analyses showed that hematologic malignancy (P = 0.005), indwelling of hemodialysis catheter (P = 0.028), high APACHE II scores (P = 0.001), hypoalbuminemia (P = 0.003), thrombocytopenia (P = 0.004), and low hemoglobin concentration (P = 0.035) were associated with mortality. Also, the length of stay before bacteremia was longer in non-survivors (P = 0.038).

(5) Please provide the definition of hypoalbuminemia
Response: We added the following sentence in the method part according to your advice. Hypoalbuminemia was defined as an albumin count of less than 3g/dL at the time of bacteremia.

→ <Method>

→ Thrombocytopenia was defined as a platelet count of less than 100,000/mL, and hypoalbuminemia was defined as an albumin count of less than 3g/dL at the time of bacteremia.

(6) In a previous study about SM bacteremia in cancer patients (Cancer. 2006 May 1;106(9):1967-73.), SM due to catheter related bacteremia has good prognosis compared to other sites of infection. Try to explain lack of difference in this study. Due to lack of effective treatment?
Response: In the above-mentioned journal, cancer patients and indwelling of CVC were identified as risk factors for SM bacteremia, and the reason for the good prognosis was that CVC was removed immediately in 95% of the patients. Indwelling of CVC has already been shown to be significantly associated with mortality and bacteremia in previous literatures (reference 9, 27-29). These also reported that the removal of CVC is an important protective factor of mortality. In this study, as mentioned in the discussion section, there was no significant difference between the two groups in the removal of CVC. It is estimated that the rate of patients who adequately removed CVC was only 40%, and therefore did not significantly affect the outcome. We would like to encourage removal of CVC through this research. We added the following contents to the discussion section.
Indwelling of CVC has already been shown to be significantly associated with mortality and bacteremia in previous literature [9]. In particular, removal of CVC has been associated with reduced mortality [27-29]. However, removal of CVC did not influence mortality and quinolone resistance in this report. It is estimated that the rate of patients who adequately removed CVC was only 40%, and therefore did not significantly affect the outcome. SM has the ability to adhere on prosthetic devices such as CVC and form a biofilm. Biofilms can increase antibiotic resistance [11]. Therefore, indwelling of CVC is a risk factor to biofilm formation and, accordingly, to quinolone-resistance. Therefore, it is necessary to actively encourage the removal of CVC.

(7) Please explain the last row of Table 2
Response: Appropriate antimicrobial therapy was defined as the administration of at least one agent to which the index SM isolate was susceptible in vitro (in method part). Inappropriate antimicrobial therapy was also explained as not using any appropriate antibiotics according to the results of antibiotic susceptibility. We provided additional explanations in the footnotes below Table 2.

(8) Only 125 cases in Table 4 (126 case in table 1). Cause?
Response: One patient died immediately on the day of bacteremia, and was excluded from the analysis due to death not related to antibiotic adequacy. The patient was a non-survivor and in the FQ resistance group. We added the following contents in the result paragraph.