Author’s response to reviews

Title: Risk factors for mortality in patients with Pseudomonas aeruginosa bacteremia; retrospective study of impact of combination antimicrobial therapy

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Author’s reply

We appreciate your good comments and recommendation. We revised the manuscript according to the reviewers’ comments and marked the changed content in red color.

As the reviewer’s recommendation, 14-day overall inhospital mortality, not infection-related mortality, was used as primary outcome. We thought that 30 day mortality was too long to reflect infection-related mortality among patients with P. aeruginosa bacteremia, because most of patients with P. aeruginosa bacteremia died in early periods. We agreed that direct cause of death is difficult to establish, and so we changed the primary outcome to 14-day overall mortality.

We clarified the definition; combination therapy vs. monotherapy, empirical therapy vs. targeted therapy, appropriate vs. inappropriate therapy. Empirical antimicrobial therapy was defined according to the initial antimicrobial therapy regimens that were administered within 24 h after blood culture samples were obtained, and before results of susceptibility tests were known. Targeted antimicrobial therapy was defined as specific antibiotics given within 24 h after the results of antimicrobial susceptibility. Antimicrobial therapy was considered appropriate when the strain showed in vitro susceptibility to the antibiotics administered, and the dosages of the drugs were adequate according to current guidelines. An appropriate combination therapy was defined if two or more antibiotics showed in vitro susceptibility. Appropriate monotherapy was defined as treatment with only one active antibiotic. Aminoglycoside monotherapy was also defined as inadequate therapy.

We absolutely agree that aminoglycoside monotherapy is inappropriate in
patients with P.aeruginosa bacteremia. Therefore we reconstructed the table after we regarded aminoglycoside monotherapy as inappropriate therapy.

Additionally, we edited the manuscript two times by a native editing company - http://www.editage.co.kr/ and http://www.edanzediting.com/.

REVIEWRE 1

General
In general studies examining combination vs. monotherapy in P. aeruginosa bacteremia are helpful, despite the existence of many previous, including recent studies, as they add to the accumulating knowledge. However, the contribution of studies examining “any” combination vs. “any” monotherapy is questionable. What hypothesis underlies such a comparison? Synergy exists for beta-lactam aminoglycoside combinations – and this is the analysis of interest. The comparison should be probably restricted to beta-lactams or quinolones but not any monotherapy. The English language should be improved throughout the manuscript.

-> As the reviewer’s recommendation, 14-day overall mortality was used as primary outcome. We agreed that direct cause of death is difficult to establish, and we changed the primary outcome to 14-day overall mortality.

Empirical antimicrobial therapy was defined according to the initial antimicrobial therapy regimens that were administered within 24 h after blood culture samples were obtained, and before results of susceptibility tests were known. Targeted antimicrobial therapy was defined as specific antibiotics given within 24 h after the results of antimicrobial susceptibility. Antimicrobial therapy was considered appropriate when the strain showed in vitro susceptibility to the antibiotics administered, and the dosages of the drugs were adequate according to current guidelines. An appropriate combination therapy was defined if two or more antibiotics showed in vitro susceptibility. Appropriate monotherapy was defined as treatment with only one active antibiotic. Aminoglycoside monotherapy was also defined as inadequate therapy. We absolutely agree that aminoglycoside monotherapy is inappropriate in patients with P.aeruginosa bacteremia. Therefore we reconstructed the table after we regarded aminoglycoside monotherapy as inappropriate therapy.

Additionally, we edited the manuscript two times by a native editing company - http://www.editage.co.kr/ and http://www.edanzediting.com/.

Abstract
The methods section of the abstract should be expanded to reflect more the complete methods of the study (years, location, inclusion criteria, statistical methods etc.)

-> We added an extra data including the year, location, inclusion criteria and statistical methods as below.
Methods; This retrospective study analyzed data of 234 patients with P. aeruginosa bacteremia at a 1,200-bed tertiary teaching university hospital in South Korea between January 2010 and December 2012. Factors associated with mortality were determined. Mortality was compared in patients with adequate empirical and targeted combination therapy, and monotherapy, and inappropriate therapy.

Introduction

P. aeruginosa is considered the most predominant bacteremia-causing gram-negative bacillus – I don’t know what you mean by predominant, but P. aeruginosa is not the most common gram-negative bacillus causing pneumonia.

-> I revised the sentence.

Pseudomonas aeruginosa represents a common cause of nosocomial infection. Immunocompromised patients such as those with malignancy or neutropenia are at high risk of bacteremia, and P. aeruginosa is one of the commonly isolated pathogens associated with bacteremia in such patients.

Samonis G had reported that gram-negative bacteria were the predominantly isolated pathogens from patients with hematologic or solid organ malignancies, and Pseudomonas spp. was the most common cause (Ref. Samonis G, Vardakas KZ, Maraki S, Tansarli GS, Dimopoulou D, Kfteridis DP, Andrianaki AM, Falagas ME: A prospective study of characteristics and outcomes of bacteremia in patients with solid organ or hematologic malignancies. Support Care Cancer 2013, 21:2521-2526.)

The other study had reported that for bacteremia in immunocompromised hosts, Gram negative bacilli represented 59.4%, the enterobacteriaceae were predominant, followed by P. aeruginosa (Ref. Papagheorghe R: Bloodstream infections in immunocompromised hosts. Roum Arch Microbiol Immunol 2012, 71:87-94)

Methods

14-day in-hospital mortality is the outcome examined in the study. Better to examine all deaths within 14 days if data are available. Appropriate/adequate empirical antibiotic treatment should be defined. In the definition of combination treatment the authors include that the combination was started with 24h of blood culture taking. Was this true also in the analysis for targeted treatment? Survival analysis is not helpful – see below.

-> 1) As your recommendation, we analyzed the data by using 14-day overall mortality as a primary outcome. We agreed that direct cause of death is difficult to establish, and we changed the primary outcome to 14-day in-hospital mortality.

2) We clarified the definition; combination therapy vs. monotherapy, empirical therapy vs. targeted therapy.
Empirical antimicrobial therapy was defined according to the initial antimicrobial therapy regimens that were administered within 24 h after blood culture samples were obtained, and before results of susceptibility tests were known. Targeted antimicrobial therapy was defined as specific antibiotics given within 24 h after the results of antimicrobial susceptibility. Antimicrobial therapy was considered appropriate when the strain showed in vitro susceptibility to the antibiotics administered, and the dosages of the drugs were adequate according to current guidelines. An appropriate combination therapy was defined if two or more antibiotics showed in vitro susceptibility. Appropriate monotherapy was defined as treatment with only one active antibiotic. Aminoglycoside monotherapy was also defined as inadequate therapy.

3) We deleted the survival plot.

Results
A description of the antibiotics included in combination and monotherapy groups should be provided, preferably in a supplementary table. The hypothesis underlying the advantage of benefit for combination therapy is based on in-vitro studies showing synergy between beta-lactams and aminoglycosides. If most of the combinations in this analysis consist of colistin + aminoglycoside or most of the monotherapies of colistin or aminoglycoside alone, for example, I don’t know what the value of this analysis is. Preferably specific combination therapies should be compared to specific monotherapies, but the sample size of this study will probably not permit such an analysis. At least monotherapy regimens of aminoglycoside alone or colistin alone should be excluded in a sensitivity analysis since both have been associated with increased mortality (Leibovici et al. Antimicrob Agents Chemother. 1997 May;41(5):1127-33 and Paul et al. J Antimicrob Chemother. 2010 May;65(5):1019-27)

-> I really appreciate your important comments.
I described the antibiotics profile administrated at the result and presented it at table. As your comments, aminoglycoside monotherapy have to be considered as inappropriate therapy, therefore we excluded the aminoglycoside monotherapy in our analysis.

For the colistin, it is unclear whether colistin monotherapy is inferior than combination therapy in P.aeruginosa infection. I described it at the limitation.

In one study, colistimethate sodium was also studied retrospectively in cancer patients with MDR P. aeruginosa (Antimicrob Agents Chemother 2007;51:1905–11). Patients treated with colistin monotherapy had higher clinical and microbiological responses than those in the control group.

A recent meta-analysis revealed no statistical difference in cure rates when colistimethate sodium alone was compared with the combinations with meropenem, piperacillin/tazobactam or ampicillin/sulbactam (Int J Antimicrob Agents 2010;35:194–9).
Further study about the effectiveness of colistin will be needed for the treatment of MDR P. aeruginosa bacteremia. In this reason, we included adequate monotherapy regimen of colistin alone.

A factor of appropriate/ inappropriate empirical antibiotic treatment of any type (monotherapy or combination therapy) should be examined separately from the comparisons of monotherapy vs. combination therapy and this factor, if significant should be entered into the multivariable analysis.

-> I absolutely agree with your comments. Combination therapy is key variable in my manuscript, and I added the variable (adequate combination/monotherapy/inadequate therapy) for univariate analysis. However it was not significant, and we exclude it for multivariate analysis.

Both supplementary tables, presenting the univariate and multivariable analyses should be presented in the manuscript.

-> We check the manuscript. We found that we described the result for univariate and multivariate analyses in the result section, and presented the analyses at the table 4.

If these are not right answer, I would revise again.

The survival plots are not informative when the outcome is 14-day mortality – they add no further information and I recommend deleting.

-> As your recommendation, we delete the survival plots. Thank you for your comments.

Continuous outcomes that do not have normal distribution should be reported with medians and some dispersion measure (min/ max, percentiles) and the statistical analysis should be done with appropriate non-parametric tests. For example, length of stay before bacteremia (42.1±125.3 and 9.7±24.7 – the mean has no meaning here).

-> It was a good point. I got the consultation from a statistician in our university, and revised the table.

In methods, 14-day in-hospital mortality is defined as the main outcome and in results the outcome provided is 14-day infection related mortality. Which is it?

-> I am sorry about the confusion. At my first manuscript, I used 14-day infection-related mortality as main outcome. However as your comments, we think that it is difficult to distinguish between all-cause mortality and infection-related mortality. We revised 14-day in-hospital overall mortality as final outcome, and corrected the manuscript.

14-day all-cause mortality should be provided, since deaths within 14 days of infection and most probably attributed to infection and the direct cause of death is difficult to establish.
As your comments, we think that it is difficult to distinguish between all-cause mortality and infection-related mortality. We agree that most of deaths within 14 days attributed to infection. Therefore, we revised 14-day in-hospital overall mortality as final outcome, and corrected the manuscript.

Absolute numbers, numerator and denominator, should be provided with all percentages.

I revised the manuscript as your recommendation.

Discretionary Revisions

The carbapenem resistance rate was very high here. It is strange that this was not associated with mortality, as carbapenem resistance probably identifies patients with extensive healthcare exposure. Perhaps the authors should valuate MDR P. aeruginosa that is resistant to carbapenems, other beta-lactams and quinolones vs. non-MDR isolates.

We had discussed about your point.

Carbapenem resistance to P. aeruginosa was very high in our study (n=118, 50.4%), however multidrug resistance P. aeruginosa that is resistant to other beta lactam, quinolone, aminoglycoside and carbapenem was not high (n=6, 2.6%).

We agree with your opinion that carbapenem resistance identified patients with healthcare exposure and it could be associated with mortality. However in our study, carbapenem resistance or MDR strains was not associated with clinical outcomes in P. aeruginosa bacteremia. Rather, underlying disease severity representing mechanical ventilator, septic shock and high APACHE score was associated with mortality.

There is controversy with regard to the effect of antibiotic resistance on mortality. Suarez et al reported that carbapenem resistance was not associated with mortality in P. aeruginosa bacteremia. In this study, Having high risk sources of bacteremia and clinical presentation with severe sepsis were identified as independent predictors of attributable death in patients with P. aeruginosa bacteremia. (Ref. International Journal of Infectious Diseases 14S (2010) e73–e78)

In cases of A. baumannii bacteremia, delay in receiving appropriate antimicrobial therapy rather than resistance has an adverse influence on clinical outcome. (Ref. Int J Antimicrob Agents 2009;34:575-9

We think that clinical severity, rather than resistance, is associated with outcomes in our data, although further larger studies are needed to clarify this point and to confirm the results.

We discussed this at the discussion part.
The authors studied 3 years of Pseudomonas aeruginosa bacteraemia at a tertiary hospital and reported that severity of illness was independently associated with 14-day mortality. They performed stratified analysis and reported that in neutropenic patients combination antibiotic was associated with survival. The study was undermined by retrospective analysis, and the inclusion of aminoglycoside as appropriate antibiotic.

Major compulsory revisions
(1) Explain why 30-day mortality was not chosen as primary outcome. If good justification cannot be provided, re-analysis using 28 or 30 day mortality should be done.

-> I appreciate your opinion and absolutely agree with you. 30-day mortality is usually used as a final outcome for assessment of mortality in infectious disease department. However as you know, patients with P. aeruginosa bacteremia died at the early period of bacteremia. Our data showed that among 78 patients with mortality during hospital stay, 66.7% (n=52) were dead within 14 days. We think that 30 day mortality did not reflect infection-related mortality in P. aeruginosa bacteremia.

In addition, as other reviewer’s comments, it is difficult to distinguish between infection-related 14 day mortality and overall 14 day mortality. Therefore we decided overall 14-day mortality as the primary outcome.

(2) Sites of infections were defined using the very old CDC 1988 criteria. Please revise using the 2011 criteria available on CDC Atlanta website. Attached for the authors.

-> Thank you for your opinion. I search the criteria at the CDC website, and revised the manuscript using 2014 criteria.

(3) Please explain and justify input variables for multivariable logistic regression analysis. Non-survivors had more neutropenia, higher APACHE score, more septic shock, more device use (CVC, IDC and MV), more pneumonia. It appears that the authors selected age, neutropenia, MV, CVC, APACHE score, septic shock, carbapenem resistance, pneumonia, inappropriate empiric and targeted antibiotic for logistic regression. Combination antibiotic which is a key finding should be included.

-> I really appreciate your comments.

When variables (such as septic shock, neutropenia and device) were significant in univariate analysis, we included the variables in the multivariable logistic regression. And I added it at the part of “Statistically analysis”

Some articles had demonstrated that antibiotics resistance and use of
appropriate antibiotics are associated with the mortality.
(Ref. Park et al. BMC Infectious Diseases 2012, 12:308

So we included these variables (resistance, appropriate antibiotics) for univariate
analysis. However these variables were not significant, and we excluded the
variables for multivariate analysis.

I absolutely agree with your opinion that combination antibiotic is a key finding in
our manuscript. Therefore we included the variable, combination antibiotics, for
the analysis.

(4) There were 234 patients. 145 had appropriate empiric antibiotic and 183 had
appropriate targeted antibiotic. Please clarify why 51 patients did not have
appropriate targeted therapy. Only 25 died early.

-> Yes, we know. As I mentioned the definition at the manuscript, targeted
antimicrobial therapy was defined according to the modified antibiotics within 24
h after results of antimicrobial susceptibility. Some patients with P. aeruginosa
bacteremia in this study did not admit to infectious disease department.
Infectious disease specialists received the consultation for the proper antibiotics
from other department (oncology, hematology, surgery...), and it sometimes took
long time to choose the proper antibiotics.

(5) Please review and include in manuscript the following essential studies.
Essentially both BMJ meta-analysis by Paul et al are on RCT's while Safdar et al
is on observational studies. The authors must be able to evaluate strength of
evidence.
(a) BMJ 2003;326:1111 on combination antibiotic for febrile neutropenia which
showed no benefit of combination antibiotic in Pseudomonas infections.
(b) Lancet ID 2005;5:192 which highlighted the flaw in reference 19.

-> Thank you for your comments. We reviewed your recommended studies, and
described the studies at the discussion part.
(a) One meta-analysis showed that there was no significant difference between
ß-lactam-aminoglycoside combination therapy and monotherapy in patients with
febrile neutropenia, however this study did not target only patients with
P. aeruginosa infection, and did not investigate the adequacy of antimicrobials.
(b) This RCT This data included the gram negative bacteremia, no targeting
P. aeruginosa.

We think that our study is worthwhile because we tried to identify the mortality
targeting P. aeruginosa bacteremia and we included the data for adequacy of
antimicrobial therapy.

(6) The authors should refrain from self-fulfilling prophecy by stating that more
patients who survived received combination therapy empirically (17.4% vs.
12.8%) and in targeted therapy (19.5% vs. 10.3%) even though they stated that
the difference was not statistically significant. With small numbers such small difference in proportion was not uncommon!

-> Thank you for your good comments. Actually we know that the difference was not statistically significant. However, it is well known that the appropriate antibiotics are associated with the patients’ outcomes (Ref. Park et al. BMC Infectious Diseases 2012, 12:308)

Although small difference was not significant, we wanted to underline the importance of appropriate antibiotics at my first manuscript.

We agree with your point, so modified the sentence of the manuscript;

The percentage of patients receiving empirical combination therapy was slightly, but not significantly higher, in the survivor group than in the nonsurvivor group (17.0% [31/182] vs. 13.5% [7/52], p=0.74). A similar tendency was demonstrated for targeted combination therapy (19.8% [36/182] vs. 11.5% [6/52], respectively; p=0.31).

(7) Please repeat analysis by removing aminoglycoside as appropriate. Please see Lancet ID 2005;5:192 above about the influence of this confounder.

-> I really appreciate your important comments. I added the antibiotics profile administrated at the table. As reviewer’s comments, aminoglycoside monotherapy have to be considered as inappropriate therapy. After we excluded the aminoglycoside monotherapy in our analysis, we repeated analysis.

Minor essential revisions

(1) Provide reference for claim in lines 3-6 of paragraph 2 of Introduction on combination antibiotic being more effective, synergistic or additive and preventing resistance, as well as in Discussion.

-> I provided the reference.


(2) In abstract 145 patients (61.9%) received appropriate empiric therapy. In manuscript, 145 patients (53.4%) were reported. Please check data.

-> I am sorry about that. I checked data again, and corrected the data. Aminoglycoside monotherapy was defined as inappropriate antibiotics and we revised the data.

(3) Line 9 paragraph 2 of results was repetitive. Please delete.

-> I found the repetition and I delete it.

(4) Please check P value for time in hospital before bacteraemia, 42 vs. 9.7 days. Likely skewed data so instead of mean, they should use median and repeat analysis.
-> Thank you for your comments. We use median days, and recheck the analysis.

(5) Please replace "lesser" with "less".

-> We are sorry about it. We checked up carefully the content in the manuscript and corrected it.

(6) Please correct spelling for APACHE not APCHE.

-> We are sorry about it. We checked up carefully the content in the manuscript and corrected all the misspellings.