Author's response to reviews

Title: Trough colistin plasma level is an independent risk factor for nephrotoxicity: a prospective observational cohort study

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Version: 6 Date: 13 March 2013

Author's response to reviews: see over
Philippa Harris  
Executive Editor  
BMC Infectious Diseases  

13th March 2013

Dear Dr Harris,

Thank you very much for your consideration of our manuscript (MS: 5430024648283306) now titled “Trough colistin plasma level is an independent risk factor for nephrotoxicity: a prospective observational cohort study” and your request for a revised version.

We have attached all reviewers’ comments, and addressed each one individually. As you will see, we have made every attempt to incorporate these suggestions as thoroughly as possible. We hope you will agree that the revised manuscript is now suitable for publication in BMC Infectious Diseases. We look forward to hearing from you at your earliest convenience.

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Yours sincerely,

Luisa Sorlí, MD,
The authors would like to thank the Reviewers for their careful review of our manuscript and for providing us with their comments and suggestions to improve the quality of the manuscript. The following responses have been prepared to address all of the reviewers’ comments in a point-by-point fashion.

Reviewer: Jason J Pogue

Reviewer’s report:
I commend Sorli and colleagues on their revised manuscript as I think it now represents a very solid and important contribution to the literature. My comments, all of which I would consider minor, are listed below

Authors: The authors would like to thank the reviewer for his positive evaluation of our manuscript and for accepting it for publication after revision. We have incorporated the following reviewer’s specific comments in preparation of a revised version of the manuscript.

Reviewer’s report:
1) Methods- line 18-20 please describe, or at the very least reference the package insert the renal dosing. The reason that I recommend this is that different products have significantly different renal dosing recommendations.

Authors: we agree with the reviewer and have transcribed the package insert’s recommended dosing.

2) Results- page 9 lines 6-8. the percents do not add up to 100. Please fix.

Authors: we agree with the reviewer. It was a mistake and we have corrected it.
3) Results- page 10 line 6-7 states, "Cmax and Cmin were higher in those without nephrotoxicity." I assume this should say higher in those with nephrotoxicity.

Authors: as you say this was another mistake and we have corrected it.

4) Discussion- this one is at the discretion of the authors, but lines 10-13 talk about the differences in toxicity between this study and others, but the difference is negligible and I don't think it is necessary to describe potential reasons for a 4% increase in toxicity.

Authors: following your recommendation we have removed the sentence.

5) Discussion page 12 lines 14-15. I don't think that it is accurate to compare two different studies and say that there is a dose dependent efficacy. If the authors would like to make the point here that higher doses increase efficacy the should reference either falagas et.al. int j antimicrob agents 2010 35: 194-199 and/or vicari et al. CID 2013 Feb;56(3):398-404

Authors: we agree with you and have changed the sentence.

6) all tables: there is no such thing as a p value of 0.000- would change all of these to p <0.0001, etc

Authors: we have corrected these data

7) In general the new tables are fantastic. Great work. Very thorough data set now!

Authors: thank you very much. Your opinion is very valuable for us.

8) Table 6- excellent table, however it is a bit confusing. I think that either in the table heading or the table itself you need to emphasize that these are day 3 levels and the associated with toxicity on d7 or EOT. If I just look at this table (as some unfortunately will) it appears that these concentrations were drawn on d7 and EOT

Authors: we agree with you and have emphasized in the table heading that we are talking about steady-state levels. We hope it is clearer now.
Point-by-point responses to the reviewer’s comments on the manuscript

Trough colistin plasma level is an independent risk factor for nephrotoxicity: a prospective cohort study

The authors would like to thank the Reviewers for their careful review of our manuscript and for providing us with their comments and suggestions to improve the quality of the manuscript. The following responses have been prepared to address all of the reviewers’ comments in a point–by-point fashion.

Reviewer: Nikolaos Markou

Reviewer’s report:
Most comments have been adequately answered by the authors. Still, I have some further things to observe:

• Page 6, 1st paragraph: clarify if the outcome you evaluated was ‘AKI’ or ‘acute renal failure’. If it was indeed AKI, then all reference to ‘acute renal failure’ seems redundant.

Authors: we evaluated AKI during CMS treatment. However, some patients have acute renal failure at the beginning of treatment due to any cause. We have clarified it in “Methods” section (Page 6, line 4-7)

Reviewer’s report:

• In the methods section as well as in the presentation of data, I would avoid mention of “nephrotoxicity” and I would only speak of AKI. Nephrotoxicity is only a possible cause of AKI in these patients. The authors can then consider the hypothesis of
nephrotoxicity as a contributing factor for AKI after analysis of data, in the discussion section, based on the association of AKI with increased colistin concentrations.

**Authors:** we agree with you and have replaced “nephrotoxicity” with AKI (Page 6, line 7. Page 11, line 6, 9, 16)

**Reviewer’s report:**

• Both SAPSII and APACHE II score were developed and validated in ICU patients. Their use outside this setting is equally problematic. Thus the use of one score for ICU patients and of another score for patients treated in the wards just results in unnecessary complexity without providing any additional benefit. If the writers insist in using any of these scores, they should select only one of the two and commend on the discussion section about limitations.

**Authors:** we finally assessed the severity of disease of all included patients by using the APACHE II score despite the fact that this score has only been validated in ICU patients. This point has been added as a limitation in the “Discussion” section (Page 16, lines 15-18).

**Reviewer’s report:**

• More detailed reference to the statistical methods applied seems warranted

**Authors:** we have reviewed and extended this section.

**Reviewer’s report:**

• Methods section: Any decision to use only one value (Cmin or Cmax) in the multivariate model can logically be the result of data analysis showing a better correlation with one of the two variables and not a decision made beforehand, especially as there is no unanimity in the literature as regards fluctuations in colistin levels.

**Authors:** because these two variables are highly correlated (Rho Spearman 0.977), and following the statistician’s recommendations only one of them was included in the
multivariate model to avoid a multicollinearity phenomenon. We chose the trough levels following the recommendations of Couet et al as we explain in “Statistical analysis” section (Page 8, lines 19-24) and in the Discussion section (Page 13, lines 19-25).

Reviewer’s report:

• In table 1 the authors provide data on presence of chronic kidney disease. A mention should be made in the methods section as well and a definition provided.

Authors: table 1 describes the different categories of AKI according to RIFLE criteria. We suppose you are talking about table 2. Is this correct? If so, we have defined chronic kidney disease in “methods” section (Page 6, lines 3-4).

Reviewer’s report:

• Results: in addition to the cumulative presence of AKI some information on the severity of AKI would also be desirable (pts with R, I and F)

Authors: we agree with you that this is valuable information. We have added a new table with this information (Table 4, page 27).

Reviewer’s report:

• Results: paragraph 3. Given the small number of patients with dose adjustment, I think it would be very difficult to make any conclusion as regards the impact of the time-to-dose adjustment or of the strategy of dose modification.

Author: we agree with the reviewer that it would be difficult to draw conclusions. We have added this information in the new version of the paper because the other reviewer asked us for it.

Reviewer’s report:

• Table 3: data are presented on clinical response. Detailed reference should be made on the methods section as to how this response was evaluated. They also add in the
discussions section that this clinical response, was not associated with colistin levels but some explanation is needed as regards the statistical method used. Colistin levels are only one of many possible variables affecting clinical response, and only multivariate analysis might offer some answer to this question. Furthermore, as the authors clearly did not plan at the inception of the study to search for associations of colistin concentrations with clinical response, any reference to associations of colistin concentrations with clinical outcome should probably be avoided.

**Authors:** we agree with you and have added in the methods section how we have evaluated the clinical response (Page 7, lines 3-5). In the discussion we said that in this group of patients, clinical response was not related to CMS doses but we did not talk about the relationship between colistin plasma levels and clinical outcome (Page 13, lines 14-16). As you say, colistin levels are only one of many possible variables affecting clinical response. We think this is an important issue that should be studied in future works. We have mentioned it and have added the table you refer to because the other reviewer had asked us for it.

**Reviewer’s report:**

- Results, last paragraph: as regards all-cause mortality: clarify statistical analysis (methods section). Associations of mortality with development of AKI should also be evaluated in the context of multivariate analysis.

**Authors:** we agree with you and have added a sentence in “statistical analysis” section (Page 9, lines 1-3), and have added the results of the multivariate analysis in “results” section (Page 12, lines 8-14).

**Reviewer’s report:**
• Table 6 in its present state does not make much sense: a) Cmin is not in fact presented as a continuous variable, b) data do not refer to degree of ‘nephrotoxicity’ but to incidence of AKI, c) no relationship is in fact provided.

Authors: we agree with you that Cmin is not presented as a continuous variable but divided in intervals. Additionally we have referred to incidence and not to degree of nephrotoxicity. According to these questions, we have changed the headline of the table in order to clarify it. Although no relationship is provided, we have maintained the table because the other reviewer asked us to do so.