Reviewer's report

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

Version: 5 Date: 1 February 2013

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.

• 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.

• 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.

• More detailed reference to the statistical methods applied seems warranted

• 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.

• 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.

• 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)

• 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.

• 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.

• 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.

• 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.

• Discussion: the finding that Cmin and Cmax values were practically identical probably merits at least some comment.

Level of interest: An article of importance in its field

Quality of written English: Acceptable

Statistical review: Yes, but I do not feel adequately qualified to assess the statistics.

Declaration of competing interests:

I have no competing interests