Reviewer's report

Title: Steady State Colistin Plasma Levels is an Independent Risk Factor for Nephrotoxicity: prospective observational cohort study

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Reviewer: Jason J Pogue

Reviewer's report:

Sorli and colleagues present a very interesting paper associating day 3 colistin levels with toxicity at day 7 and day 14. This paper has the opportunity to be a significant add to the literature base surrounding colistin nephrotoxicity, however, the following need to be addressed first.

Major:

1. While I would agree that the concentration time profile of colistin in patients appears to be relatively flat, I think it is inaccurate to call these levels $C_{ss}$, as the authors did not verify it in their patient population. Additionally, with no data given regarding the dosing schedule this would be impossible to ascertain. The authors should call these levels $C_{min}$, which is a more accurate measure of what they are. They are free to comment in the discussion that they feel they are an accurate marker for $C_{ss}$, but in the context of this trial, they are trough levels.

2. Dosing. The authors should describe in their methods, as well as the results, the dosing regimens used (methods) and average daily doses (results). While I appreciate that a wide range of doses might have been used, they should do a better job of describing daily doses. This is of particular interest to those of us in the USA, who will likely use higher daily doses (assuming the majority of these doses are in the 6-9 M IU range.

3. Along the same lines as question #2, I am very interested to know if there was a) an association between daily dose and toxicity and b) an association between daily dose and levels in patients. I understand that the authors might not have these data readily available (particularly the association between dose and levels) and if they cannot put them in the manuscript they need to comment on this as a limitation. In the results section they twice comment on patients having higher doses of CMS (one says "doses of CMS" at day 7, and the other says "CMS cummulative dose" at EOT)- are these the same variable? different? is this first one daily and the second cummulative? please clarify.

4) Is there a reason the authors only looked at toxicity on day 7 and EOT? Any info on what day toxicity occured?

5) Results: "Globally 51.9% developed AKI during treatment," but then you list RU1LE rates as 25% and 49%. which one is accurate?

6) Is it possible to get into more detail on those who had dose adjustments and
recovered their baseline renal function? I think this would be a huge contribution to the literature if you could better explain. What were the numbers of patients that did versus didn't? Was there a dose adjustment (when compared to others) that was associated with return of renal function?

7) Please show multivariate model in results- this one is just a suggestion.

8) Is it possible to get into more detail regarding the levels and toxicity rates? Looking at the results table there is a huge difference between levels in those with and those without toxicity, and the cutoff levels associated with toxicity (particularly the 3.3 level at day 7) were much higher than i would have thought they would be. This is also more of a suggestion, but i think it would add great value if you added a table that showed rates of toxicity when the concentration was <= 1.0; between 1.0-1.9, 2.0-2.9, 3.0-3.9, etc. As clinicians this would help us assess the risk better of shooting for a higher level from an efficacy standpoint

9) Did any of the patients develop toxicity before the levels were drawn? Could lead to falsely elevated levels.

10) Suggestion- I think in the discussion readers would benefit from a bit clearer explanation with regard to the statement "these results confirm this is a drug with a narrow therapeutic range." What i mean is that the authors could tell us more about why this toxicity occurring at 2.5-3.3 is so concerning (as the needed levels to achieve AUC/MIC goals are right there as well)

Level of interest: An article of importance in its field

Quality of written English: Not suitable for publication unless extensively edited

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:

none