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: NIKOLAOS MARKOU

Reviewer's report:

This is a highly interesting study on colistin nephrotoxicity, which for the first time explores associations between colistin trough concentrations and AKI. Although presence of a control group would be desirable (a case-control study probably), the finding of a strong association between colistin trough levels and AKI is unequivocal proof of colistin toxicity and perhaps this should be stressed more emphatically in the paper.

Although I understand the difficulties of acquiring full pharmacokinetic curves for colistin, I would still wish for at least peak levels.

Also, I believe that more precise information about dosing is needed. What was daily colistin dosage schedule? Did dosage schedule affect outcome?

What was the survival in patients who developed AKI vs those who did not? Was mortality associated with AKI or with levels of colistin?

Minor comments

Abstract

In the paper, colistin concentration at steady state (Css) refers to colistin trough levels and this should be made clear in the abstract.

Background

Page 4

Line 1: ‘Colistin is an old class … bacteria (MDR-GNB)’: rephrase (colistin is an antibiotic and not a class of antibiotics). Increase in NDR-GNB is one reason but retained antibacterial activity of colistin against MDR-GNB is another for the resurgence of this drug.

Line 6: Provide detailed references for the individual studies in this paragraph as well as in the next.

Methods

As regards definitions: RIFLE criteria were clearly used to not only for stratification but for detection of AKI as well. Rephrase and substitute ‘AKI’ for ‘nephrotoxicity’, as AKI is the evaluated outcome and nephrotoxicity a possible explanation.
It should also be added that RIFLE was estimated with exclusion of the urinary output criterion.

In addition to chronic kidney disease at baseline, were there also any patients with already established AKI at baseline? What about patients with increased creatinine at baseline and no information as regards chronicity?

APACHE II is used on admission to the ICU and outside this context its use is problematic.

Explain why that particular time limit (4 days from start of treatment) was selected for evaluation of nephrotoxicity

Page 5
Line 5: ‘all consecutive’- all is superfluous.
Paragraph 4- line 5: I believe that “with or without kidney damage” is superfluous.
Paragraph 4: Follow up after termination of treatment; obviously follow up was also interrupted in case of death or earlier exit- note should also be made of this

In the statistical analysis section, rephrase 1st and 2nd paragraph.
2nd paragraph: replace ‘range’ with ‘interquartile range’.
3rd paragraph: p value of 0.2

Results
I would stress that none of the patients who developed AKI had need of RRT, while all survivors had full recovery of renal function. Before observing in the text that early recovery was associated with colistin dose reduction, some additional information about the time-course of renal recovery would be welcome.

ROC analysis for nephrotoxic Css levels: please provide data on sensitivity and specificity of the selected breakpoints

Discussion
While colistin levels were the strongest predictor of AKI, no relationship was found between AKI and colistin daily or cumulative dose. This discrepancy merits probably some discussion: was it the result of a low association between colistin dose and colistin levels - eg great variability in colistin levels for the same colistin dose? Were lower troughs of colistin associated with less frequent drug administration?

Conclusion
I would transfer discussion of limitations to the discussion section. I would site as additional limitation the lack of a control group.

Table 1-legend: RIFLE criteria are not used for assessment of nephrotoxicity but for assessment of renal injury. Correct the definitions for RIFLE L and E in the table.
Table 2: correct alignment in the row referring to patients with nephrotoxicity at the end of treatment.

**Level of interest:** An article of importance in its field

**Quality of written English:** Needs some language corrections before being published

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

**Declaration of competing interests:**

I have no competing interests