Author's response to reviews

Title: Quantifying the clinical virulence of Klebsiella pneumoniae producing carbapenemase Klebsiella pneumoniae with a Galleria mellonella model and a pilot study to translate to patient outcomes

Authors:

Milena M McLaughlin (milgriff@nmh.org)
M. Renee Advincula (radvin2@gmail.com)
Michael Malczynski (mmalczyn@nmh.org)
Grace Barajas (glazzara@nmh.org)
Chao Qi (cqi451@northwestern.edu)
Marc H Scheetz (mscheetz@nmh.org)

Version: 4
Date: 3 January 2014

Author's response to reviews: see over
Reviewer: Jason J Pogue

Reviewer's report:
I commend McLaughlin and colleagues for their revised submission. I find that the presentation of the data follows a more logical progression, and the authors do an excellent job of explaining the novel methodology. Furthermore, they do a nice job of emphasizing throughout the exploratory nature of the translational model and the limitations imposed by the lack of power. The revised manuscript present a few new issues that need addressed, but presuming the authors can appropriately address, these data warrant publication.

- Major/Minor Compulsory Revisions

1. Page 7, line 130- please define time to active therapy as different publications have different definitions. Additionally, if the patient received a carbapenem, and it had in vitro activity, was that considered active? I don't think the authors need to justify that one way or the other as the data are mixed, but they need to define for the readership

AU: We thank the reviewer for the comment and appreciate the opportunity to clarify. We have now been less ambiguous in our definitions. We have clearly defined the variable “directed therapy” and “time to directed therapy” in the methods section (lines 137-140 and line 507).

2. Line 147 and throughout- the authors frequently talk about carbapenem use post culture. It is also added to the models, however, there is no real explanation for why. I am unclear the relevance.

AU: We thank the reviewer for the comment and appreciate the opportunity to clarify. Several studies have documented in-vivo activity [1, 2] for carbapenems even in the setting of KPC. We have added this information to the manuscript (lines 140-143).

3. Line 217-219: The authors do an excellent job in the revision explaining the interplay between the virulence score and mortality, suggesting that virulence had no impact on mortality (and perhaps actually associated with a decrease!) This is an extremely important finding, and well described. The authors also point out in their models the importance of APACHE II and mortality. The one aspect that the authors do not comment on, that could still significantly impact mortality is therapy. There have been multiple studies showing the improvement of combination therapy over monotherapy for the treatment of KPC bloodstream infections. Also, assuming these patients received colistin therapy- the question of dosing would inevitably come up. To be fair to the authors, the sample size is too small to truly delve into these
complex issues, but I do believe they could/should do two things: 1) describe the
definitive regimens that patients with KPC received and 2) Add a quick blurb on this
to the discussion (how optimal therapy remains undefined, and the impact of that on
survival cannot be assessed in this study)

AU: We thank the reviewer for the comment. We have added a table of the definitive
regimens received by KPC(+) patients (Table 4, lines 502-507). Also, we have now
included a statement that discusses our limited ability to assess treatment on survival to
the limitations section (lines 340-341).

References

1. Wiskirchen DE, Nordmann P, Crandon J, Nicolau DP. Efficacy of humanized
antibiotic exposures against Enterobacteriaceae producing the OXA-48
carbapenemase in a murine infection model. 53rd Interscience Conference on
2. Wiskirchen DE, Nordmann P, Crandon J, Nicolau DP. In-vivo efficacy of
humanized regimens of carbapenems and comparators against NDM-1
producing Enterobacteriaceae. 53rd Interscience Conference on Antimicrobials
Reviewer: Susan M Logan

Reviewer’s report:
Based on revisions made and explanations provided by authors I feel the manuscript is suitable for publication.

AU: We thank the reviewer for the comment.