Author's response to reviews

Title: A comparison of microbiology and demographics among patients with healthcare-associated, hospital-acquired, and ventilator-associated pneumonia: a retrospective analysis of 1184 patients from a large, international study

Authors:

Andrew A Quartin (aquartin@med.miami.edu)
Ernesto G Scerpella (escerpella@aol.com)
Sailaja Puttagunta (s_puttagunta@yahoo.com)
Daniel H Kett (dkett@med.miami.edu)

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Author's response to reviews: see over
To the *BMC Infectious Diseases* Editorial Team,

On behalf of my co-authors, Andrew Quartin, Ernesto Scerpella, and Sailaja Puttagunta, thank you for your recent response to our submission of the manuscript “A comparison of microbiology and demographics among patients with healthcare-associated, hospital-acquired, and ventilator-associated pneumonia: a retrospective analysis of 1184 patients from a large, international study.”

We thank the two reviewers for their helpful comments, which have led to revisions that we believe have made the manuscript stronger. We have revised the manuscript, with changes shown in track changes in the submitted Word document. A detailed response to the reviewers’ comments is included in this letter.

Thank you again for considering this manuscript for publication in *BMC Infectious Diseases*.

Kind regards,

Daniel Kett, MD
Response to Reviewer Comments

Reviewer 1:

Comment:
The study is based on a retrospective analysis of data previously collected for multicenter trial on MRSA pneumonia and is aimed at evaluating the reliability of the HCAP concept as a risk condition for MDR infections. The manuscript is very well written, concise and clear in its conclusions. Nevertheless I have a few comments on its content.

BACKGROUND When the authors say that references 12-15 describe lower frequencies of MDR infections they are possibly underestimating the differences with USA and Asia studies since in many European studies the microbiological pattern is simply CAP-like. Maybe a clearer description of the current worldwide situation would fit better with the objectives of the paper.

Author response:
We agree. Changes throughout the paper, including near the text referenced by the reviewer (page 4), have been made to reflect this.

Comment:
METHODS Could the authors explain the reasons to modify the HCAP criteria used for study inclusion?

Author response:
The underlying clinical trial (Wunderink et al, 2012) was designed prior to publication of ATS/IDSA guidelines defining HCAP. The study was later amended to include HCAP subjects as they were considered at risk for MRSA infection. The modification was made to reflect data dating back to the start of the study.

Comment:
RESULTS
It is clear that the study mainly reflects a Northern America perspective since the big majority of cases are reported from USA and only few cases were included in Europe where the majority of papers contrasted the “nosocomial” hypothesis of HCAP. In my opinion the authors did not stress enough the geographic differences of the distribution of MDR infections and the fact that this study basically confirms the “American perspective” while European data show a completely different scenario (as reported by references). For this reason in my opinion it would be
desirable a description of eventual microbiological differences between USA HCAP patients and the rest of HCAP cases and a bigger effort to make clear these results are reflecting a local situation.

**Author response:**
Changes have been made to reflect these concerns, which we share. Because non-US cases contribute so little to the HCAP burden in the study population, assessing their microbiology separately is not productive.

**Comment:**
Another observation on table 2 is very low percentage of culture negative cases: does that mean that the authors achieved an etiologic diagnosis in 75% of HCAP, 74% of HAP and 87% of VAP? It sounds too high in comparison to normal rates of microbiological etiology. I suggest checking this data (percentage related to global population including those with no microbiological tests?). Moreover, the polymicrobial etiology has not been described despite the fact that represents the majority of cases. Finally it is not said whether Klebsiella, proteus and the rest of GNB were MDR or not.

**Author response:**
The underlying clinical trial strongly encouraged identification of causative pathogens, with invasive cultures suggested. This emphasis likely resulted in fewer cases being labeled as “culture negative” than is typical of epidemiologic studies with wild-type diagnostic approaches. The distribution of pathogens among patients with potentially polymicrobial infection is now delineated in the text (page 7).

**Comment:**
As it is known that HCAP definition includes heterogeneous patients, a better description of HCAP patients (how many in each HCAP category) is recommended and in particular the percentage of previous hospitalization and previous antibiotic therapy that is the strongest risk factor for MDR infections of patients classified as HCAP. Moreover a multivariate analysis for HCAP patients would help to identify specific factors associated with the risk of MDR infections (for example previous antibiotic therapy rather than nursing home).

**Author response:**
We agree that this data would be very nice to know. Unfortunately, it was not collected for the study.
Comment:
A final aspect that could be discussed further is the fact that HCAP has worse APACHE II score but not a higher mortality: is there any possible explanation for this?

Author response:
APACHE II awards points for both acute and chronic conditions. Because we have only composite scores, we cannot comment with any certainty, but we suspect HCAP patients, having more comorbidities, acquire more APACHE points through chronic rather than acute score components. These may weigh differently on acute mortality.

Reviewer 2:
Comment:
This is a solid secondary analysis of a RCT of treatment for MRSA nosocomial pneumonia and HCAP. I have no major objections to anything the authors did or stated. There are just a couple of points that need to be brought out.
1. To be precise, this is a study of culture-positive pneumonia. A part of the argument against HCAP and broad treatment is that over 50% of patients with HCAP do not have a positive culture, and many of those do just fine on CAP antibiotics. It is important to be very clear on the fact that what is studied here, as in most HCAP literature, is culture-positive pneumonia. This impacts the generalizability of the findings.

Author response:
As is already noted in the manuscript, study criteria might have biased enrollment to favor patients who would ultimately turn out to be culture-positive. On the other hand, a greater effort was probably expended at microbiologic diagnosis after enrollment than would be the case outside of a prospective study setting.

Comment:
2. The authors should consider removing any mention of mortality in this paper. There are several reasons for it, the most important of which is that the numbers seem to stand in a vacuum. That is, the pneumonia groups are clearly different from one another, and the similar mortality rates quoted are neither here nor there without further data or analysis. Furthermore, if I am not mistaken, this ITT population from the trial includes patients who were later excluded from further analysis if they did not have MRSA. So their hospital treatment and course were not followed, is this correct? Without understanding these variables, the raw mortality is not informative.
Author response:
Patients in the ITT population were followed for outcome, irrespective of whether or not they had MRSA. We included mortality outcomes because they demonstrate the equivalent “seriousness” of the various pneumonia types, and make almost no comment regarding mortality beyond this.

Comment:
3. The authors advocate for keeping the HCAP classification as a tool to risk-stratify patients with potential MDR pneumonia presumably so as to treat with appropriately broad spectrum drugs. How do the authors reconcile this conclusion with the findings in Ref #24?

Author response:
Very few patients in the IMPACT-HAP study (reference 24) were untreated for either MRSA or potentially resistant gram negative pathogens. Rather, the question of guideline compliance that the study addressed was primarily whether dual gram negative coverage was helpful. We do not see that paper as conflicting with this one.

Comment:
4. I am having trouble with the MDR designations as used in this paper. More recent literature (see Marangakis et al) has attempted to reduce the definitional confusion around MDR definitions among Gram-negatives in particular. The authors should consider using the updated language when appropriate or come up with an alternative name (e.g., potentially resistant organisms).

Author response:
We have changed the terminology to “potentially multidrug-resistant” where appropriate.

Editorial requirements:
Request:
-- Please include the source of funding in the ‘Competing Interest’ section.

Author response:
We have moved the sentence “This study was sponsored by Pfizer Inc.” from the Acknowledgments section to the Competing Interests section.

Request:
-- Requesting name of ethics committee:
Please update your ethics statement to include the name of the ethics committee that approved your study.

**Author response:**
The underlying clinical trial (Wunderink et al, 2012) was a multicenter international study. We would be happy to provide a list of participating centers, but we feel that listing each IRB/ethics committee in the manuscript would not add, and would rather detract from, the paper.