Author's response to reviews

Title: Imipenem resistance of Pseudomonas in pneumonia: A systematic literature review

Authors:

Marya D Zilberberg (Marya@evimedgroup.org)
Joyce Chen (jchen63@its.jnj.com)
Samir H Mody (smody2@its.jnj.com)
Andrew M Ramsey (andrewram@gmail.com)
Andrew F Shorr (afshorr@dnamail.com)

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Author's response to reviews:

Dear Dr. Norton,

Thank you for the opportunity to address the reviewers’ comments. We believe that our paper is now stronger thanks to the reviewers. In addition to our responses below, we have also now included a flow chart of paper selection, as requested, as Figure 1.

We look forward to your decision.
Marya Zilberberg, MD, MPH

Reviewer: Saad Nseir

Reviewer’s report:

Major Compulsory Revisions:

Dr. Zilberberg and colleagues performed a systematic review of the literature to determine the incidence of resistance to imipenem among patients with pneumonia related to Pseudomonas aeruginosa, clinical success, microbiologic eradication and on-treatment emergence of resistance. The rate of resistance to imipenem was initially high and increased during treatment. In addition, clinical success appeared to be lower in imipenem patients compared with controls. However, microbiologic eradication appeared to be similar in imipenem and control group.

1. The major limitation of this review is the absence of statistical comparison between imipenem and control group with regards to different outcomes.

Therefore, as acknowledged by the authors no definite conclusion could be drawn based on the results presented in the manuscript.

AU: We concur with the reviewer. In fact, on page 14 of the paper we stated the following to explain why we did not attempt quantitative comparisons:
“Second, despite the aggregate sample size of over 4,000 subjects with pneumonia, the subgroup growing out Pseudomonal pathogens was small, accounting for 12% of all cases. Furthermore, since not all endpoints of interest were reported in every study, the number of PA isolates continued to drift lower in specific analyses, lending limited power for drawing firm conclusions. For this reason, and due to inherent limitation of the data (i.e., PA was never the primary focus of the study) we did not attempt to perform statistical testing. Nevertheless, the fact that most sensitivity analyses resulted in similar proportions of resistance detection lends further credibility to the numbers.”

2. No information is provided by the authors on the doses of imipenem and comparator used in different studies. Underdosing is a major risk factor for clinical failure, microbiologic failure and emergence of resistance during treatment. I suppose that the dose of imipenem differed among these studies. Was there any difference in outcomes between patients with different doses? 
AU: All of the studies included were randomized controlled trials comparing imipenem to other regimens. While in most of the trials the dose of imipenem was 500 mg IV Q6 or Q8 hours, it is not consistently reported what the patients actually received. Thus, it is not possible to comment on underdosing.

3. No information is provided on the method used to infuse imipenem. Was it administrated using i.v. bolus or prolonged perfusion? The authors are probably aware that prolonged perfusion of carbapenems could be associated with better outcomes compared with i.v. bolus. Was there any difference in outcomes between patients with different perfusion modes? 
AU: Again, given the nature of the primary studies, imipenem was for the most part administered as 500 mg IV Q6 or 8 hours.

4. Abstract: no information is provided on microbiologic eradication. The authors stated in methods that this was one of the studied outcomes. Therefore, results regarding this outcome should be provided in results and in conclusion section.
AU: We have now added the following to the Results section:
“Microbiologic eradication was achieved in 47.6% (range 0.0%-100.0%) of isolates in the imipenem and 52.8% (range 0.0%-100.0%) in the comparator groups.”
We have also added a corresponding statement to the Conclusions section.
In addition, conclusion should be limited to study results. Please delete the statement on how “the current environment of resistance….”
AU: We have deleted this sentence as requested.

5. No clear definition is given for outcomes. Please define P. aeruginosa resistance, clinical success, microbiologic eradication, and emergence of resistance. Have all these studies used similar definitions for these outcomes? 
AU: We used the definitions as they were provided in each primary study. We have now added the following to the Methods section on page 5 to clarify this
“All outcome definitions were those used in the respective primary studies.”

6. The results presented in tables 2, and 3 should be completed by providing actual values and not only percentages. In addition, the last line of Table 2 is misleading since results were not available for all outcomes. Therefore, authors should provide the results as number of patients with each outcome / number of patients for whom the information was available (%).

AU: To clarify: The numbers in the column labeled “PA isolates (n)” in Table 2 represent the denominator for each of the respective proportions in the subsequent columns. Thus, the numerators can be easily derived. The last 2 lines simply represent the aggregate of what appears in the rows above. The footnote to the table states the following:

“empty cells indicate that the corresponding data were not reported”

7. In Table 2, it appears that the number of patients with PA isolates was higher in subgroup analysis on VAP performed by Dr. Shorr (ref #44) than in the initial study performed by Dr. West (ref #46), which is technically impossible. Please comment.

AU: The reviewer has astutely pointed out a discrepancy between the two reports. Both West and Shorr report the same total number of PA isolates in the two arms (n=34), but the distribution between the West publication and the Shorr analysis has shifted by 1 isolate being moved from the levofloxacino to the imipenem group. We have noted this now in the following footnote to the table:

“†Although the total pseudomonal isolates in the two arms of each analysis add up to the same number (n=34), the distribution between the arms is different presumably due to reclassification of a single PA isolate from the levofloxacino to the imipenem arm, which occurred between the West [46] publication and the Shorr [44] analysis.”

8. I am not sure that the same patients could be included twice in this review (ref # 44 and 46) even though some of the outcomes were not provided by the initial study.

AU: We chose to include both study to maximize the data points provided. We explained our rationale on page 6 in the following way:

“To avoid double counting, we ultimately excluded both of the meta-analyses (36, 37), since all relevant papers examined therein had already been included, as well as one additional primary report (38) which duplicated a previously reported study (57). One exception was made to include the study by Shorr and coworkers (44), which is a subgroup analysis of VAP patients enrolled into another study of NP in our study set (46). This was done for the following reasons: 1). Shorr et al. (44), but not West and colleagues (46), reported on several outcomes of primary interest (specifically PA resistance emergence) in the current review, 2). Eliminating the Shorr study from the analyses did not alter the results substantively, and 3). Several of the sensitivity analyses used only
one or the other of the studies, but not both (see below).”

9. Table 3: lines 5, 12, 15, 18, and 21: references?
AU: We have to apologize, as we are not sure what the reviewer is referring to. All references for each outcome are provided in brackets in the corresponding column.

10. Discussion: page 12, line 5: what means “For other interventions”?
AU: We have substituted the word “comparator” for the word “other” to clarify.

11. Discussion: page 12, para 2, line 1-6: this section overlaps with the introduction and should be deleted.
AU: We have now replaced the sentences in question with the following clause: “As antibiotic resistance continues to escalate among both gram-positive and gram-negative pathogens (1, 3-5),”

Reviewer: Ilias Siempos
Reviewer’s report:
Zilberberg and colleagues performed a systematic review on the imipenem resistance of Pseudomonas aeruginosa in patients with pneumonia (either community-acquired or nosocomial). The topic (i.e. antimicrobial resistance) is hot and, thus, their review is of value.

Their contribution may be improved by the following revisions.

Minor Essential Revisions:

1. Zilberberg and colleagues were aware of observational studies that reported rates of imipenem resistance among Pseudomonas aeruginosa as high as 20%. Having this information into mind, they attempted to exploit another source of publications, namely interventional studies and, specifically, randomized controlled trials, to better estimate the burden of Pseudomonas aeruginosa imipenem resistance in pneumonia. They provided a rationale for this in the Discussion section of their paper (third paragraph of the Discussion); thus, the reader should wait until the Discussion section to be informed why observational studies were not considered for this review. I think that this paragraph (third paragraph of the Discussion) should be moved in the Introduction of their paper.

AU: We appreciate the reviewer’s attention to this detail. In the Introduction, second paragraph starts with the following sentence: “PA in particular is reported to have 20% resistance rates to imipenem, a drug considered to be first-line therapy for ventilator-associated pneumonia, for example, and one that is frequently utilized when the suspicion of PA is high”. In the same section the next-to-last sentence clarifies that the data on resistance
rates come from observational studies (epidemiologic and microbiology):

“While several primary epidemiologic and microbiology studies have
demonstrated reduced imipenem susceptibility among PA (4, 5, 11, 12), the full
burden of emerging imipenem resistance reported in the literature has not been
quantified. “

Given space considerations, we felt that these concise statements set the
rationale adequately for our examination of the RCTs. Please, let us know if you
still feel that we need to clarify.

2. Abstract, Background: If we know that imipenem resistance of PA is # 20%,
which is the value of this review? The authors may want to delete the sentence
“# 20% of which are resistant to imipenem” or write “# 20% of which are resistant
to imipenem as reported by observational studies. We sought to identify the
burden of PA imipenem resistance in pneumonia by exploiting the information
given by randomized controlled trials”.

AU: thank you for pointing this out. We have now done as you have advised, and
the sentence reads as follows:

“Pneumonia, and particularly nosocomial (NP) and ventilator-associated
pneumonias (VAP), results in high morbidity and costs. NPs in particular are
likely to be caused by Pseudomonas aeruginosa (PA), ~20% of which in
observational studies are resistant to imipenem.”

3. Abstract, Results: How many trials referred to community-acquired pneumonia
and how many to nosocomial pneumonia? This information should be provided in
the Abstract.

AU: Because of space considerations we refrained from providing such detail in
the abstract, particularly given that some studies were mixed. The information is
easily available to the reader in Table 1.

4. Abstract, Conclusions: The focus of the paper was to “identify the burden of
PA imipenem resistance in pneumonia”. Thus, the first sentence of the
Conclusions should directly respond to this question.

AU: The first sentence of the Conclusions now reads as follows:

“In the 15 years of RCTs of imipenem for pneumonia, PA imipenem resistance
rates are high, and PA clinical success and microbiologic eradication rates are
directionally lower for imipenem than for comparators.”

5. Methods: Given that the authors chose to exploit interventional studies to
identify the burden of PA imipenem resistance, why their search was limited to
randomized controlled trials? Non-randomized trials could also be used. A
rationale for their choice should be provided.
AU: We did not exclude other types of clinical trials, as noted in this sentence in the Methods section:

“We restricted this search to papers published in English between January 1993 and December 2008 that were randomized controlled trials, clinical trials, or meta-analyses.”

6. Methods: Please state in detail the inclusion criteria for this systematic review.
AU: In the third para in Methods section on pages 4-5, we have altered the sentence to read:

“The outcomes of interest were clinical and microbiological eradication rates for PA among the included patients, as well as initial and emerging resistance of PA to imipenem and comparator drugs, and PA superinfection rates. “

We have also added the following last sentence to the same paragraph:

“Studies were excluded if they failed to report at least one of the outcomes of interest.” We hope that this clarifies our inclusion/exclusion criteria.

7. Methods: The definition of “clinical success” may be variable in the included randomized controlled trials. Please state the definition of “clinical success” used for this systematic review.
AU: We have now added the following sentence to para 4 of the Methods on page 5, to clarify the definitions of the outcomes:

“All outcome definitions were those used in the respective primary studies.”

8. Methods, “all pooling was performed qualitatively and no attempt at quantitative analyses was made”: Please provide here a rationale for this choice.
AU: We provide a lengthy explanation for this choice in the Discussion section on page 14:

“…despite the aggregate sample size of over 4,000 subjects with pneumonia, the subgroup growing out Pseudomonal pathogens was small, accounting for 12% of all cases. Furthermore, since not all endpoints of interest were reported in every study, the number of PA isolates continued to drift lower in specific analyses, lending limited power for drawing firm conclusions. For this reason, and due to inherent limitation of the data (i.e., PA was never the primary focus of the study) we did not attempt to perform statistical testing.”

9. Results: Ranges as high as 0.0%-100.0% were found in several cases. Please comment on it.
AU: We ask that the reviewer clarify what comment we should add. The ranges signify the results of the primary studies.

10. Results: Usage of a statistical test to compare (for example) the clinical success rates of both groups (imipenem versus other antibiotics) may be required.
AU: We again refer the reviewer to the paragraph in the Discussion section on page 14 explaining why the validity of statistical comparisons would be questionable:

“...despite the aggregate sample size of over 4,000 subjects with pneumonia, the subgroup growing out Pseudomonal pathogens was small, accounting for 12% of all cases. Furthermore, since not all endpoints of interest were reported in every study, the number of PA isolates continued to drift lower in specific analyses, lending limited power for drawing firm conclusions. For this reason, and due to inherent limitation of the data (i.e., PA was never the primary focus of the study) we did not attempt to perform statistical testing.”

11. Discussion: A meta-analysis recently published by our research group (Siempos II, et al. Carbapenems for the treatment of immunocompetent adult patients with nosocomial pneumonia. Eur Respir J 2007;29:548-60) reported that development of resistance of Pseudomonas aeruginosa during treatment was increased in patients treated with carbapenems (mainly imipenem) compared to other antimicrobials and that treatment of patients with nosocomial pneumonia due to P. aeruginosa with carbapenems (mainly imipenem) was associated with lower treatment success when compared to other antimicrobials. The authors may want to mention this meta-analysis.

AU: We thank the reviewer for bringing up this important study. We have now inserted an additional paragraph in the Discussion section on page 13:

“Our study has additionally documented substantial rates of emergent PA resistance while on treatment, particularly with imipenem. This result echoes the data reported in the meta-analysis by Siempos and colleagues, where development of resistance by PA during treatment for nosocomial pneumonia was higher in patients on carbapenems (mainly imipenem) than other antimicrobials, and that carbapenems were associated with lower treatment success when compared to other antimicrobials (64).”

12. Please edit the paper for typos, for example “21 included studies” (Results, 5th paragraph).

AU: Thank you!

Discretionary Revisions:
1. Title: “Pseudomonas aeruginosa” instead of “Pseudomonas” could be written.

AU: In some of the studies the genus name only was used, and we decided to stick to that for accuracy.

2. Methods: Databases other than MEDLINE, such as Scopus, could also be used.

AU: We limited ourselves to Medline, as this provides a relatively complete
listing.

3. Methods: Quality assessment of included randomized controlled trials could be performed.
AU: Because we did not perform any statistical testing, we chose not to report these data.