Comparative Effectiveness Review Disposition of Comments Report

Research Review Title: *Pharmacokinetic/Pharmacodynamic Measures for Guiding Antibiotic Treatment for Nosocomial Pneumonia*

Draft review available for public comment from October 30, 2013 to November 26, 2013.

Research Review Citation: Lux LJ, Posey RE, Daniels LS, Henke DC, Durham C, Jonas DE, Lohr KN. Pharmacokinetic/Pharmacodynamic Measures for Guiding Antibiotic Treatment for Hospital-Acquired Pneumonia. Comparative Effectiveness Review No. 136. (Prepared by the RTI–University of North Carolina at Chapel Hill Evidence-based Practice Center under Contract No. 290-2012-00008-I.) AHRQ Publication No. 14(15)-EHC032-EF. Rockville, MD: Agency for Healthcare Research and Quality; November 2014. www.effectivehealthcare.ahrq.gov/reports/final.cfm.

Comments to Research Review

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The tables below include the responses by the authors of the review to each comment that was submitted for this draft review. The responses to comments in this disposition report are those of the authors, who are responsible for its contents, and do not necessarily represent the views of the Agency for Healthcare Research and Quality.

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Commentator & Affiliation	Section	Comment	Final Response
Peer Reviewer #1	**Executive Summary**	The Executive Summary on page ES-1 or page 8/95, is well done and underscores the lack of convincing data from which to draw firm conclusions on importance and efficacy of PK/PD therapy. As stated above, nosocomial pneumonia included HAP, HCAP and VAP as defined in the 2005 ATS/IDSA Guidelines. However, each of these types of pneumonia involve heterogenous patient populations, with a wide spectrum of pathogens, as well as differences in disease severity and underlying host diseases. As suggested later, perhaps VAP data should have been evaluated separately from HAP and HCAP data. Of note is that recommendations to increase dosing levels for many antibiotics were included in the ATS/IDSA guidelines released later in 2005, and may not have been routinely used until a later time. Also, there may be different responses for therapy in emerging bacterial pathogens, such as Staphylococcus aureus (methicillin-sensitive-MSSA & methicillin-resistant-MRSA), as well as Pseudomonas-aeruginosa and other multi-drug resistant (MDR) enteric Gram-negative pathogens. For example, some S. aureus isolates have higher minimum inhibitory concentrations (MICs) to vancomycin that may increase the clinical failure rates and some P. aeruginosa strains produce toxins that increase complications and mortality.	Thank you for your comment. Unfortunately, only one study that qualified for inclusion (Lorente, 2004) looked in patients with VAP separately. Most studies looked broadly at "nosocomial pneumonia" without a breakdown by HAP or VAP. Additional information regarding S. aureus and other pathogens with high MICs was added to the text.
Peer Reviewer #1	**Introduction**	Executive summary was excellent	Thank you for your comment.
Peer Reviewer #2	**Introduction**	Specifically, the epidemiology data in the first few paragraphs is dated (published in a review that is 9 years old, meaning the data is even older than that).	Unfortunately, there are no newer epidemiologic data; all of the more current publications refer back to the citations from the 2005 ATS/IDSA guidelines or the 2008 Chawla paper.
Peer Reviewer #2	**Introduction**	Line 44-51 on page 1: The pathogen information is slightly misleading, and almost makes S. aureus an afterthought, whereas it is equally as prevalent in nosocomial pneumonia as many of the other organisms listed (Kollef, Chest 2006 may be a reference to consider).	We have revised the text to include more detail regarding S. aureus. both in the Introduction and elsewhere throughout the report. HAP is most often caused by bacterial pathogens, and it may be polymicrobial. *Staphyloccus aureus (S. aureus)*—especially methicillin-resistant *S. aureus (MRSA*)—and aerobic Gram-negative bacilli, including *Pseudomonas aeruginosa*, *Escherichia coli*, *Klebsiella pneumoniae*, and *Acinetobacter* species, are the common causes of HAP.

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Peer Reviewer #2	**Introduction**	Page 3, line 55 – discussing the increasing incidence of multi drug resistant Gram-negative organisms (partially discussed on page 5, line 39), or increased MICs of MRSA organisms should be added to the introduction.	We revised the text to add more information on MRSA MICs
Peer Reviewer #2	**Introduction**	Reference 10 is from Up to Date; could original articles be referenced?	We have updated the references to include all of the citations used by Dr. Fine in his analysis (References 10 through 21).
Peer Reviewer #2	**Introduction**	Overall, the introduction is framed very well, and the authors effectively "frame the gap" in the literature.	Thank you for your comment.
Peer Reviewer #2	**Introduction**	Page 5, vancomycin and S. aureus mentioned, which was very helpful and clinically relevant.	Thank you for your comment.
Peer Reviewer #3	**Introduction**	Detailed and accurate introduction that explained all issues related to the use of PK/PD principles in optimizing antibacterial therapy.	Thank you for your comment.
Peer Reviewer #4	**Introduction**	The Intro is generally good. My only comment is that on page 1 of the Intro the authors use HAP to include VAP and HCAP. While VAP fits nicely into the HAP definition, HCAP does not. In fact, the distinction of HCAP is that, just like CAP, its onset is frequently in the community rather than in the hospital. Thus, if anything is a subset, it is HAP that is a subset of HCAP.	These are the terms used in the ATS/IDSA 2005 review and in many research publications. We have added text to clarify why HCAP has been included (it is treated the same way as HAP).
Peer Reviewer #5	**Introduction**	It is important to recognize that many of the pharmacodynamically optimized dosing schemes evaluated in "PK/PD" focused clinical trials, both randomized and observational, are optimized at onset by use of well-described mathematical modeling techniques (population PK modeling and Monte Carlo simulation). I ask that the authors refer to the article by Dr. Drusano in Nat Rev Microbiol for a detailed review of the methods (PMID: 15031728). By optimizing up-front, you ensure that the vast majority (>90%) of patients, even critically ill patients with highly variable PK profiles, will receive an antibiotic regimen that will achieve the pharmacodynamic target associated with maximal effect over the range of MIC values among potential pathogens. In these types of trials, the optimized PK/PD regimen is typically compared to the current standard of care. Given the data supporting the importance of early, appropriate therapy, it is critical to evaluate the initial regimen received within the first 24-48 hours vs. the regimen received at a later time point that is optimized.	Thank you for your comment. This reference has been reviewed and included in the background section of the report where optimal dosing based on PK/PD principles is discussed. We did not evaluate the effect of early optimized therapy. We agree that the first 24 to 48 hours is a critical time, but this is an entirely different systematic review question and not part of the scope of this review. We did not include optimizing dosing studies based on prior PK/PD modeling data as these are a "one size fits all" approach. We looked for studies which were based on individual data for patients.

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TEP Reviewer #1	**Introduction**	Page 1 and ES-1 While I have no disagreement with the inclusion of HCAP in the target population, the statement that "Unless otherwise specified, HAP includes VAP and HCAP" is going to raise eyebrows. Nobody in this field considers HCAP as a subset of HAP despite the fact that they share some similarities. Would reword to avoid calling HCAP a subset of HAP. Just say that the target population includes HAP (including VAP) and HCAP.	Our introduction states that the target population is HAP which includes VAP and HCAP. This is the same approach used in the 2005 ATS/IDSA guidelines. As none of the included studies were specifically in patients with HCAP, this should not affect our results.
TEP Reviewer #1	**Introduction**	PAge ES-1 and 1, second bullet in the middle of the page. Agree with all, except the final phrase "its prognosis is poor". While many patients with VAP die, the majority die due to their underlying illness. Most studies have shown an attributable mortality due to VAP of 10% or less. Would clarify or delete.	We have revised the introduction to state that due to the difficulty in treating VAP, its prognosis can be poor. As mortality due to VAP was not separated from all-cause mortality in the studies included in this review, we were not able to examine this issue in the results section.
TEP Reviewer #4	**Introduction**	Please look at the abbreviation section under Figure A in the executive summary - there is a typo there under AUC.	Thank you for your comment. This error has been corrected.
TEP Reviewer #4	**Introduction**	Good job clearly defining HAP, VAP, HCAP; the notion of using PK/PD measures for dosing and monitoring of antibiotics as well as the scope of the reviews and the key clinical questions which the authors are trying to answer.	Thank you for your comment.
TEP Reviewer #5	**Introduction**	Well written and of good size.	Thank you for your comment.
Peer Reviewer #1	**Methods**	Some questions on the risk of bias methods used.	The method used in this report for rating Risk of Bias is the agreed-upon methodology for AHRQ, and our Risk of Bias Tables offer transparency of judgment. As stated in our Methods section, "To assess the risk of bias (i.e., internal validity) of studies, we applied predefined criteria based on the Agency for Healthcare Research and Quality (AHRQ) Methods Guide. This approach uses questions to assess selection bias, confounding, performance bias, detection bias, and attrition bias—that is, it addresses issues of adequacy of randomization, allocation concealment, similarity of groups at baseline, masking, attrition, whether intention-to-treat analysis was used, method of handling dropouts and missing data, validity and reliability of outcome measures, and treatment fidelity."

Commentator & Affiliation	Section	Comment	Final Response
Peer Reviewer #2	**Methods**	Criteria were justifiable, and search strategies were well stated. All provided strict measure for the review, though external/clinical validity may have been compromised, as many Infectious Diseases studies don't follow such stringent criteria. Outcome measures were appropriately chosen, and reflective of the current body of ID literature. All work was appropriately double/triple-reviewed, which enhanced the strength of the conclusions.	Thank you for your comment. In designing this review we have tried to be as inclusive of studies as possible, understanding that there is not much literature addressing these questions. It is also important to note that this review is a systematic review of the evidence and not a clinical practice guideline. While we have identified little evidence, we believe it is important and have outlined a number of specific research needs to be addressed in future studies.
Peer Reviewer #3	**Methods**	This is a detailed review with a solid and explicit search strategy. Outcome measures and statistical methods are appropriate.	Thank you for your comment.
Peer Reviewer #4	**Methods**	I have no comments on the Methods, other than that they are appropriate.	Thank you for your comment.
Peer Reviewer #5	**Methods**	Rather than considering studies that compared initial PK/PD dosed optimized regimens vs. standard of care in KQ 1, the authors "required studies to assess an intervention focused on using PK/PD measures to inform decisions: serum concentration, volume of distribution, protein binding, time above MIC, ratio of AUC to MIC." By doing so, the authors only evaluated the effect of therapeutic drug monitoring and adjustments downstream in care. More importantly, the authors negated their ability to evaluate the effect of early, optimized therapy. As mentioned above, the critical time window to delivery optimal antibiotic therapy is the first 24 to 48 hours. Studies that evaluated therapeutic drug monitoring after the availability of measured drug concentration do not fully assess this. Because of their systematic review design, it is not surprising they only ended up with 1 study for KQ1 (less than 0.1% of possible studies). From policy perspective, it is more important to evaluate the impact of optimized doses schemes at onset vs. standard of care since this is what has been mostly evaluated in the literature. In addition, therapeutic drug monitoring (TDM) is only performed for a few selected antibiotics in practice (vancomycin and aminoglycosides). Since TDM is not commonly performed, the impact of this review as currently constructed will have minimal effect on current practice and policy.	This is correct, the evaluation of early optimized therapy was not the intent of this systematic review, and therefore these studies do not fit within our PICOTS framework. In this review, we have evaluated the effect of therapeutic drug monitoring and adjustments downstream in care. We did not evaluate the effect of early optimized therapy. We agree that the first 24 to 48 hours is a critical time, but this is an entirely different systematic review question and not part of the scope of this review. We did not include optimizing dosing studies based on prior PK/PD modeling data, as these are a "one size fits all" approach. We looked for studies which were based on individual data for patients.
TEP Reviewer #1	**Methods**	Yes	Thank you for your comment.

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TEP Reviewer #2	**Methods**	The methods are appropriate, including: search strategies, outcome measures, and statistical methods.	Thank you for your comment.
TEP Reviewer #3	**Methods**	Limiting the search to HAP led to a problematic scarcity of eligible articles for inclusion in the review. Recognizing that redoing the study entirely at this point is not practical, a stronger justification needs to be provided in the paper for restricting the focus to this condition. A review looking at use of PK/PD on clinical outcomes in a broader range of infections (e.g., treatment of severe sepsis/septic shock) might have yielded better results (in this case, success equates to a sufficient # of articles that allows one to draw a more definitive conclusion).	The focus on the specified nosocomial pneumonia population (HAP/VAP/HCAP) was specified by the nominating stakeholder panel and our Key Informants and the Technical Expert Panel affirmed this focus on the lung. As nosocomial pneumonia is associated with a wider spectrum of pathogens, a greater degree of drug resistance, and a higher risk for multi-drug resistance, the effects of PK/PD interventions are expected to be different from other conditions employing PK/PD measures, such as sepsis. For example, serum concentrations for other conditions, such as sepsis, do not necessarily correlate with optimizing dosing for pneumonia.
TEP Reviewer #4	**Methods**	There are some abbreviations such as PICOTS, EPC program which are spelled out in the paper but not so in the executive summary. Readers who look initially or only at executive summary may benefit if these abbreviations are spelled out.	Thank you for your comment. This error has been corrected.
TEP Reviewer #4	**Methods**	The inclusion and exclusion criteria seem justified. The search strategy are clearly stated and logical. The definitions for outcome measures seem appropriate. The statistical methods used appear appropriate.	Thank you for your comment.
TEP Reviewer #5	**Methods**	Inclusion and exclusion criteria are justifiable, and search strategies are well stated and logical. The statistical methods and the outcome measures are appropriate.	Thank you for your comment.

Commentator & Affiliation	Section	Comment	Final Response
Peer Reviewer #1	**Results**	P 15-16/95. Key Question #1 PK/PD data for dosing or monitoring are summarized in Table B, which demonstrated significantly better (p <0.001) outcomes, defined as lower clinical failure and lower mortality, but issues of potential bias in this study were raised. See excellent Figure A and discussion on P 11/95. As noted on P 38/95 on prospective cohort study of MIC monitoring and serum concentrations versus those who had one test or none, found significantly improved outcomes in terms of cure rates and mortality shown on Page 39/95: Tables 4-5. Summary of the study by Scaglione et al in 2009 which reported (clinical success 82% vs 68%, p = NS), clinical failure (18% vs 32%, p<0.001) a trend toward decreased ventilator days (p<0.09) and reduced mortality (10% vs 24%, p<0.001). However, the study was judged to have a high risk of bias, as did many of the other studies shown in Table 4. (page 37/95). The question arises how good and reproducible is bias scale?	This specific question relates to risk of bias considerations (rather than grading strength of evidence per se), and the approach has a long history for the EPC program and corresponds well to internationally accepted methods and instruments for recording risk of bias ratings. It is true that inter-rater reliability or reproducibility (for risk of bias determinations for individual studies) generally has not been well tested; for that reason, we cannot answer the reviewer's question about "how good and reproducible" the instruments and scales are. Nonetheless our approach includes a common (internationally recognized) approach of published instruments and dual, independent ratings and, when necessary, adjudication by a third, senior (experienced) systematic reviewer. We believe that the description in our methods section, "To assess the risk of bias (i.e., internal validity) of studies, we applied predefined criteria based on the Agency for Healthcare Research and Quality (AHRQ) Methods Guide.[a] This approach uses questions to assess selection bias, confounding, performance bias, detection bias, and attrition bias—that is, it addresses issues of adequacy of randomization, allocation concealment, similarity of groups at baseline, masking, attrition, whether intention-to-treat analysis was used, method of handling dropouts and missing data, validity and reliability of outcome measures, and treatment fidelity. We would note that risk of bias plays directly into methods for grading strength of evidence in this review, and that step is based on the AHRQ *Methods Guide,* consistent application of the methods, and transparently recording decisions. The method we used for grading the strength of evidence, which includes the domains for of risk of bias (formerly "quality" and understood to be internal validity) together with consistency across studies, directness, and precision, is the agreed-upon methodology for AHRQ. Risk of bias as a domain for strength of evidence is now referred to as "study limitations." The entire approach corresponds to a great degree to that used in many organizations (namely, GRADE).
Peer Reviewer #1	**Results**	P 18/95. Key Question #2: evidence was insufficient to draw conclusions about continuous flow therapy vs intermittent infusions of beta-lactam antibiotics. (Table C)	Thank you for your comment.
Peer Reviewer #1	**Results**	NO STUDIES QUALIFIED	Thank you for your comment.

Commentator & Affiliation	Section	Comment	Final Response
Peer Reviewer #1	**Results**	Details in results section were very good, messages explicit, and the figures, tables and key messages were well done. Studies reviewed over the study period were well done.	Thank you for your comment.
Peer Reviewer #2	**Results**	Only six studies were chosen, which significantly limits the review as there is a considerable amount of excellent peer review well done retrospective studies on the subject that should be included. If the paper is intended to help make decisions guiding clinical practice, more detail would strengthen the results section.	While retrospective studies were included in this comparative effectiveness review, only studies with an eligible comparator were included. As most retrospective studies in the field did not include a comparator, they were excluded for this reason. We have added text to our Methods section regarding the inclusion criteria and the need for an eligible comparator. It is also important to note that this review is a systematic review of the evidence and not a clinical practice guideline.
Peer Reviewer #2	**Results**	If the paper is intended to help make decisions guiding clinical practice, more detail would strengthen the results section. Specifically: What organisms were studied?	Information on the organisms studied has been added to the results section. Our included studies reported on a wide variety of pathogens, and did not consistently break out their results by pathogen, therefore it was not possible to break down the outcome results by pathogen in a way that provides meaningful data.
Peer Reviewer #2	**Results**	If the paper is intended to help make decisions guiding clinical practice, more detail would strengthen the results section. Specifically: What were the MICs of the organisms (if available)?	Information on MIC was provided in only three of the six included studies and we have added this data to the results for KQ2.
Peer Reviewer #2	**Results**	If the paper is intended to help make decisions guiding clinical practice, more detail would strengthen the results section. Specifically: What were baseline characteristics of patients in these studies?	More information regarding patients' baseline characteristics, particularly renal clearance, APACHE scores, and other measures of illness at baseline, have been added to the text in the results section.
Peer Reviewer #2	**Results**	M If the paper is intended to help make decisions guiding clinical practice, more detail would strengthen the results section. Specifically: Why were 3/6 considered high bias? Page 12 stated that high risk of bias could invalidate results, yet three out of six studies in the review were considered high risk of bias	We have added reasons for the high risk of bias for each study into the text.

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Peer Reviewer #2	**Results**	Page 17, line 9: the study with reference #42 was considered poorly constructed. Why?	We have revised the text to make this more clear regarding the 2009 Scaglione study in KQ1. One prospective cohort study (high risk of bias) found significantly improved outcomes in terms of cure rates and mortality, although both measures were poorly constructed. Specifically, the study defined "cure" as no further specimens obtained for microbiologic testing, and the mortality outcome included both death and patients who left the hospital against medical advice.
Peer Reviewer #2	**Results**	Page 18, line 52 and onto page 19 – not enough detail. Again, given that there were so few studies, more detail about the studies, the baseline characteristics, organisms, dosing would have added to the results. Going back to the original studies would provide the information to the reader, but explicitly stating it in the results would strengthen the review.	In the results section, we have added more details when available on baseline characteristics, particularly renal clearance, APACHE scores, and other measures of illness. These can be found in Table 4, Table 7 and in the text. Table 10 presents the organism characteristics for KQ2. Information on dosages used in each included study are located in the Appendix, Evidence Table D-3.
Peer Reviewer #2	**Results**	The results for key question 3 are unclear. Would Dr. Moise's work on using PK/PD measures to dose vancomycin for S. aureus pneumonia not fit here? If not, why not? If there really are no studies that met the criteria, it would have been helpful to read why not.	Thank you for your suggestion. We have reviewed Dr. Moise's work, and unfortunately, it does not fit our inclusion criteria, as it does not include a breakdown of data for patients with a nosocomial infection.
Peer Reviewer #2	**Results**	More detail would strengthen the results section. Specifically: Information on outcomes of extended infusions or high dose on therapy of gram negative bacteria with high MIC yet within the susceptible or intermediate range.	This level of granularity was not given in the studies included, as none of the included studies related eligible outcomes data to MIC or pathogen type. We have added more information, when available.
Peer Reviewer #3	**Results**	Authors showed appropriate amount of results. Answers for key questions were presented with adequate details and precision. Due to the nature of the review, there was no plenty of figures and tables included.	Thank you for your comment.
Peer Reviewer #4	**Results**	The Results are presented well and fully.	Thank you for your comment.
Peer Reviewer #5	**Results**	It is unclear why they excluded so many references for KQ2. I was unable to locate to two critical references in their general review for KQ2 (Dulhunty JM et al. Clin Infect Dis. 2013 Jan;56(2):236-44 and Falagas ME et al. Clin Infect Dis2012;56:272-82	We have examined the studies referenced here, and none meet our inclusion criteria. The Dulhunty paper is in a population with sepsis, and Falagas does not mention pneumonia.

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Peer Reviewer #5	**Results**	The results posted in Table 7 do not match the available data. The study by Lorente et al is referenced in the text but not included in Table 7. In the study by Lorente and colleagues, clinical success was higher with continuous infusion. This group also demonstrated comparable outcomes with continuous infusion of meropenem vs. intermittent dosing.	The Lorente study is retrospective and therefore ineligible as evidence for the intermediate outcomes it reported, although it did meet our inclusion criteria for harms data.
Peer Reviewer #5	**Results**	It is unclear why there was not attempt to stratify the findings by pathogen (i.e. Pseudomonas aeruginosa) or MIC value. The recent editorial by Lodise and Drusano in Clinical Infectious Diseases (PMID: 23074312) provides a good overview as to why prolonged infusions are only likely to be beneficial for certain populations.	Information on the organisms studied has been added to the results section. Unfortunately though the included studies reported on a wide variety of pathogens, their outcomes data does not stratify by pathogen or infecting MIC value
Peer Reviewer #5	**Results**	In light of the comments offered above, the authors should reconsider the focus on the review for KQ1. For KQ2, I anticipate many studies are missing and the results need to be reformulated based on a re-review of the data. When adding data to KQ2, the authors should stratify the findings by pathogen and infecting MIC value.	The scope and focus of the KQs were determined following discussion with the KIs and TEP. Unfortunately, much of the available literature on the topic did not include analyses for a HAP population, limiting the potential number of included studies, as the initial question asked specifically about HAP and was not interested in other populations. The studies which meet the eligibility criteria for KQ2 do not include stratification by pathogen or infecting MIC value in their outcomes data.
TEP Reviewer #1	**Results**	I can't remember why studies addressing once daily dosing of aminoglycosides were not included. This may result in criticism.	Studies addressing once daily dosing of aminoglycosides were not included because studies were required to have a comparator PK/PD target goal for inclusion. As none of the once daily aminoglycoside studies fit this profile, none were included.
TEP Reviewer #2	**Results**	The results section is clear and sufficiently descriptive.	Thank you for your comment.

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TEP Reviewer #3	**Results**	Given the results, a more detailed recap of the process for how this specific question was prioritized by AHRQ as part of the EPC program would also be useful (i.e., readers will want to know why federal funding was allocated to pursue this particular area as opposed to say, a CER review of different antibiotics in treating HAP, which would be much more helpful to most frontline clinicians). I do realize that there was an opportunity for public comments on the study design, and that this was the stage where the overall approach could be more readily addressed.	Our topic was nominated by a stakeholder panel. This panel was convened for the purpose of identifying relevant topics for systematic review. All topics are reviewed and assessed for appropriateness for systematic review (see EHC website for information on the process for selecting topics: www.effectivehealthcare.ahrq.gov/index.cfm/submit-a-suggestion-for-research/how-are-research-topics-chosen). Once a topic is assessed and determined to be appropriate for further product development in the EHC program, it is assigned to a research team, and further development of the topic occurs with the input of key informants and technical experts. (see EHC website for information on the research process: www.effectivehealthcare.ahrq.gov/index.cfm/submit-a-suggestion-for-research/what-is-the-research-process)
TEP Reviewer #3	**Results**	Table 7, page 41. Please flip continuous infusion/intermittent infusion formatting convention so that it matches the convention used in Table 8.	Thank you for your comment. The table has been revised.
TEP Reviewer #4	**Results**	The amount of detail in results section seem appropriate. Characteristics of the studies are well described. The key messages are explicit and applicable. The figures, tables and appendices are sufficiently descriptive. I did not notice any studies which should have been included or excluded.	Thank you for your comment.
TEP Reviewer #5	**Results**	No further comments on results.	Thank you for your comment.
Peer Reviewer #1	**Discussion/ Conclusion**	P 23/95. Discussion: Key Points: there is a dearth of evidence for the use of PK/PD measures in dosing or monitoring and strength of evidence was judged as poor. There was a lack of data to support the use of continuous infusion of betalactam antibiotics compared to intermittent infusion. Overall Conclusion: theoretical data is not supported by current clinical data.	Thank you for your comment.
Peer Reviewer #1	**Discussion/ Conclusion**	Data on cost should also be considered	We engaged a panel of Key Informants and a Technical Expert Panel to help with determining the scope of this project, including identifying the most important outcomes to include. Based on input from the KIs and TEP, although important, cost was not selected as one of the prioritized final outcomes to include in this review. We have added text regarding cost effectiveness of the use of PK/PD measures in the discussion section.

Commentator & Affiliation	Section	Comment	Final Response
Peer Reviewer #1	**Discussion/ Conclusion**	P 25-26/95; Research Gaps are nicely summarized and also included on page ES-11. Specific recommendations for study design, dosing, monitoring antibiotic levels should be included and highlighted. The potential advantages of optimizing dosing strategies in the clinical setting may translate in to decreased antibiotic resistance and improved outcomes. Recommendations for specific dosing of antibiotic for infections such as pneumonia are needed, as well as defined clinical endpoints, as well as short and long-term outcomes to be measured. See additional suggestions for a future studies below.	As a rule, EPCs do not make clinical recommendations, but rather present the evidence to answer the key questions. Regarding study design, we have included recommendations that future studies should be larger scale, blinded, and prospective and should compare different strategies and examine clinical endpoints. We think this covers the current future research needs for study design on this topic.
Peer Reviewer #1	**Discussion/ Conclusion**	P 30/95. Search Strategy: Tables and Figures in the document were excellent. Also, Key Questions 1-3 were clearly delineated. Key findings and evidence are summarized on page ES-10. Recommendations for models or standards for future studies of PK/PD measures, continuous versus intermittent infusions of betalactams, and their effect on different short and long-term outcomes are needed.	Thank you. We have included these recommendations in the updated discussion and research gaps sections.

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Peer Reviewer #1	**Discussion/ Conclusion**	P 37/95. Table 4 and Table C (page 16/95). Bias was medium or high for all studies listed. The question arises how accurate and reproducible are measures of "bias assessments, directness, precision and strength of evidence?"	As to risk of bias, we note the explanation given earlier about risk of bias ratings and repeat here our description in the Methods section: "To assess the risk of bias (i.e., internal validity) of studies, we applied predefined criteria based on the Agency for Healthcare Research and Quality (AHRQ) Methods Guide.[a] This approach uses questions to assess selection bias, confounding, performance bias, detection bias, and attrition bias—that is, it addresses issues of adequacy of randomization, allocation concealment, similarity of groups at baseline, masking, attrition, whether intention-to-treat analysis was used, method of handling dropouts and missing data, validity and reliability of outcome measures, and treatment fidelity." We agree that the reviewer's question about how accurate and reproducible these measures are, which in this case relate to grading strength of evidence and not simply assessing risk of bias, are important (and difficult) issues for research in the methods of systematic reviews. Some work in reliability testing has been published (by researchers at the RTI-UNC EPC) on these questions (Berkman et al. JCE, 2013). More investigation of these issues is warranted. Meanwhile, methods used in grading strength of evidence in this review are based on the AHRQ *Methods Guide*, consistent application of the methods, and transparently recording decisions. This approach is very consistent with the GRADE approach (used in both the United States and abroad). Thus, although the metrics the reviewer asks about have not been empirically tested to any great degree, we judge our approach to be the best available for reviews pertinent to the United States, to adhere to AHRQ standards and guidance, and to be rigorously and transparently applied.
Peer Reviewer #1	**Discussion/ Conclusion**	Discussion and Research Gaps sections were excellent: P 18 & 19. Perhaps the most important recommendation is the emphasis on the need for future investigations to compare different PK/PD studies conducted as large-scale, preferably blinded, prospective designs with well defined endpoints.	Thank you for your comment.

Commentator & Affiliation	Section	Comment	Final Response
Peer Reviewer #1	**Discussion/ Conclusion**	Implications and major findings were clearly stated and limitations of the studies reviewed were clear. I have added some recommendations for future studies focused on VAP to assess PK/PD therapy and believe these data could be extrapolated to HAP and HCAP.	Thank you for your comment. Your recommendations were taken into account in the final report, as outlined in other comments.
Peer Reviewer #1	**Discussion/ Conclusion**	Serial microbiologic data in intubated patients are needed to assess antibiotic efficacy and the value of a PK/PD model. Bacterial tracheal colonization usually precedes lower airway infection due to ventilator-associated tracheobronchitis (VAT) and/or ventilator-associated pneumonia (VAP). This model could expedite research, evaluate more effective antibiotic therapy strategies to improve patient outcomes and reduce healthcare costs.	Ventilator associated tracheobronchitis (VAT) does not meet our eligibility criteria. We agree that serial microbiologic data in intubated patients might be useful in preliminary studies to develop a dosing strategy that could then be used for clinical efficacy trials, but these data would not be a useful endpoint for studies, even future ones, that fall under the scope of this review.
Peer Reviewer #1	**Discussion/ Conclusion**	Serial endotracheal aspirates (ETA) Gram stain and cultures evaluated by semiquantitative methods (SQ-ETA >+++ growth) or quantitative (Q-ETA >105 cfu/ml) cultures are critical to identify specific bacterial pathogens, provide data on inflammation, serial antibiotic sensitivity data over time and the impact of antibiotic therapy in reducing bacterial load in the lung and improving patient outcomes.	We have revised the future research needs section to include these other outcomes as possible outcomes to assess the impact of PK/PD studies, although we believe that other clinical outcomes such as clearing the pneumonia and survival are more useful and of much higher priority.
Peer Reviewer #1	**Discussion/ Conclusion**	VAT/VAP patients could be treated with either “targeted” or broad spectrum antibiotic therapy followed by de-escalation, or use of a PK/PD model versus conventional ATS/IDSA Guideline therapy. VAT/VAP data would also assess specific outcomes: ventilator days, ICU days, days to becoming afebrile and return to normal WBC count, or changes in biomarkers, such as C-reactive protein or procalcitonin levels while on experimental versus conventional antibiotic therapy. These data on VAP could be extrapolated to patients with HAP and HCAP.	Ventilator associated tracheobronchitis (VAT) does not meet our inclusion criteria. We have included a broad recommendation for study designs in the report stating that future studies should be larger scale, blinded, prospective, compare different strategies, and look at clinical endpoints. The specific research idea that the reviewer suggests falls within our recommendations, but we do not believe that a recommendation this specific is applicable.

Commentator & Affiliation	Section	Comment	Final Response
Peer Reviewer #1	**Discussion/ Conclusion**	Summary: Future study clinical endpoints should include eradication or log reduction of the ETA pathogens, as well as data on patient outcomes, such as reduced ventilator days, antibiotic days, ICU days, febrile days, need for tracheostomy, relapse rates and mortality at 14 and 28 days. Follow up data at 1 month, 3 mo and 6 mo after discharge and cost studies could also be included. For example, patients randomized to PK/PD antibiotic therapy vs a control group, could assess results with more virulent pathogens, such as S. aureus (MSSA & MRSA) or Pseudomonas aeruginosa, as well as MDR Gram-negative bacilli, such as E. coli, Klebsiella pneumoniae, Enterobacter species, Stenotrophomonas maltophila or Acinetobacter baumanni.	Recommending using serial quantitative BAL cultures for following the clinical progress of patients is controversial. In our judgment, these other future research suggestions are encompassed by our statement that future studies should be larger scale, prospective, and designed to compare different strategies, and should evaluate clinical endpoints. We have included suggestions of study designs to address both clinical and microbiological outcomes without limiting our suggestions to specific techniques, especially invasive monitoring techniques such as BAL collection on compromised patients.
Peer Reviewer #1	**Discussion/ Conclusion**	As suggested in this review, future studies should be larger scale, multi-center, randomized clinical trials, in well defined patient populations, experiencing infection due to specific pathogens, in order to address the data limitations included in this review.	Thank you for your comment.
Peer Reviewer #2	**Discussion/ Conclusion**	Page 23, line 50-53: well stated, and helps the reader understand more what was being looked at for this review. Something to this effect should be considered to be put in the introduction.	We have added text regarding our focus on the use of PK/PD measures to adjust dosing rather than setting a single target and reporting on target attainment will be added to the introduction.
Peer Reviewer #2	**Discussion/ Conclusion**	Even if there is not good data on S. aureus to be included in the reviews, more discussion about why none of the studies on S. aureus met the criteria is needed. This is a very clinically relevant discussion at the moment, and a reader of this subject matter would likely expect to see some discussion of optimal dosing of vancomycin for S. aureus pneumonia using PK/PD measures	In the Results chapter, we have added pathogen information reported in the included studies. We have also revised the Methods to make it clear that our goal is not to look at an individual drug's performance, but rather to examine critically the use of PK/PD measures to guide treatment. We have also included text regarding the reasons why many vancomycin studies did not meet our inclusion criteria. The investigators did not prospectively compare two or more different dosing approaches, such as targeting two different troughs. The data in this area primarily look retrospectively at what trough different patients *achieved*, relating those data to the MIC of the organism and trying to draw conclusions from there.
Peer Reviewer #2	**Discussion/ Conclusion**	More discussion of MICs and specific organisms in the discussion is needed. Again, readers of such a review are likely looking for guidance on dosing antibiotics for multi-drug resistant organisms, or organisms with high MICs to traditional antibiotics.	The scope of our review is not to guide readers to particular doses for particular organisms, resistant or not.

Commentator & Affiliation	Section	Comment	Final Response
Peer Reviewer #2	**Discussion/ Conclusion**	Since only 6 studies were considered robust enough, it is helpful that the authors have provided guidance on what future research should actually be done to be considered robust. Page 25 and 26 do accomplish this, although few Infectious Diseases studies are able to be conducted this way with the recommended degree of rigor (as evidenced by the fact that most available published literature was excluded by the authors)	Thank you for your comment. In designing this review, we tried to include a broad range of study types; we also have specified included studies with all quality ratings in our results section. Unfortunately, few studies on this subject include a comparator, making it difficult to draw useful conclusions from them and therefore removing them from eligibility for our report. Studies lacking a comparator PK/PD target goal were not eligible; similarly, retrospective cohort studies without an appropriate comparator group were not eligible. Our goal was not to examine an individual drug's performance; rather, we focused on use of PK/PD measures to guide and optimize treatment.
Peer Reviewer #3	**Discussion/ Conclusion**	In this study, discussion about the major findings were nicely stated and obvious limitations were adequately discussed. The authors did explain the reasons for their negative finding and pointed to the research gaps and recommended methods to fill such research gaps.	Thank you for your comment.
Peer Reviewer #4	**Discussion/ Conclusion**	The investigators did a good job presenting the implications of their review. The questions I am left with are how fruitful the investigations into alternative infusion regimens can be expected to be. Is there a way to steer future researchers to more fruitful/valid designs? Is there a way to advise in the power and the specific outcomes that need to be measured? Also, and this may well be beyond the scope of this review, is there a way to estimate how much resources a meaningful investigation into these questions would require? It seems from the pragmatic standpoint these studies are cumbersome and expensive. If there is absolutely no valid signal in these smaller studies, is there any reason to think that larger sample sizes and better designs would change the results? Is there a way to quantify these issues?	As these questions (e.g., how fruitful the investigations into alternative infusion regions; estimate of resources a meaningful investigation would require) seem to be beyond the scope of the review to answer, we will not be revising the text. We have addressed some of the other concerns in the future research needs section: Future investigations could be conducted in large-scale blinded prospective designs intended to compare different PK/PD strategies in patients with HAP. The two primary goals of such investigations are (1) to document the impact of different dosing strategies on meaningful clinical and patient-centered endpoints, such as survival in different patient populations, and (2) to determine their effects on the development of antibiotic resistance in bacteria. In addition, such studies can provide important data on other outcomes of interest to both clinicians and patients; these include ventilator days, rates of relapse, rates of reinfection, mortality risk, and timeliness of laboratory results in terms of being clinically useful in managing treatment. Measuring microbiological outcomes such as eradication of bacteria, microbiologic relapse, decrease in colony counts of culture, and development of antibiotic resistance can also yield information useful for developing dosing guidelines and recommendations.

Commentator & Affiliation	Section	Comment	Final Response
Peer Reviewer #5	**Discussion/ Conclusion**	The discussion needs to be revisited. It is not acceptable as written. I am concerned with many of the statements made by the authors. For example, on page 24, the authors state that "the present PK/PD approaches do not directly consider the variety of antibiotic resistance genes in pneumonia-causing bacteria or other clinical settings." This is not true. The resistance gene is captured in the MIC value and animal studies have shown that optimization of the exposure profile in relationship to the MIC, regardless of the underlying mechanism, optimizes the outcome. Please see the work on ESBLs and KPCs by William Craig and Paul Ambrose for a detailed review. The comment that "PK/PD may actually contribute to the development of resistant organisms and result in treatment failure" is based on no data nor is substantiated by any reference. This needs to be removed from the discussion. I view these are very careless, non-evidence based statements. The discussion should focus on the importance of future studies to evaluate initial dosing schemes and regimens relative to standard of care for the reasons mentioned above.	We have reviewed the content of the discussion and conclusion to ensure accuracy and have revised the text regarding the PK/PD approaches considering antibiotic resistance and contributing to the development of resistant organisms. We have removed two sentences, one that stated PK/PD may actually contribute to the development of resistant organisms; and the second that stated that the present PK/PD approaches do not directly consider the variety of antibiotic resistance genes in pneumonia-causing bacteria or other clinical settings. We acknowledge that evaluating initial dosing schemes and regimens relative to standard of care is an important area for future research, but it falls outside the scope of this systematic review.
Peer Reviewer #5	**Discussion/ Conclusion**	The discussion should focus on the importance of future studies to evaluate initial dosing schemes and regimens relative to standard of care for the reasons mentioned above.	We acknowledge that evaluating initial dosing schemes and regimens relative to standard of care is an important area for future research, but it falls outside the scope of this systematic review.
TEP Reviewer #1	**Discussion/ Conclusion**	All is clear. Not aware of any missing studies of importance.	Thank you for your comment.
TEP Reviewer #2	**Discussion/ Conclusion**	The discussion is adequate and the findings are clearly stated.	Thank you for your comment.
TEP Reviewer #3	**Discussion/ Conclusion**	Again, given that refitting the entire study is not practical at this point, a paragraph in the discussion/limitation section along the lines of "knowing what we know now, here is what we would have done differently" would resonate with the readers and help other researchers in the CER field with their design of systematic reviews.	We respectfully disagree with this comment. Given the scope of this review, we have followed the appropriate EPC (systematic review) methodology and these are the findings. We are not certain that trying to explain what we might have done differently would help researchers (i.e., systematic reviewers. We have added further explanation in the introduction section of the report about why applying the findings from the use of PK/PD measures in other conditions do not apply to nosocomial pneumonia (i.e., to the lung).

Commentator & Affiliation	Section	Comment	Final Response
TEP Reviewer #4	**Discussion/ Conclusion**	The findings are clearly stated and the limitations of the studies are adequately described. I did not see any obvious omission of any important literature. The future research section was sufficiently clear.	Thank you for your comment.
TEP Reviewer #5	**Discussion/ Conclusion**	In the "research gap" section (page 26), another point that is missing is regarding the metrics to evaluate the development of bacterial resistance, e.g. individual infections that become more resistant in the same patient versus in the same ICU, versus in the same hospital?; value of hospital antibiogram changes versus ICU antibiogram changes versus patient antibiogram changes? In summary, several resistance metrics have to tested and validated in relationship to meaningful clinical outcomes.	We have added text to the discussion section addressing the development of bacterial resistance.
TEP Reviewer #3	**Appendix C**	Looking through the titles of the excluded articles in Appendix C, it seems like there would have potentially been useful information in many of them. A concern is that the attempt to find "perfect" studies (unbiased, meeting a high evidence standard) undermined the relevance of the review by parsing out so many papers. One of the tenets of CER is identifying "real world" practice patterns-under that principle, incorporating alternative study designs/approaches into the evidence base is going to be increasingly important. It would be worthwhile to include a paragraph to that effect in the discussion/limitations sections (i.e., how does one balance rigorous methodology without sacrificing utility?).	We respectfully disagree that we have sacrificed utility for the sake of the rigorous methodology. Given the scope of this review, we have included only those studies which clearly answer the questions (benefits and harms) regarding the use of PK/PD measures to guide the use of intravenous antibiotic treatment in patients with nosocomial pneumonia. We have mentioned in the discussion section other studies that may inform judgments and we have added more details to the Future Research Needs section.
Peer Reviewer #1	**Clarity and Usability**	The report is nicely written and well organized. Suggestions included a better study model for future studies of PK/PD therapy in ventilated patients developing infection due to VAT and/or VAP.	Ventilator associated tracheobronchitis (VAT) that has not become VAP would not meet the inclusion criteria for our review. PK-PD studies of VAT alone would need to be separate from VAP because the concentration of drug at the site of infection differs. We have added text to our Methods section to help make this clear.
Peer Reviewer #2	**Clarity and Usability**	The report is organized, but more detail in the results and discussion is needed. Because of limited inclusion of available literature, the review will have limited impact to inform policy; rather, it could be used to guide researchers to conduct future investigation	We have added more detail in the Results and Discussion section. In the Results section we added data on baseline characteristics, particularly renal clearance, APACHE scores, specific pathogens identified in each study and other measures of illness for each included study. We have enhanced the future research needs section with additional discussion on bacterial resistance, and we have added further discussion in the Implications for Clinical and Policy Decisionmaking section.

Commentator & Affiliation	Section	Comment	Final Response
Peer Reviewer #3	**Clarity and Usability**	This a nice useful review with a nice structure and adequate methodology. Despite indecisive conclusion, practitioners will benefit from that review.	Thank you for your comment.
Peer Reviewer #4	**Clarity and Usability**	These aspects are fine.	Thank you for your comment.
TEP Reviewer #1	**Clarity and Usability**	Yes to all	Thank you for your comment.
TEP Reviewer #2	**Clarity and Usability**	The report is clear and well-structured, but as stated in the conclusion, the major gaps in available evidence preclude drawing any meaningful conclusions or impact policy and practice decisions.	Thank you for your comment.
TEP Reviewer #3	**Clarity and Usability**	PK/PD is typically the domain of clinical pharmacists and infectious disease specialists-the manuscript fits that target audience nicely. If the goal is to make the manuscript more relevant to a broader range of stakeholders (hospitalists, administrators, insurers), the "business case" for how this review is germane to them needs to be articulated more clearly in the executive summary and introductory sections.	Because of the clinical nature of this report, we purposely focused this report for use by clinical pharmacists and infectious disease specialists. We included hospitalists on the Technical Expert Panel. We have added text to the Discussion section about the relevance of this review for hospitalists, administrators, and insurers (at least those with substantial concerns about nosocomial pneumonia per se). We are not completely certain whether the reviewer, in recommending a "business case," was concerned with costs (or cost-effectiveness or even cost-benefit and returns on investments). Cost and resource utilization was not within scope of the review. Hopefully this evidence synthesis can contribute to decisionmaking; however it is true that a hospital administrator will need additional information from their specific site to inform their decision. Circumstances vary across settings; a systematic review brings together the evidence, but ultimately individuals (clinicians and hospital administrators) have to apply the evidence to their circumstances.
TEP Reviewer #4	**Clarity and Usability**	The report was well organized and the main points were clearly presented to the reader. The conclusions were clear and can be used to inform practice decisions.	Thank you for your comment.

Commentator & Affiliation	Section	Comment	Final Response
TEP Reviewer #5	**Clarity and Usability**	On page ES-10, the penultimate paragraph ("First, the present PK/PD approaches do not directly…with IV antibiotics") states that PK/PD "may actually contribute to the development of resistance organisms and result in treatment failure" has no supportive evidence from this systematic review or from the selected individual studies. In addition, most studies did not systematically evaluate the development of bacterial resistance. Please clarify that, or explain that this is a speculation, or remove it. Another explanation that I suggest to incorporate in the discussion section is the following: "On the other side, because mortality has been a marker of variable sensitivity in patients with HAP/VAP (decreasing event rates, and potential confounding by patients' comorbidities), even if the PK/PD approaches are beneficial, this may be difficult to prove without a trial with a very large sample size.	We have removed the text in which we state that "PK/PD 'may actually contribute to the development of resistance organisms and result in treatment failure,'" and have revised the remainder of the paragraph
Peer Reviewer #1	**General Comments**	Selected References for VAT and VAP Model & Patient Outcomes: 1. Nseir S, Antimicrobial treatment for ventilator-associated tracheobronchitis: a randomized, controlled, multicenter study. Crit Care, 2008; 12:R62. 2. Craven, DE. Natural history and outcomes of patients with ventilatorassociated tracheobronchitis (VAT) and pneumonia (VAP), Am J Med 2013:126:542	Thank you for your comment. We have investigated these references, and they do not meet our criteria for inclusion, as the first reference is in a ventilator associated tracheobronchitis (VAT) population only, and the second does not examine PK/PD measures.
Peer Reviewer #1	**General Comments**	Report is clinically meaningful and key questions explicitly defined. Tables and figures were superb	Thank you for your comment.

Commentator & Affiliation	Section	Comment	Final Response
Peer Reviewer #1	**General Comments**	This document is a well written, detailed and defined systematic review of PK/PD strategies to dose and monitor antibiotics administered for the treatment of nosocomial pneumonia, which includes hospital acquired (HAP), healthcare-associated (HCAP) and ventilator-associated pneumonia (VAP). Numerous data sources, including Pub Med, Cochrane Library, International Pharmaceutical Abstracts and Clinical Trials. Gov, were reviewed from January 2004 to May 2013 by two investigators independently, who graded the strength of evidence “based on established guidance”. Six studies (4 clinical trials and two cohort studies met inclusion criteria, but only one study, with a high rating for bias, used PK/PD measures to study the impact of different dosing levels on clinical responses and outcomes including ventilator days, treatment failures and patient mortality. Unfortunately, the literature review revealed a “near absence of any strong evidence of clinical applications to support the use of PK/PD strategies.” The authors also emphasized that dosing recommendations were largely based on PK/PD studies in healthy volunteers rather than critically ill patients, which may limit generalizability. This could also translate into “sub-therapeutic” concentrations of antibiotics prescribed in sick patients, reduce survival, or increase the growth of antibiotic resistant pathogens.	Thank you for your comment.

Commentator & Affiliation	Section	Comment	Final Response
Peer Reviewer #2	**General Comments**	The subject matter of PK/PD for treating nosocomial pneumonia is very timely and of great importance at a time when options for treating increasingly resistant microorganisms are becoming more scarce. The target population of nosocomial pneumonia is clearly stated, though it would have been helpful to more specifically review Gram-negative nosocomial pneumonia, or MRSA pneumonia, etc., as that what is seen and treated in clinical practice. Readers of this review are likely to be Infectious Diseases or Critical Care physicians/pharmacists, who are generally well versed with nosocomial pneumonia. A little more detail of organisms and resistance characteristics would be helpful in asking these key questions. Questions 1 and 2 are well stated; but question 3 does not necessarily follow the same logic of PK/PD and the effect on clinical response. There is no direct mention of PK/PD in the question at all (at least on page 7, lines 24-28).	We have added more information regarding the pathogens to the Results section. As most studies included a wide variety of pathogens, and did not include a breakdown of results by pathogens, it is not possible for us to provide this level of detail in the results section. We have revised the text to state that a variety of pathogens were included in the studies, most of which were gram negative. The wording of KQ3 has been revised to more clearly reflect our intent of examining the use of PK/PD measures in a population with nosocomial pneumonia and its effect on outcomes in different subgroups. It now reads: For people with nosocomial pneumonia, does the evidence for clinical response, mechanical ventilation, morbidity, mortality, or antibiotic-related adverse events differ for subgroups defined by age, sex, race, ethnicity, renal dysfunction or need for dialysis, severity of illness, microorganism, or susceptibility patterns, when examining the use of PK/PD measures to inform decisions about dosing and monitoring antibiotic treatment or when comparing prolonged or continuous infusions versus bolus infusions for beta-lactams?
Peer Reviewer #3	**General Comments**	This is a nice review aimed to conduct a systematic review of the use of pharmacokinetic/pharmacodynamic (PK/PD) measures or strategies to dose and monitor intravenous (IV) antibiotics in the treatment of nosocomial pneumonia in hospitalized adults. The research questions are explicitly stated and the work is definitely meaningful.	Thank you for your comment.
Peer Reviewer #4	**General Comments**	In general the report is well done and clinically meaningful in that it identifies the dearth of evidence for strategies to treat HCAP. The investigators did a good job defining the population(s) of interest as well as the questions.	Thank you for your comment.
Peer Reviewer #5	**General Comments**	Thank you for the opportunity to review this report. I scored this report as “poor.” Overall, I do not believe this report accurately captures the data evaluating the application of PK/PD principles in clinical practice for HAP. In particular, I do not believe the key questions and study criteria afforded an opportunity to quantify the existing data accurately and make meaningful inferences.	Thank you for your comment. The key questions and scope of this report were determined following discussion with a panel of key informants and technical experts.
TEP Reviewer #1	**General Comments**	Yes to all.	Thank you for your comment.

Commentator & Affiliation	Section	Comment	Final Response
TEP Reviewer #2	**General Comments**	This is a good report with appropriate and clear key questions. It is disappointing that there is not more evidence pertaining directly to the PK/PD question.	Thank you for your comment.
TEP Reviewer #3	**General Comments**	Lux et al. present a systematic review of application of PK/PD in relation to guiding antibiotic therapy for HAP. From a technical standpoint, the review is very well done in terms of a rigorous methodology and clear writing. However, the dearth of evidence (limited to 7 eligible articles) in this area does raise the key issue of whether the initial underlying questions were appropriate and whether the article inclusion criteria were too restrictive- the ultimate conclusion that more prospective RCTs are needed to really understand the role of PK/PD in HAP is a bit unsatisfying for a 95 page report (and one wonders if those sorts of studies would ever be competitive for federal funding given other research priorities).	Thank you for your comment. We were also disappointed that a larger body of evidence was not available to answer the questions posed in this evidence report. This topic was identified, prioritized, and nominated by a group of stakeholders. . Preliminary searches and discussions with Key Informants were conducted to develop appropriate key questions. These were posted for public comment on AHRQ's website and subsequently revised based on the comments. During the early stages of the systematic review phase, the key questions were discussed with our Technical Expert Panel. Throughout discussions with the nominators, key informants, and technical experts, it was affirmed that this topic is important and relevant to the field. Regarding the future research needs, we agree that outlining the specific research needs to be addressed in future research studies is just as important as answering the key questions. In that way, similar key questions might be better answered in the future. We have revised our text to make it more specific in outlining the elements most important for future studies, as suggested in this comment.
TEP Reviewer #4	**General Comments**	Well written report which is clinically meaningful. Helps readers clearly understand the lack of data to support the use of PK/PD measures in guiding antibiotic treatment for nosocomial pneumonia. The target population is well defined and the key clinical questions are clearly stated.	Thank you for your comment.
TEP Reviewer #5	**General Comments**	The report has little clinical appllicability, but this is not due to the study design, this is due to the lack of stronger evidence.	Thank you for your comment.

Commentator & Affiliation	Section	Comment	Final Response
TEP Reviewer #6	**General Comments**	The definition of terms like “clinical response” and “treatment failure” are often vague. They are often surrogate endpoints in disguise since they are often defined in infectious diseases trials as “clinicians’ judgments regarding signs, symptoms, radiology and lab values such that the clinician does not prescribe further antimicrobial therapy”. This type of outcome can be driven by biomarkers such as body temperature and white blood cell count. How mortality is included in “clinical response” is often poorly defined or not defined at all, or “clinical response” is measured early in the course of treatment so death that occurs one or two days later (or on the same day) is ignored. The definitions used in each of the studies for both clinical response and “treatment failure” should be presented as they are meaningless terms without further definition.	We agree that patient-centered outcomes are most important to consider, which is why we have designated treatment failure and clinical response as intermediate outcomes, not final health outcomes; and have included mortality and morbidity as final health outcomes. We have added clinical response and treatment failure definitions to the KQ1 and KQ2 summary tables. We highlight that the impact of antimicrobial resistance on patient outcomes is not fully understood, and patient clinical outcomes are likely influenced by several confounders. In the future research needs section we have identified the need for clearly defined outcomes, such as clinical response and treatment failure. For certain patient-centered outcomes, such as clinical response and treatment failure not otherwise explained, clearly identifying how the investigators defined those outcomes (e.g., clinician judgment of patient signs and symptoms, laboratory values, quality of life assessed through patient self-reports, or mortality as measured at specific points in time) will improve interpretation of the findings. We believe research teams should be precise in delineating their conceptualization of all such outcomes.
TEP Reviewer #6	**General Comments**	Some of the conclusions of the review assume in vitro mechanism of resistance is important in influencing patient outcomes (p 17 of document, page ES-10) This in and of itself should be evaluated as emerging evidence shows that patient factors are as important if not more important than organism factors in influencing outcomes, and that MIC may be a predictor of patient outcomes rather than a measure of drug efficacy (see Holmes N et al. Clin Microbiol Infect 2013;19(12);1163-8.).	We have updated the research gaps section to include text regarding the uncertainty of the link between patient specific factors, organism MIC, antibiotic dose, and clinical outcomes and the need for more studies examining this link.
TEP Reviewer #6	**General Comments**	Emergence of “resistance is in and of itself also not a patient centered outcome since it relies on in vitro testing of MICs once again. One way to decrease “resistance” is to increase mortality as dead patients cannot spread bacteria but this is obviously not an optimal outcome for patients. The focus on in vitro measures and what happens to “bugs” rather than patient-centered outcomes seems to be more widespread in the infectious diseases literature than these organisms are in medical practice. The measurement of emergence of resistance should be based on what happens to these patients – does emergence of resistance increase bad outcomes?	Emergence of resistance was a “secondary endpoint” of this review. The more important outcomes are the clinical outcomes. We did not refer to “emergence of resistance” as a clinical (or primary) outcome in this report. We have added text to the Research Gaps section stating that the correlation between the emergence of resistance and clinical outcomes is not fully understood. Although we believe that the emergence of resistance is an important endpoint for obvious reasons (resistance is a patient concern as well as a societal concern), its usefulness as a surrogate marker for clinical outcomes requires further study.

Commentator & Affiliation	Section	Comment	Final Response
TEP Reviewer #6	**General Comments**	This review does not address the issues related to the methodology used in making PK PD assessments. These assessments are based on modeling which makes some inherently unverifiable assumptions (such as using data from healthy subjects to infer concentrations in seriously ill patients)	We agree that because present dosing recommendations derive largely from PK/PD studies in healthy volunteers, the recommendations may lead to suboptimal clinical outcomes in patients with HAP (or VAP or HCAP.
TEP Reviewer #6	**General Comments**	Waste of time and money that would not improve patient outcomes regardless of the concentration achieved.	We understand the reviewer to mean that, if information on concentration is not predictive of patient outcomes, then checking concentrations would be a waste of (hospital) resources. We agree the patient-centered outcomes are most important in clinical practice (as contrasted solely with laboratory test results). Systematically reviewing the association between serum concentration and patient-centered outcomes was beyond the mandate for this study; it might have called for a very different set of studies that may or may not exist. For this reason we represent the relationship between intermediate and final health outcomes in our analytic framework as a dashed line, but we did not have any key question specifically about this association.

Commentator & Affiliation	Section	Comment	Final Response
TEP Reviewer #6	**General Comments**	The lack of evidence related to PK PD on patient centered outcomes is stunning and almost inversely proportional to the vociferousness of advocates of this methodology, who recommend it's use for everything from "decreasing the amount of evidence" needed for approval of new drugs based on no evidence, "optimal" dosing of currently available drugs, and setting of susceptibility criteria for older drugs without data. Rather some proponents of use of PK PD strategies have argued that clinical trials with patient centered outcomes are "unethical" because we "already know" that PD affects patient outcomes even in the absence of unbiased evidence. These same proponents also argue that larger amounts of biased evidence someone make these biases disappear because of "consistency" of the results. It is not surprising that similarly biased studies result in similar findings of more precisely wrong conclusions. The review should point out that there is still equipoise to do randomized trials evaluating PD relationships to outcomes given the lack of evidence.	We agree that the lack of evidence is frustrating. The lack of studies linking PK/PD to clinical (patient-centered) outcomes in this setting has been discussed in the Discussion section.

[a] Viswanathan M, Ansari MT, Berkman ND, et al. Assessing the Risk of Bias of Individual Studies in Systematic Reviews of Health Care Interventions Methods Guide for Effectiveness and Comparative Effectiveness Reviews. Rockville MD: Agency for Healthcare Research and Quality; 2008.