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|  | **Comment** | **Response** |
| **Reviewer 1** | | |
| 1 | Recently, an individual patient data metaanalysis on the same topic has been published (see Schuetz, P., M. Briel, et al. (2013). "Clinical outcomes associated with procalcitonin algorithms to guide antibiotic therapy in respiratory tract infections." JAMA 309(7): 717-718 and Schuetz, P., B. Muller, et al. (2012). "Procalcitonin to initiate or discontinue antibiotics in acute respiratory tract infections." Cochrane Database Syst Rev 9: CD007498). This should be discussed in the introduction and authors should make their argument where the current manuscript closes further gaps. In the above mentioned study, a significant effect was found in regard to treatment failure when looking at all patients, as well as CAP and ED patients. This was not reported in the current manuscript -  how can these different results be explained? | The two articles referenced by reviewer 1 summarize and discuss data from a Cochrane Review on the utility of procalcitonin (Schuetz, et al. Procalcitonin to initiate or discontinue antibiotics in acute respiratory tract infections. Cochrane Database of Systematic Reviews 2012). This review looked at 14 randomized trials from 2004 to 2011 of adult patients with respiratory tract infections that compared antibiotic therapy with or without procalcitonin guidance. Treatment failure was lower in patients from the ED and with CAP in the procalcitonin group.  Treatment failure was not reported in the individual studies, but the authors of the Cochrane review calculated a composite outcome of treatment failure based on setting-specific definitions. In our review, we only pooled primary data that was reported by the studies. We did not define or calculate new composite outcomes.  Our review is unique because we included all randomized, controlled studies published to date, and we sorted studies according to patient population, type and severity of infection, and different uses of procalcitonin measurements, either for reduction or intensification of antibiotic therapy. |
| 2 | The exclusion criteria are not clear “Studies with any of the following criteria were excluded: published in non-English language; not reporting primary data from original research; irrelevant design; irrelevant disease; or irrelevant outcomes”. Why excluding non-english papers? What is the definition of “irrelevant”? | We did not find any non-English randomized controlled trials, but we did not systematically search non-English gray literature, such as conference abstracts, due to limited resources for the project. The relevant study designs for inclusion were randomized controlled trials or nonrandomized comparative studies. Clarification to study design exclusion has been added to the manuscript. |
| 3 | In the results section, the authors have included only part of the available studies into the different analyses.  For example, Figure 2A and B only 3 ICU studies were included while in 2C all 5 studies were included. The same is true for 3A where only 4 studies of the available 8 were included and 4D where again only 4 were included. If the reason for not inclusion was the reporting of medians instead of means, I would suggest to contact the authors to provide this missing information, or use a statistical approach for changing medians to means (if contacting is not possible). | If the study did not report the mean and standard deviation, it was excluded from the meta-analysis. Also, if the reported event rate was zero, the study was not included in the meta-analysis. We did not contact the authors of the individual studies. |
| 4 | There were some other “real life” studies which need to be discussed in the manuscript (Arch Intern Med 172(9): 715-722.; Eur J Clin Microbiol Infect Dis 29(3): 269-277). | Mention of these studies has been added to our Discussion. Both of these papers were excluded from inclusion in our systematic review because they were observational quality control studies evaluating the impact of specific procalcitonin algorithms. |
| **Reviewer 2** | | |
| 1 | The authors should discuss the limitations of the manuscript which include the small numbers of patients in three of five of the patient groups analyzed and the mixing of ICU patient populations that were included in the meta-analysis. | We have expanded our discussion of limitations of the review in the Discussion section of the manuscript. |
| **Reviewer 3** | | |
| 1 | Given the paucity of literature on neonatal sepsis, pediatric fever of unknown origin, and post-op infections, how did you decide to include these papers in your review?  Why not choose other similarly sparsely studied PCT applications? | We included only randomized control studies that compared procalcitonin-guided antibiotic therapy to use of clinical criteria alone. There are several other applications of procalcitonin that are mentioned in observational studies, but these studies were excluded from our review due to their study design. |
| 2 | You list 4 prior reviews (refs 11-14) in your reference list but don't actually refer them in the body of your paper.  Please add these references and help the reader understand what you believe your study adds to these prior reviews, as there is significant overlap with the studies you and prior authors have examined.  If the answer is the addition of information on antibiotic intensification, FUOs, neonatal sepsis, and post-op patient infections, please justify why we need a new study to talk about these four disparate topics with so few studies on each.  If you disagree with the conclusions of prior authors, please also explain that. | A section has been added in the introduction and discussion to describe past systematic reviews and characteristics that distinguish our review from past reviews. |
| 3 | It would be helpful to include your search strategy here instead of referring the reader to the AHRQ website as that is critical for judging the completeness of your search (which looked quite complete). | We have added more details about our search strategy to include the search terms. |
| 4 | On p5, in your search strategy section: You state you searched Medline and Embase 1990-2011 and Cochrane Controlled Trials without date restrictions.  What were the time parameters for your search for systematic reviews as noted in the sentence that followed and the grey literature. | The gray literature was searched from 2006 to June 2011. This information has been added to the manuscript. |
| 5 | P6. Data Extraction and Quality Assessment - What was your mechanism for reconciling if the 2nd author reviewing the accuracy of the data abstractor didn't agree with the abstractor's findings?  Similarly, what if the 2 reviewers assessing quality didn't agree on the USPSTF quality framework assessment? | Quality of the abstracted studies was assessed by at least two independent reviewers. Disagreements between the two reviewers were resolved by group discussion among the research team and final quality rating was assigned by consensus adjudication. Manuscript now reflects this information. |
| 6 | P7 Results: You chose to break the analysis down into 5 subgroups with the biggest 2 being Adult ICU patients and Adult respiratory infections.  I would wonder your comments on whether this latter group (which included both inpatient and ambulatory studies) lumped populations together who should not be fairly combined. | The current studies that have evaluated the utility of procalcitonin for respiratory tract infections included ambulatory patients that presented to clinics or emergency departments, or non-critically ill hospitalized patients. This patient population was not subdivided because the studies did not clearly delineate percentages of patients in each setting, and our research team felt these patients with respiratory tract infections were clinically similar with similar use of procalcitonin to guide the initial management, including antibiotic therapy. |
| 7 | P7 Antibiotic Usage: You refer in the text to studies ranging from 1.7 to 5 days difference but in Fig 2A show 1.7 to 3.  Was the 5 a typo?  Also, as the studies referenced in this section were not designed to address C diff and other complications you note, I am not sure I would include the comments you do at the end of the paragraph.  Also please define your column heading: "IV, Random" - it appears to be a difference in the means but please clarify. | The study by Stolz demonstrating a reduction in antibiotic usage by 5 days was excluded from the meta-analysis because standard deviation was not reported, but inclusion of this study would have only strengthened the effect. The statement about C. difficile has been removed. “IV” is for “inverse variance weighted.” A legend defining all abbreviations has been added to each figure. |
| 8 | P8 Morbidity. You report no change in morbidity, "including hospital and ICU length of stay."  Are you implying you looked at things besides those 2 issues?  Figure 2B only appears to address ICU LOS - not hospital.  Please address. | Morbidity outcomes included hospital length of stay, ICU length of stay, SOFA/SAPS II scores, ICU-free days, and days without mechanical ventilation. Only ICU LOS was pooled into meta-analysis because it was reported by more studies than hospital LOS. Reference to Table 5 was added to see other morbidity outcomes. |
| 9 | P8 Mortality. You quote "-1%" mortality difference in the text and 0.00 Fig 2C.  Please explain. Also, in this table you list events and totals but no standard deviations (except in your risk difference column).  Why?  Also, in 2C you list the study year both after the author name and in the final column. | The actual mortality rate was 0.0043 or 0.43%, which was rounded up in the text, but rounded down by the computer in the meta-analysis. We will update the manuscript to include the exact percentage. We are working within the constraints of the meta-analysis software. For continuous outcomes, RevMan requires SDs (Figs 2A, 2B). For binary outcomes such as mortality, there is no SD (the outcome either happens or does not happen, the outcome is expressed as a proportion and there is no associated measure of variability). Effects for both continuous and binary outcomes can be estimated and have associated standard errors (not the same as standard deviations). Standard errors are used to compute 95% confidence intervals, which are computed by RevMan for individual studies and for the pooled effects. The final column with study year has been removed. |
| 10 | P9-10: Adult Pt with RTI: Again, as noted above, you lump ICU, inpatient, ED and ambulatory settings here.  I recognize with only 8 studies in this section, it's hard to split them much more granularly than you are doing, however, your first sentence in "Antiobiotic Usage" becomes somewhat misleading.  Duration is decreased in the hospital based studies but prescription rates were reduced in ambulatory/ED studies. Similarly, meta-analyzing across the settings also, therefore, becomes hard to interpret so you should state explicitly why, for example, you picked the 4 (of the 8) studies to look at in 3A.  Were these the only studies reporting this outcome (abx duration) or did you choose them for another reason?  Similar comments should be considered for the remainder of this section.  In Figure 3D on short term mortality, your figure reports a summary risk difference of 0.00 but your text reports 0.03%.  Explain.  Also, as noted previously, I would recommend restricting your comments to PCT impact on the primary outcome discussed (e.g. LOS or ICU admission) and not address antibiotic adverse events (middle of p10) as most studies didn't adequately investigate those issues. | For adult patients with respiratory tract infections, the most important consideration was the presence of a respiratory tract infection (see comment 6 above). Data from only 4 of the 8 studies with respiratory tract infections was pooled. The studies excluded from meta-analysis did not report sufficient details in outcome measures to be included in the analysis (clarification has been added to manuscript). If the excluded studies had been included, the difference likely would still favor procalcitonin. In Figure 3D, the discrepancy between the text and figure is due to the meta-analysis showing the absolute risk difference to 2 decimal places and the text reporting the percentage. Thus, 0.003 is shown as 0.00 in the meta-analysis and 0.3% in the text. Because there has been heightened interest in reducing antibiotic adverse effect, we will keep the statement that, “There was insufficient evidence to judge effect on days of restricted activity or antibiotic adverse events.” |
| 11 | P10-11 Neonates: Antibiotic use: Minor point.  It's not necessary to say that the findings are significant if you supply the p value in the text. | We will remove the word “significant.” |
| 12 | P11 - Children FUO: You comment that the strength of the evidence "was judged insufficient to draw conclusion."  Why include that comment here and not in the section above in the neonate study?  Was this study underpowered or otherwise flawed and that one wasn't?  Without further explanation, it appears that because no significant findings were identified we can't conclude anything when in fact there may have been no real differences between the groups. | The strength of the overall body of evidence rated using a system developed by the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) working group (Owens et al., 2010). The strength of evidence of the study of neonatal sepsis by Stocker was rated “moderate” while the strength of evidence of the study of children with fever of unknown source by Manzano was rated “insufficient.” We will add a qualifying statement in the manuscript. |
| 13 | P11 - You include the study by Cromik re post-op patients at risk of infection. While this clearly represents a novel use of PCT vis-a-vis infection, I am curious why you don't also look separately at Hochreiter and Schroeder who look at post-op patients WITH infections as a separate group also given the differences that population represents.  Also, you again state the evidence "was judged insufficient to draw conclusion."  As above, please explain. | The studies by Hochreiter and Schroeder included critically ill patients with sepsis, and although these patients may have been postoperative, they had a known infection (sepsis), were in an ICU, and were most clinically similar to other ICU patients. The study by Chromik evaluated the using procalcitonin to monitor postoperative patients for early identification of patients that might benefit from antibiotic therapy for local or systemic infections. Patients with an elevated procalcitonin were randomized to empiric IV ceftriaxone vs. standard management. In contrast to the abovementioned studies, the patients in the Chromik study did not have a known infection and were not critically ill. |
| 14 | Discussion: I think you make several important points but overall, your discussion is disorganized.  You have no apparant framework for the order of the comments that I can follow (ICU abx --> intensification --> RTIs -->other populations...). It lacks an introduction to your discussion that frames the study and your subsequent comments.  Additionally, as noted at the top of my comments, it is unclear why we need another meta-analysis of this topic.  Where do the prior studies fit with yours (or not).  I do like your "gaps in the literature" section - your work here is very helpful for framing the future research.  Indeed your section in your AHRQ publication is even more fleshed out and useful.  This brings up, again, the issue of duplicative publication. | We have reorganized and rewritten the discussion. We included comments on past systematic reviews, justification for our review, limitations, and explanation of gaps in the literature for future research. |
| 15 | See embedded comments above re Figures 1, 2, and 3.  (FYI: you use the UK spelling of FAVORS in 2A but the US spelling elsewhere.) | We changed the spelling of “favors” to the U.S. spelling. |
| 16 | I don't see reference to Figure 4 or 5 in your text. | The numbering of tables has been corrected. Tables 4-6 are now referenced in the last sentence on the introductory paragraphs under “Results.” |