Author’s response to reviews

Title: Procalcitonin-guided diagnosis and antibiotic stewardship revisited

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Author’s response to reviews:

Reviewer #1: SUMMARY:

A narrative review on all new observational and randomized studies on PCT since 2012. A lot has been published since 2012 and many of these studies are highlighted in this comprehensive review.

MAJOR POINTS OF COMMENT:

1. (page 11, line 37): I was intrigued by the outcome of the endocarditis study. Cornelissen et al. found PCT useful in prediction of poor outcome (cut-off 0.5ng/ml; Sensitivity 73% and specificity 79%) and a odds ratio of 12.8 (95% CI 2.5-66.2) for finding staphylococcus aureus in blood cultures [67]. How can a cutoff of only 0.5 ng/mL be used for good versus bad outcome in endocarditis? Endocarditis often is a severe infection (severe sepsis) and you'd expect much higher values of PCT.

Reply:

We agree we the reviewer that one might expect higher PCT levels in patients with severe endocarditis. In fact, the authors reported median PCT levels of 2.1 ng/mL in patients with staph aureus endocarditis in their study. However, empirical evidence gathered in the study by Cornelissen et al. found PCT the optimal cut-point was rather low at a cut-off of 0.5ng/ml to be useful in prediction of poor outcome. In the literature higher PCT levels were mostly found for patients in the ICU setting with severe sepsis or shock, but lower in the medical wards.

2. It would be very nice to see a level of evidence of all the studies that are discussed in this review. Some statements are very well based in evidence while others are merely uncontrolled
claims (observational cohorts). It is very difficult for the reader to discern good quality in all these studies. This level of evidence can best be added to Table 1.

Reply:

Because this is a narrative review and not a systematic review for all these types of infections, we did not systematically assess the quality of evidence for all types of infections. However, we have a quality of evidence in table 1 (“Benefit of PCT use?”).

MINOR POINTS OF COMMENT:

1. (page 4, line 26): The studies included employed somewhat similar... use included or employed but not both.

Reply: thank you - changed as requested.

2. (page 6, line 33): 3’343 patients. Use the same way of writing throughout the manuscript. One paragraph earlier 3244 patients (no ’) was used.

Reply: thank you - changed as requested.

3. (page 7, line 12): positive Blood culture. Blood does not need to be written with a capital B.

Reply: thank you - changed as requested.

Reviewer #2: The authors review some recent studies on PCT.

The text is well written but it is very biased; this is not too surprising as the authors have been strong advocates of this biomarker, and have largely contributed to the field.

Although PCT is certainly a valuable marker, it is far from perfect.

This text should be either counterbalanced by another view or considerably revisited to underline the limitations of any biomarker, including PCT.

Reply: we have now added limitations of PCT as suggested by the reviewer. Our initial aim was to provide an overview where PCT might be useful for clinicians and have thus focused more on the positive indications. We, however, agree that the marker is far from being perfect and have added this now in the revised manuscript.

In the abstract we have added the following text: “Also promising findings have been published in these different types of infections, there are a number of limitations regarding PCT including suboptimal sensitivity and/or specificity which makes a careful interpretation of PCT in the clinical context mandatory. This narrative review aims to update clinicians on strengths and
limitations of PCT for patient management focusing on research conducted within the last 4 years.”.

In the main text we have added the following limitations section: “This narrative review has limitations. First, we did not do a systematic review for each type of infection but have selected studies based on a pubmed search and the authors expertise. Our conclusions may thus be too enthusiastic. Second, most of the studies did not blind patients and/or investigators and thus subject to possible bias. Third, we focused on studies published between 2012 and mid of 2016. Papers before or after this time frame may have been missed.

Importantly, PCT is far from being perfect and thus levels must be evaluated in the context of a careful clinical and microbiological patient assessment. Because the kinetics of PCT are of particular diagnostic and prognostic importance, repeated measurements should be performed. This is particularly true for persistently sick patients and in situations where antibiotics are withheld. Limitations of PCT include false-positive and false-negative results[81]. PCT levels may increase in the absence of a bacterial infections in patients with severe trauma or surgery[81-83]. Here, PCT usually shows a rapid decline in follow-up measurements when the patient recovers. Also, chronic renal failure patients may have a slower PCT decrease. PCT levels may also be low in the early course or localised state of an infection with later measurements showing an increase in levels. Thus again, repeated PCT measurements are advised in case of uncertainty.”.

1. How were the studies selected? The negative multicentric study from ANZICS (published in the American Journal of Respiratory and Critical Care Medicine in 2014) is simply omitted. Likewise, the study by Oliveira et al showing PCT may not be superior to CRP for guiding antibiotic therapy.

   Reply: We agree with the author. Some studies may have been missed. We now added the study to the manuscript as follows: “Interestingly, a multicentre trial including 11 Australian ICU and almost 400 patients found only a modest effect of PCT testing in regard to antibiotic reductions (median number of antibiotic treatment days 9 versus 11){Shehabi, 2014 #13521}. The authors used a 0.1 ng/ml cut off to stop antibiotics which may explains the differences to other sepsis trials which used a 0.5 ng/mL cut-off.”.

2. The studies evaluating the place of PCT were not blinded; admittedly, it would be extremely difficult to have a blinded protocol, but this should be listed as a limitation.

   Reply: We agree with the reviewer and have added this to limitations as follows “Second, most of the studies did not blind patients and/or investigators and thus subject to possible bias.”.

3. How can one be sure that the antibiotic treatment was not too long in the control group? In other words, that reducing the duration of antibiotic therapy without the use of PCT could result in similar outcomes.

   Reply: We agree that the true needed duration is difficult to know. The studies have had a pragmatic approach asking the questions whether use of PCT improves “current care” in regard
to antibiotics without increase adverse outcomes. But as there is no gold standard for “truly needed duration” it may not be possible to answer this question.

4. How can one be sure that PCT is superior to other biomarkers in this setting of reducing the duration of antibiotic therapy? This is supported by the study of Oliveira et al. (Crit Care Med) which is not cited.

Reply: There are several observational studies comparing CRP and PCT in the context of infection. Most studies found PCT to be more specific compared to CRP which seems to be more of an inflammation marker. Having said that – there is an important lack of interventional studies comparing these two markers for antibiotic stewardship. The study by Oliveira did only include 94 patients and was thus underpowered to find a difference between markers (if one exists)?

We have added the following limitation to the manuscript: “However, there is a lack of well done and large studies comparing the effect of both markers when used in the context of antibiotic stewardship.”.

5. The cost of PCT is not even mentioned. The yearly hospital budget for routine measurement is very high. If the antibiotic treatment can indeed be shortened in the absence of PCT measurements, or with the support of cheaper CRP measurements, the cost/benefit may not be very reasonable.

Reply: We agree and have added the following text: “While some reviews found PCT to be cost efficient in respiratory infections when antibiotics can be reduced by the measurement of this marker[87], this may not be true for other indications.”. Due to word limits we did not further explain on costs.

6. The authors should more clearly recognize that biomarkers can only complement the clinical assessment and not replace it.

Reply: We agree and have added the following text: “Importantly, PCT is far from being perfect and thus levels must be evaluated in the context of a careful clinical and microbiological patient assessment.”

Specific comments

1. Background: "unnecessary and prolonged exposure to antimicrobial agents adversely affect patient outcomes (e.g., risk for clostridium difficile infection),": there is also a risk of emerging resistant organisms in the patient himself.

Reply: This was now rephrased to “… while inappropriate antibiotic therapy increases antibiotic resistance in patients resulting in a public health threat.”

2. Middle of page 7: "Sepsis, as defined by SIRS criteria…": SIRS are not (or no longer) part of the sepsis criteria.
Reply: We now rephrased to “A meta-analysis from 2013 including 3244 critically ill patients classified using the former definition of either sepsis or systemic inflammatory response syndrome (SIRS) of non-infectious origin pooled the diagnostic power of PCT.”

3. Page 8: "In addition, PCT was found to predict severity of illness.": this is true for any sepsis marker.

Reply: We agree and rephrased to “In addition, similar to other sepsis markers, PCT was found to predict severity of illness.”.

4. Page 10: "Thus, further investigation is needed in the surgical setting.": is it until PCT is shown superior to CRP? why not recognizing that CRP is just as good as PCT in this setting?

Reply: We agree and change the sentence to “Thus, further investigation is needed in the surgical setting, also to compare accuracy and cost-effectiveness of PCT with other infection markers such as CRP.”.

5. The Figure 1 seems promotional

Reply: We believe Fig 1 gives a graphical overview of the evidence regarding PCT in different infections. If the editor feels that this figure is inappropriate we would be happy to put it in the appendix.

------------Editorial Requests--------------

Figures: Please confirm if the figures are original, or if they are subject copyright. If the latter, permission must be sought from the copyright holder, and a statement to explain this must be included in the figure legend.

Reply: Yes. All figures are original

Discussion: To ensure balance, please also discuss data from RCTs that did not show a beneficial impact of using PCT.

Reply: please see our answers to reviewer 2. We have now added several limitations and also discuss more critical paper as suggested. We believe the current manuscript gives a balanced overview of PCT.

Conclusions: please comment on what further research questions needs to be addressed.

Reply: we have now added the following paragraph to the outlook section: “While there is strong evidence regarding antibiotic stewardship in respiratory infection and sepsis, PCT has not as well been studied for other types of infections. Thus future research should focus on non-respiratory
infections and investigate whether PCT improves antibiotic decisions in these patients. Also, PCT should be compared to other markers such as CRP in regard to diagnostic accuracy and cost-effectiveness.”.