Author’s response to reviews

Title: Serum procalcitonin for the early recognition of nosocomial sepsis in the critically ill patients: a preliminary report

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Version: 2 Date: 28 February 2009

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ANSWER TO REVIEWERS

Reviewer 1

1. 
   a) We agree with the fact that PCT elevation might be greater in the patients with bacteremia than in those with VAP. We have mixed both populations because VAP and BSI are the most frequent nosocomial infection met in our ICU. In addition, although controversial, a significant attributable mortality has been associated with both of them. Finally, similar findings were obtained while considering the sole patients with either suspected or proven VAP as already specified in the results section (p. 7, l. 17). This could however be considered as a limitation since PCT elevation was found to be greater in the patients with bacteremia than in those with VAP. As a result, attempting to clarify this point, a sentence has been added to the discussion section (p. 10 1st §).
   b) VAP diagnosis criteria are those used in the Clinical Pulmonary Infection Score developed by J Pugin in 1991, as cited into the references section, while sepsis criteria are those defined by the SCCM conference (1992). The corresponding reference has been added.
   c) We acknowledge that a lot of patients with bacteremia have to be excluded from the analysis because of the stringency of the excluding criteria. It is however worth noting that most of them should not be considered as missing data related to the study design as suggested by the reviewer’s comment. Thus, almost half of these episodes (51 out of 123) were community-acquired and was therefore excluded. Among the 72 remaining ones, 37 were excluded because of sepsis within the past 7 days, 13 because of surgery, 17 because the isolated microbial
agent was Candida sp and only 8 because of missing PCT measurement. Such information has been added to the results section.

d) We apologize for the mistake regarding patient numbers. Actually, the proven sepsis group is made of 47 patients as specified in the Tables and the abstract as well (and not 51 as written in the result section of the main text). The text has been therefore corrected. In addition, a flow chart was constructed and added to the Figure section (Figure 1) in an attempt to clarify this point.

2. A new Table (Table 3) has been added in order to compare within the proven sepsis group the patients with bacteremia to those with VAP. The result section has also been completed with these new data (p.7 3rd §).

3. We do not agree with the reviewer comment. We found important to show that PCT could be an independent predictor of sepsis in our population of ICU patients. Accordingly, this strengthens the interest of PCT as compared to other sepsis markers such as fever, CRP, etc…

4. The difference between both ROC curves was not found to be statistically different. This point has been clarified in the text.

5. We do not think that sepsis and VAP should be considered as different disease. However, as shown by Bonten et al in the late 1990s (AJRCCM 1998), there might be 2 kind of VAP: those complicated with severe sepsis or septic shock, and those without. PCT elevation might be different since the inflammatory cytokine pattern of response was found to vary according to the severity of the disease, as also recently suggested by Luyt et al (AJRCCM 2005). As a result, PCT elevation might reflect rather the degree of the systemic inflammatory response to the infection, than its origin. We should however acknowledge that PCT elevation was greater in the patients with bacteremia than in those with VAP. This limitation has already been detailed in the discussion section as an answer to comment 1.a).

Minor essential revisions:
1. “objective” has been added to the abstract
2. We acknowledge that age is not statistically different between groups. The sentence has been modified accordingly.
3. We have chosen the cut-off values that provide the best compromise between sensibility and specificity according to the ROC curve. We acknowledge that PCT has a bad NPV in this setting with the chosen threshold.

Reviewer 2:
General Remark:
We use routinely PCT measurement in high risk patients, as a way to diagnose promptly ICU-acquired sepsis, as suggested by the recently published study by Jensen et al (CCM 2006). We have tried in the present study to assess the relevance of such a practice and we believe that it might be useful in subset of
patients as those included herein. Our title looks therefore appropriate.

Specific remarks:
1. We do not agree with the reviewer since we have actually tested PCT in the sole patients with either suspected or proven ICU-acquired sepsis.
2. PCT measurement before the day of clinical suspicion were available in most of the included patients (45 out of 57) because we routinely do this test in our patients for the reasons detailed above.
3. We apologize for this English expression mistake. Dosage has been replaced by measurement.
4. We acknowledge that the methods section needs to be clarified. Substantial changes have been brought in an attempt to improve this section of the manuscript. A flow chart (figure 1) has been added, as also suggested by other reviewers.
5. We acknowledge that critically ill patients are prone to develop nosocomial viral infections (and fungal as well) but we have decided to considered the sole bacterial infections. This point has been yet discussed as a limitation in the Discussion section (p. 10, 1st §).
6. Our hypothesis was that PCT elevation could be earlier and more sensitive than any other marker of infection used in the ICU setting such as fever or WBC. We believe that our findings, in spite of the limitations of the study, support this hypothesis.
7. Half error bars are presented instead of full error bars in order to provide a more readable figure.

Reviewer 3:

Major compulsory revisions:
1. we should acknowledge that the CPIS we used was slightly different than the original one. Accordingly, we used quantitative culture results (i.e., tracheal aspirates culture was considered as positive only if the 106 cfu/mL threshold was reached). This point has been yet clarified in the Methods section (p. 5 1st §).
2. We acknowledge that the concern raised by the reviewer about the CPIS diagnosis value is relevant and appears now more clearly as a limitation of the study in the discussion section. We also should admit that some patients with positive tracheal aspirates culture were included into the control group, given the lack of additional evidence supporting the diagnosis of VAP. CPIS below the 6 points threshold was not the only criteria used for delineating VAP from no VAP patients, since the presence of new pulmonary infiltrate was also required.
3. The variables associated with the risk of proven bacterial sepsis with a p value less than 0.20 were included in the multivariate analysis model as told in the methods section. The CPIS was not included since our group of proven sepsis included patients with BSI and not VAP.
4. The required data have been added to Table 1. As the reviewer will see, our patients are not so different from “usual” medical ICU patients.
5. As told in the Methods section, the patients with a previous history of sepsis within the 7 day preceding the studied event have been excluded. As a result, some patients with early ICU-acquired sepsis such as early VAP have been excluded from the study if sepsis was the primary cause of ICU admission. Therefore, we mainly report late-onset nosocomial sepsis. This point appears now as a limitation of our study that could hamper any generalization of our findings (p. 9, 3rd §).

6. We agree with the reviewer about the fact that likelihood ratios should be added. The conclusion regarding PCT diagnosis value could actually be mitigated but is not so bad. Any way, PCT looks more reliable than the other tested variables as illustrated by the comparison of the corresponding AUROCC.

7. As previously requested, the study population is now more accurately described in Table 1. The main difference with the population of the cited article is the absence of prior surgery which is known to increase PCT per se.

8. We agree with the reviewer when he said that PCT measurement cannot be performed every day in every ICU patient. We believe however that it could be useful in a subset of patients in whom the risk of nosocomial sepsis is particularly elevated, as those included in our study. As emphasized by the reviewer, those patients are peculiar since ICU length of stay is rather long. Basically, we believe that a daily monitoring of PCT is desirable in such patients. In theory, since PCT half-life is near from 24-hour, a two-time a week measurement won’t allow an accurate PCT kinetic assessment. Accordingly, delta PCT were not found to be relevant when any previous value (instead of the day before value) was considered for the early diagnosis of VAP in the mentioned study. In our study, it is worth noting that every included patient had at least 2 PCT measurements within the 3 day preceding the suspicion of sepsis (see Methods). Following the reviewer suggestion, other delta values than between D-1 and D0 have been tested (i.e., delta D-2-D0 and delta D-3-D0). We obtained also interesting results that have been included in the Table 2. These findings are now cited in the text and discussed as suggested by the reviewer. Accordingly, such findings could support the routine measurement of PCT on a 2 or 3 time-a-week basis instead of a daily assessment.

9. We agree with the reviewer comment. The sentence has been modified as suggested by the reviewer, in an attempt to be more cautious with our data interpretation.

Minor essential revisions:
1. The number of patients with PCT available at each day has been added to “figure 1”, which is now Figure 2 since a flow chart has been added.
2. The Table 3 has been deleted as required by the reviewer.
3. The economical concern regarding PCT daily measurement is now presented as a limitation of the study (P. 10 1st §).