Author's response to reviews

Title: Procalcitonin is not sufficiently reliable to be the sole marker of neonatal sepsis of nosocomial origin

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Author's response to reviews: see over
Comments to Reviewer’s report

First of all, we would like to thank the reviewers for their valuable comments and corrections.

Reviewer: Daynia Elizabeth E Ballot

1. The question posed by the authors is well defined but not new. However, it is a current topic that is still under evaluation, especially in neonates. Procalcitonin is considered to be an excellent marker of sepsis in some circumstances, but this has not been shown consistently in neonatal sepsis.

2. The methods are appropriate and well described and there are sufficient details provided to replicate the work but I have the following comments.

   a. The sample size is a little small

   Response: We agree that the absolute precision we got for sensitivity (10%) and specificity (12%) would be improved with a bigger sample size. Anyway we think they are enough for an estimation of the utility of PCT in nosocomial neonatal sepsis, and not only bigger but also comparative studies with other markers of infection are needed determine the real value of PCT in daily practice. The paragraph (page 11) now reads:

   “Although this may be considered a limitation of the present findings, the study was to assess the diagnostic usefulness of PCT as a single marker of neonatal sepsis of nosocomial origin. In addition, a comparative study would have required a bigger sample size in order to detect differences between infection markers.”

   b. The confirmed and not confirmed sepsis needs to be defined better. Although the whole definition of neonatal sepsis is difficult, as discussed at length by the authors, the “not confirmed” group is not clearly defined. Were these symptomatic babies with abnormal laboratory tests and a negative blood culture (i.e. is the only difference between the two groups a negative blood culture)?

   Response: Yes, the only difference between the two groups is negative blood culture. We have revised the manuscript to clarify this point, since it was a bit confusing. The paragraph (page 6) now reads:

   “Sepsis of nosocomial origin was suspected in the presence of at least three clinical signs and one risk factor for the nosocomial origin of the infectious process (as shown in Table 1), and laboratory signs consistent with infection (abnormal hematologic values and/or C-reactive protein > 1.2 mg/dL). Diagnostic of confirmed nosocomial sepsis was established when blood culture was positive.”

   c. What about false negative blood cultures in truly septic babies? A certain proportion of the “not confirmed” group is actually septic with negative cultures. This should be discussed.

   Response: This point is already discussed in page 10: “it may be possible that some cases of true bloodstream infection could not have been confirmed due to false negative blood cultures.”

   d. The issue of contaminated blood cultures is not addressed.

   Response: We have not addressed this point because including only symptomatic patients, joined to strict microbiologic criteria and the use of Maki technic for catheter cultures, makes highly improbable a false positive in our study.
e. Were all the coagulase negative staphylococci regarded as significant? Were there none regarded as contaminants? This should be discussed in more detail, although the sepsis with CoNS is well defined.

Response: 7 patients had coagulase negative staphylococci on blood culture that were regarded as contaminants because they did not meet criteria established in Methods section. We have revised the text to include this data in the Results section (1st paragraph).

f. On page 7, 0.5 mls of blood for culture is generally considered sufficient in VLBW infants.

Response: Not every authors agree with this assertion (i.e. Schelonka et al., J Pediatr 1996;129:275-8), and we tried to minimize the risk of false negative cultures using not less than 1 mL.

3. The data appear to be sound and there is a “not confirmed” sepsis to act as a control group. It may have been better to include a “well” group, although the authors do discuss this concern in the paper adequately.

Response: In fact, we think using control group of healthy infants is not the better option since it tends to overestimate the reliability of a diagnostic test (Jaeschke et al. JAMA 1994, 271: 389-391), and the test is intended to be used over newborn infants with clinical signs of sepsis.

4. The manuscript appears to adhere to standards of reporting.

5. The discussion and conclusions are well presented and supported by the data.

6. The title and abstract convey the findings well.

7. The writing is acceptable.

There are a few lines where spacing is incorrect:
Page 7 after PCT assay and Statistical Analysis
Page 8 p < 0.05
Weight is expressed in incorrect units – should be grams and not kilograms (page 8 line 7).

Response: Thank you; we have revised the text to include these corrections.

Reviewer: Jean-Louis Vincent

1. The authors should emphasize in the discussion section that this study has the advantage of being multicenter.

Response: We have revised the manuscript, including a note in the discussion. The paragraph (page 9) now reads:

"However, there are relatively few studies of the value of serum PCT for the diagnosis of nosocomial neonatal sepsis, and none of them is a multicenter one."

2. Discussion section middle of page 10, is this really a homogeneous group of neonates? Why?

Response: We say this is a homogeneous group of neonates because we use a group of newborn infants with clinical suspicion of sepsis and then we apply the test, instead of starting with two groups with different clinical signs (i.e., healthy asymptomatic neonates vs septic neonates) as other authors did.
3. **End of the discussion section (second half of page 11):** Anyhow; the SIRS criteria have not been very helpful so that clinicians rely on them less and less (see Levy et al. Crit Care Med 2003). This is precisely why sepsis markers may be helpful. This entire paragraph could be either deleted or reoriented to emphasize the limitations of the SIRS criteria.

**Response:** We just try to discuss an important point regarding any research about sepsis. Levy et al. conclude that “While SIRS remains a useful concept, the diagnostic criteria for SIRS published in 1992 are overly sensitive and nonspecific” and also that “use of biomarkers for diagnosing sepsis is premature”. Studies as ours might be focused to investigate if a biomarker (i.e. PCT) applied to patients with SIRS can differentiate sepsis from other causes of SIRS, keeping sensitivity of SIRS criteria but improving specificity for sepsis. We think lack of SIRS and sepsis consensus criteria for premature neonates is an important limitation for diagnostic test trials.

4. **Table 2 does not really present the etiology of sepsis (but simply sepsis caused by CONS versus other pathogens.)**

**Response:** We have revised the table description according to the comment. The table 2 description now reads:

"Differences in serum PCT values according to final diagnosis (confirmed vs. not confirmed) and etiology (coagulase-negative staphylococci vs. other pathogens) of sepsis."

5. **Actually it would be nice to have more clinical and bacteriologic information concerning these 61 neonates.**

**Response:** We have added information about CoNS findings in not confirmed sepsis group that were considered as contaminants. We have not included a comparison of clinical variables between groups, since the diagnostic test is applied to just one sample of patients and not to two separate groups for which one must assess comparability. Anyway, we will consider including more information if the reviewer specify which one he is talking about.

Thanks again for your comments that help us to improve the manuscript. We would be pleased to respond if any further response were needed regarding this manuscript.

The Editorial Team ask us for indicating whether we obtained ethical approval for our study in the manuscript. This was already indicated in the Methods section (page 6, 1st paragraph): 
“"The study was approved by the Ethics Committees of the participating hospitals and the parents gave their informed consent.”

Sincerely,

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