Author's response to reviews

Title: Evaluation of procalcitonin for diagnosis of neonatal sepsis of vertical transmission

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Author's response to reviews: see over
We thank again the reviewers for their valuable comments and corrections. We have amended the manuscript to take account of them, with the exception of some points for which we have a different point of view. The changes and our responses are detailed below:

**Reviewer: Lucia Pacifico**

**Major Compulsory Revisions**

A. Authors' response to item #1 of my previous review is still inappropriate since "over a wide range of sensitivity and specificity Youden's index does not change very much";

**Response:** Selecting of a cutoff point is always an arbitrary decision, often difficult to take, and considering when and index "does not change very much" is also quite subjective. We have finally decided to add another table (Table 6) showing sensitivity, specificity, and other parameters when selecting cutoff points to achieve sensitivity>90%. Using these last cutoff points Youden’s index diminishes 0.46, 0.22, and 0.14 at birth, 12-24, and 36-48 h respectively compared to Table 5.

B. Authors' response to item #2 of my previous review is still inappropriate. Group C is most likely to comprise the uncertain or ill-defined subset of patients. In the real word we have these kinds of neonates. Thus, all data from this group should be included in the ROC analysis. It goes without saying, sentence on page 11, lines 3-4, should be deleted;

**Response:** A ROC curve analysis must be done classifying patients in ill and healthy ones (in this case infected and non-infected). As we pointed last review, we are not able to classify group 2C neither as infected nor as non-infected since, as exposed in the discussion, intrapartum antibiotics had been used in 22/79 neonates of this group (that may induce negative blood cultures), and 66/79 were treated with antibiotics after birth (as they were also infected). Any decision about this issue may imply a bias, and it is a limitation of our study. So, we have not made any changes to the text.

C. Authors responses to items #4 and #5 of my previous review are still inappropriate. The reader of the Journal needs to know the limit of quantification (rather than the detection limit) to quantify the precision of the method as well as the reliability of the diagnostic marker (PCT). Query to Authors: according to the manufacturer, what is the limit of quantification of LUMItest? In a few words, according to the manufacturer, what is the lowest PCT measured concentration with CVs (i.e. coefficients of variations) less than 10%? Thus Authors should report as undetected values not those read as 0.04 ng/mL, but those falling below the limit of quantification (i.e. ......);

**Response:** We just considered the limit of detection according to manufacturer (0.08 ng/mL), as most studies we know about PCT. Those values <0.08 ng/mL, that may include values from 0 to 0.08 ng/mL, were considered as 0.04 ng/mL for the statistical analysis.

D. Authors’ response to item #7 of my previous review is still flawed;

**Response:** We have redone the multiple regression analysis, with the advice of an expert in this method. Now we have log-transformed PCT values and then removed extreme values, so the variable shows better homocedasticity and can be considered as normal. We have included B coefficients. Both resuscitation and chorioamnionitis are independently associated to PCT.

The changes in the manuscript are in methods section (page 8, 1st paragraph), results (page 9, 2nd paragraph), discussion (page 11, 2nd paragraph), and new Table 3.

E. Authors' response to item #8 of my previous review is still flawed;

**Response:** Our objective was to study variables that might be associated to PCT values in asymptomatic non-infected neonates, in order to explain why they have relatively high PCT
during the first days of life. So we applied multiple lineal regression to newborns in group 1. As the “infected” variable is not present in that group, we don’t compare increases associated with the other variables to those observed for the presence of infection. Our opinion is that this question, from a clinical point of view, is better answered with the diagnostic efficacy analysis.

F. Authors’ response to item #9.d of my previous review is still inappropriate. Reference #25 includes infants with increased risk of infection (premature PROM > 12 hours, discoloring of amniotic fluid, or clinical signs of maternal or neonatal infection). Indeed, Authors of reference #25 state "Our data ..... give a more detailed picture of the time course of PCT in infants without infection......We cannot rule out subclinical infection in these infants". On which grounds can these neonates labelled as "healthy" neonates? It goes without saying, reference #25 is misleading since it does not report at all on the PCT "physiologic" (in neonates without any evidence of an abnormal state) peak. Yet, reference #26 is inappropriate since Monneret et al. did not provided evidence that the postnatal course of the 32 "healthy" neonates was unremarkable throughout the neonatal period, implying therefore no need of any management throughout this period.

Response: We agree that newborns of Sachse et al. and Monneret et al. may not be considered healthy as those of the other references (and so the term “physiologic” is not appropriate), although it is possible they describe the same phenomenon, since we think the probability that these neonates were infected or they had significant pathologies is very low. In order to avoid confusion, we have separate the references and the sentence now reads:

“[…]The physiological peak of serum PCT concentrations in healthy neonates has been previously reported [12,23], and increased PCT concentrations have also been found in neonates with very low probability of infection [27,28]…”

We think after the revision process the paper is much improved, and we hope you will find it suitable for publication in BMC Pediatrics.

Sincerely,

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