Author’s response to reviews

Title: Characteristics of neonates with culture-proven bloodstream infection who have low levels of C-reactive protein (<10 mg/L)

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Author’s response to reviews: see over
RE: MS# 5077672091640319  
Title: Characteristics of neonates with culture-proven bloodstream infection who have low levels of C-reactive protein (≤ 10 mg/L)

Dear Editor,

Thank you for your appreciated comments on our manuscript. We had the manuscript revised, mostly according to the reviewers’ suggestions. We will respond in detail to the reviewers’ comments. The replies for the reviewers’ criticisms are as followsings. We hope this revised version can be acceptable.

Best regards,

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Reviewer #1’s report:  
I read with great interest the revised version of the reference manuscript. Kindly consider the following comments for corrections.  
This current version had significantly improved from the initial submission and necessary corrections were made accordingly.  
Minor Essential Revisions:  
1. Under Results section, page 10: you may want to change the following words e.g. peri-natal (line 190) to perinatal, hypo-glycemia (line 195) to hypoglycemia, and leucopenia (line 199) to leucopenia  
Reply:  
Thank you for your instructive advice. I will change these words accordingly, thank you.

2. Table 2, page 28: you may want to italicize the scientific names of the organisms found in the legends of the Table 2; also no need to capitalize the species name e.g. Neisseria meningitides  
Reply:  
Thank you for your instructive advice. I will italicize the scientific names of the organisms found in the legends of the Table 2, and not to capitalize the species name, thank you.
3. Figure 1, is there a better version of the figure that has a better contrast and easier to read Kaplan-Meier graph?

Reply:
Thank you for your instructive advice. I will try to make the figure a better contrast and easier to read Kaplan-Meier graph as the revised figure 1, thank you.

Reviewer #2’s report:
Discretionary Revisions (which are recommendations for improvement but which the author can choose to ignore)

RESULTS
1. Table 1: add median (Q1-Q3) for birth-weight and gestational age

Reply:
Thank you for your instructive advice. I will add median (Q1-Q3) in the table 1 accordingly.

2. For me, data in the tables 1 and 2 are repeated too much in the text.

Reply:
Thank you for your instructive advice. I will try to summarize them in the text as possible as I can, thank you.

3. Statistics: I am interested in the association with sepsis attributable mortality for all three CRP groups and if you find an association for a particular CRP group, you do can execute a Cox regression analysis. This analysis can be stratified by birth-weight, for example for birth-weight groups 1500g or less and >1500g.

Reply:
Thank you for your instructive advice. An increased sepsis attributable mortality was significantly associated with the high CRP group when compared with the low CRP group. However, it was comparable between the middle and low CRP groups. The analysis by doing a Cox regression analysis will have similar results. To avoid too long paragraph, I choose to ignore this issue in the result section, thank you.

DISCUSSION
1. Line 241: extremely pre-term infants are defined as #28 weeks of gestational age; your mean is 30.2 weeks for low CRP group, so I really recommend to provide median gestational age (and median birth-weight); or change extremely into very-low gestational age.

Reply:
Thank you for your instructive advice. I will change “extremely pre-term” to “very-low gestational age” in line 241, thank you.

2. The article I suggested for comparison, i.e. Modi et al. (2009), is indeed entitled ‘A Case Definition for….. ’; I do see some elements you can use for comparison, but your focus is indeed different.

Reply:
Thank you for your instructive advice. I really appreciate your suggestion. However, if you allow me to ignore this reference, I will think it not very closely related to this study, thank you.

Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)

ABSTRACT:
1. Line 47: I wanted data on the elevated CRP-levels and the p-value but I do realize that this is much info for an abstract; for me, you can drop the percentages; I don’t like the term ‘tended to have’: they have elevated CRP or not; when the elevation is not significant I propose you say ‘a non-significant elevated CRP’…. 

Reply:
Thank you for your instructive advice. I will delete the term “tended to have”. I will drop the percentages. I will change the sentence to be “Patients with underlying gastrointestinal pathology, renal disorders, cholestasis, and pulmonary hypertension had a non-significant elevated CRP levels at the onset of sepsis.

2. Line 49: more common compared to who (which group)?

Reply:
Thank you for your instructive advice. I will add “than the other two groups” in Line 49.

3. Line 56: please rephrase ‘tended to occur’

Reply:
Thank you for your instructive advice. I will rephrase as “was more likely to occur” in Line 57, thank you.

RESULTS
1. Table 2 check: Enterococcus spp. belong to group D Streptococcus; you mean non-enterococcal group D?
Thank you for your instructive advice. In our blood cultures, most of the Enterococcus spp. is *E. faecalis*. If the blood culture showed group D streptococcus, it mean non-enterococcal group D streptococcus. I will revise it in the legend of Table 2, thank you.

**DISCUSSION**

1. Line 244: Although CoNs..., app ¼ of them are infected with...: grammatically ‘¼ of them’ refers to the CoNS episodes, so for me this is not clear/correct.

   **Reply:**
   Thank you for your instructive advice. “Approximately 1/4 of them” refers to BSI episodes with normal CRP. To avoid confusion, I will revise it as “approximately one-fourth of those with normal CRP are infected with Gram-negative bacteria, polymicrobial pathogens, and fungus” (in Line 245)

2. Line 247: same problem ....’ 30% of them’....

   **Reply:**
   Thank you for your instructive advice. I will revise it as “those with normal CRP” in Line 247.

3. 267-268: if I do interpret well, you cannot conclude that there is a strong association between CRP and ‘severity of illness’ (do you mean ‘infectious complications’?) and ‘treatment outcomes’ (do you mean ‘sepsis attributable mortality’?) because you only looked at the difference between the 3 CRP groups; you can rephrase by : Although we found that significant more infectious complications and sepsis attributable mortality occur in the CRP group >100 mg/L,.... If you want to find an association between CRP level and ‘infectious complications’ and between CRP and ‘mortality’ you have to examine (univariate analysis) the proportion of neonates with and without the characteristic; for example for the low CRP group: n (%) alive and n (%) death and calculate the p-value etc., further you can execute cox regression analysis as I already proposed.

   **Reply:**
   Thank you for your instructive advice. I will rephrase this sentence to be “Although we found that significant more infectious complications and sepsis attributable mortality occurred in the CRP group > 100 mg/L,........” in line 267,
thank you.