Author's response to reviews

Title: Procalcitonin Guided Antibiotic Therapy of Acute Exacerbations of Asthma: A Randomized Controlled Trial

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Author's response to reviews: see over
Dear editor,

Thank you again for the comments from two reviewers, which help us to polish our manuscript entitled “Procalcitonin Guided Antibiotic Therapy of Acute Exacerbations of Asthma: A Randomized Controlled Trial” (MS: 1761065640801709). We agree with the comments and would like to revise our manuscript point by point. The revised manuscript has been re-submitted to your journal.

Yours Sincerely,

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On behalf of all authors

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Replies to reviewers:

Reviewer 1

Q1: On page 12 and in your response letter you talk about IL-6 and PCT as indicators of infection and that the fact that they are both higher in patients with more severe disease, that this type of patient must have more bacterial infections. While you may be correct, I think we overall see more inflammatory mediators in more severe asthma and this supposition seems potentially flawed to me. If you can defend this thought with published work that describes only elevated IL-6 in infection, then state it and reference it and include it. Otherwise, I am not convinced of this statement.

Answer: We are sorry for this missing point in our manuscript. By retrieving concerned literatures, we can be sure that the elevation of IL-6 levels may predict the severity of lung infection. The related argument has been quoted in page 12 line 12 and key references have been added in our revised manuscript.

Q2: WRT Limitations, the fact that NO secondary factors were impacted is a touch concerning and indicates either overtreatment with antibiotics (possible) in the control group or that antibiotics don't seem to matter! Did you look at any other issues of resolution such as duration of illness etc.?

Answer: We are sorry for these misunderstandings. In your opinion, the fact that NO secondary factors were impacted seems to be concerning, while it happens to be our expectation that the therapeutic outcomes was not affected. This trial aimed to demonstrate that PCT can be used to determine whether the acute asthma patients have bacterial infections. The ultimate objective is to reduce unnecessary antibiotic use and avoid antibiotics abuse without compromising the therapeutic outcomes. In PCT group, the antibiotic usage rate was lower than that of the control group and the treatment did not affect the secondary outcomes. This point has been strengthened in
our manuscript in page 11 line 23. Last but not least, the severity of exacerbations of asthma of each patient was evaluated according to the GINA guidelines, which includes the parameters such as breathless, respiratory rate, SaO2%, wheeze, etc. (Reference 1). At the follow-up visit, we assessed the levels of asthma control in the same way and the parameters included daytime symptoms, limitation of activities, nocturnal symptoms/awakening, need for reliever/rescue treatment, lung function. However, duration of illness as well as other issues is not included in the guidelines.

Q3: Most of the antibiotic differential seems to be in milder asthma (table 3). This needs some commenting on as it seems that all the severe asthmatics needed antibiotics? This again speaks to my first point.

Answer: This is a vital question. By retrieving concerned literatures, we find bacterial colonization of the lower airways is common in patients with chronic severe asthma and is linked to the duration of asthma and the exacerbations in the past years. Besides, there is also a strong association between fungal sensitization and severity of asthma. Therefore, PCT test prevents antibiotics usage mostly in patients with mild to moderate asthma but without bacterial infection, while most patients with severe to critical asthma do suffer from bacterial infection and need to be treated with proper antibiotics. However, bacterial infection seems to only play a minor role in mild to moderate asthma. So patients with mild to moderate asthma in the control group would not have improved prognosis even though they were treated with unnecessary antibiotics. Related references and statements have been added in page 13 line1.

Reviewer 2

Major compulsory revision:

I realize, the manuscript does not include a paragraph on the power calculation, which is a major limitation. Such a paragraph should be added for readers to be able to
interpret the results.

**Answer:** Thank you for your suggestion. The power calculation paragraph has been added in page 13 line 15.

**Minor essential revisions:**

A reference has been added to the discussion and the sentence about PCT stability has been changed. However, the sentence is not understandable. When is the human body at room temperature? "At room temperature, PCT is stable in human body [23].

**Answer:** We are very sorry for this misleading point. The original meaning is the human body under normal physiological conditions. This error has been corrected in the submitted manuscript.