Author's response to reviews

Title: Two severe cases of H7N9 pneumonia patients with immunoneuroendocrine axis dysfunction and vitamin D insufficiency

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Cover letter (response)

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Prof. Dale Barnard and Nathaniel Nazareno, Editor
BMC infectious diseases
Re: MANUSCRIPT No. 2020232478109660: “Two severe H7N9 pneumonia patients with immunoneuroendocrine axis dysfunction and vitamin D insufficiency”

Dear Prof. Dale Barnard and Nathaniel Nazareno,

We wish to thank you and the two reviewers for considering our paper (“Two severe H7N9 pneumonia patients with immunoneuroendocrine axis dysfunction and vitamin D insufficiency”, MANUSCRIPT No. 2020232478109660), for publication in BMC infectious diseases.

As requested, we have enclosed a revised clean copy. Below, we provide point-by-point responses to all of the reviewers’ comments.

We look forward to hearing from you.

Sincerely,
In this manuscript, the authors report two cases of H7N9 pneumonia patients with immunoneuroendocrine axis dysfunction and vitamin D insufficiency. Both cases had been confirmed H7N9 infection by Chinese CDC. These two patients showed loss of cortisol rhythm, low serum phosphorus and vitamin D levels and decline of cellular immune function. I think the laboratory data are authentic. I have the following comments.

1. What are the relative clinical manifestations of immunoneuroendocrine axis dysfunction and vitamin D insufficiency in H7N9 pneumonia patients?.
Response: Some clinical manifestations of immunoneuroendocrine axis dysfunction and vitamin D insufficiency in H7N9 pneumonia patients can not easily be distinguished from the clinical manifestations of H7N9 pneumonia per se, for example fatigue, body ache, and so on.

2. Since vitamin D is known to possess anti-inflammatory and immune-modulating effects, whether vitamin D deficiency population were susceptible to H7N9 pneumonia?
Response: We think so. But one limitation of this study was that we didn’t know whether our patients had low level of 25OH-VitD before they had H7N9 pneumonia, so we can not conclude vitamin D deficiency population were susceptible to H7N9 pneumonia from my cases report.

3. Whether vitamin D deficiency before H7N9 pneumonia will lead to adverse outcome in H7N9 infection.
Response: We think so. But we need prospective studies to confirm this hypothesis.

4. Whether vitamin D replacement therapy will improve the outcome of H7N9 pneumonia?
Response: We think so. But we still need prospective studies to confirm this hypothesis.

5. Immunoneuroendocrine axis dysfunction is the result of H7N9 or Immunoneuroendocrine axis dysfunction can make people susceptible to H7N9?
Response: We think that H7N9 can cause Immunoneuroendocrine axis dysfunction. On the other hand, immunoneuroendocrine axis dysfunction can
also make people susceptible to H7N9.

6. Please refer the format of case report for BMC Infectious Disease.
Response: We are sorry for our mistake. We have revised my manuscript according the author guideline of BMC Infectious Disease.

7. Please provide the year when the patients were admitted.
Response: We have provided the year in our revised manuscript.

8. It is not necessary to repeat the therapeutic intervention in paragraph 3.
Response: We have deleted the therapeutic intervention in paragraph 3.

Reviewer: 2
Comments to the Author
In this case report, Dr. Yao et al. addressed novel immuno- and neuroendocrine dysfunctions in prolong phase of severe H7N9 pneumonia. The following are my comments.

- The authors should read the instructions for authors by BMC Infectious Diseases and improve their paper accordingly. The two cases can be presented in two paragraphs separately.
Response: We have revised the manuscript as suggested. The two cases is presented in one paragraphs because of word limit.

- Detailed methods of avian-origin influenza A (H7N9) virus identification should be included. Detailed information of the patients should also be provided, such as occupation, duration of antiviral agents and exposure to poultry in the last 7 days et al.
Response: We don’t supply detailed methods of avian-origin influenza A (H7N9) virus identification because of word limit of manuscript, H7N9 virus was identified by realtime PCR by CDC. Two patients don’t have occupation.

- Is HPA axis failure a common presentation in other influenza? What is the potential mechanism of HPA axis failure in H7N9 virus?
Response: Some studies showed that HPA axis dysfunction happened in other influenza. The potential mechanism of HPA axis failure in H7N9 virus include inflammation factors release, stress, cytokines, and so on.

- Similarly, is vitamin D insufficiency common in other influenza? What is the rationale and dosage of rocaltril treatment in these cases?
Response: Few studies showed that vitamin D insufficiency in other influenza. We used rocalirol 0.25ug qd.

- P3. The author mentioned “First, whether loss of cortisol rhythm, elevated cortisol…Second, whether correction…”. Stronger evidence is required to answer
those questions. This should be addressed.
Response: We only propose hypothesis.

- The manuscript should be read by a native English speaker.
Response: We have revised my manuscript.

- Page 2&3, Rocaltrol was mispelt rocalirol..
Response: We have revised my manuscript.

- Define an abbreviation/acronym at its first use in text such as CDC, PRL, PTH, ARDS et al.
Response: We have revised my manuscript.