Author’s response to reviews

Title: Clinical characteristics and managements of severe hand, foot and mouth disease caused by Enterovirus 71 and Coxsackievirus A16 in Shanghai, China

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Prof. Yoke-Fun Chan
Editor
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Dear Prof. Yoke-Fun Chan,

Many thanks for the letter dated January 12, 2018, regarding our manuscript entitled “Clinical characteristics and managements of severe hand, foot and mouth disease caused by Enterovirus 71 and Coxsackievirus A16 in Shanghai, China” (Manuscript ID INFD-D-18-01940R1). We appreciate the valuable comments of the editor and reviewers. Based on the editor and reviewers’ comments and suggestions, we have revised the manuscript. Our specific point-by-point responses to the editor and reviewers’ comments and suggestions are as follows:
1. According to ICTV taxonomy (www.picornaviridae.com), EV-71 should be changed to EV-A71; enterovirus 71 to enterovirus A71.
Response: We thank for the valuable comments from the editor, and we have changed EV-71 to EV-A71, and enterovirus 71 to enterovirus A71 in the revised manuscript.

2. Table 2. Since you have 50 mild EV-A71, and 50 mild CV-A16, are there any difference between mild and severe EV-A71 and CV-A16, respectively?
Response: The 50 mild EV-A71 and 50 mild CV-A16 cases were random selected from outpatients of different age groups (<1year: 5; 1-3 years: 52; 3-5 years: 25; >5 years: 12). None of those children were developed to severe HFMD. There are no statistical differences in gender, age between mild and severe EV-A71 and CV-A16 cases, respectively.

3. Table 2. The values of severe CV-A16 are different from the previous submission, which one is correct? Also, severe EV-A71 and CV-A16 cytokine profiles in this Table 2 should be before treatment?
Response: The values of severe CV-A16 in Table 2 of current version are correct, and all values of severe EV-A71 and CV-A16 cytokine profiles in Table 2 were before treatment.

4. Values of cytokines in mild patients are different in Table 2 and 3, which one is correct? Authors should proofread all the results.
Response: Values of cytokines in table 2 were from all 100 mild cases. In table 3, only 50 mild EV-A71 cases were included to the analysis, and as the same in Table 4 (only included 50 mild CV-A16 cases). Based on the comment 6, we have modified the table 3 and 4 to compare the changes of cytokines levels before and after antiviral treatment.

5. Table 3 versus Table 2. I am not sure why the cytokines for IL-1β, IL-2 and IL-6 are similar in severe EV-A71 for Table 2 and EV-A71 RBV+IVIG in Table 3. Pls explain.
Response: There are no statistical differences in cytokines levels between severe EV-A71 treated with RBV+IVIG and RBV only. In addition to the limited number of the study subjects, the median and IQR data are similar between those two groups. We have modified the table 3 according to the comment 6.

6. Table 3 and 4. The current statistics "a vs b, statistical significance" make these Tables very confusing. If the objectives are to determine if IVIG and RBV effectiveness, and lowering cytokine levels are used as better outcome, then comparison should be between severe EV-A71 before and after treatment? The description of results are accurate in pg13, but that’s not reflected in the Table 3 and 4. Pls modify accordingly. Also double check all the values since the number of patients are different.
Response: We fully agree with this important concern. We have modified Table 3 and 4 to compare the cytokine levels before and after IVIG+RBV/RBV treatment in severe EV-A71 (Table 3) and CV-A16 (Table 4) cases.
In addition, we observed the values of IFN-γ were presented in Table 2, 3, and 4 in mistake. We have corrected the values of IFN-γ and re-performed the statistical analysis after carefully checking the original data by Drs. Cai Kang and Qingli Zhang (see Table 2, 3, and 4 in revised manuscript). We have proofread all the results presented in the tables and confirmed by all co-authors.

Koh Mia Tuang (Reviewer 1): The authors have addressed most of the points raised in my earlier review of the manuscript. However, there still exists a number of grammatical errors which need to be corrected before it can be
considered to go to proof. I have taken the liberty to make those corrections on the revised manuscript and submitted to the Editor. I would suggest that the authors make those corrections and re-submit.

Response: We highly appreciate all the valuable comments of reviewer 1, and have corrected the grammatical errors accordingly in the revised manuscript (see revised manuscript with track changes).

We hope that our revised manuscript is now suitable for publication in BMC Infectious Diseases.

Sincerely Yours,

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