Reviewer’s report

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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Reviewer: Koh Mia Tuang

Reviewer's report:

1. Overall this study is of major interest and clinical importance and merits to be published.
2. However, there are far too much corrections needed from the point of the English grammar and phrasing of the sentences to reflect their true meaning. I have attempted to make suggestions for this but there were others which need fairly extensive correction.

Pg 3 Line 27: minor grammatical correction and paraphrasing
However, neurologic and systemic complications, such as encephalomyelitis, aseptic meningitis, acute flaccid paralysis, and even brainstem encephalitis, can developed rapidly in a small minority of cases.

Pg 3 Line 49: In past decades HFMD outbreaks worldwide causing epidemics were reportedly due to EV71 and CV-A16.

Pg 4 Line 24: Severe and fatal cases of HFMD caused by CV-A16 were also reported [18].

Pg 4 Line 45: Inclusion criteria were children aged 1 month to 14 years, with severe EV71 or CV-A16 HFMD which required hospital admission under the Pediatric Department of Infectious Diseases at Xinhua Hospital.

Pg 4 Line 52: Children with significant underlying disease, and children with mild EV71 or CVA16 HFMD who do not require admission were excluded from the study.

Pg 6 Line 55: … possible HFMD and/or herpangina and/or aseptic meningitis would be better to replace "and/or aseptic meningitis" with "with or without aseptic meningitis"

Pg 5 Lines 4, 16: For definition of aseptic meningitis these two lines could be merged and better defined in terms of both clinical and CSF laboratory criteria instead of separating them into different lines for easier reading.

Pg 5 Line 41: It should be "Indications for antiviral treatment"
0.5 mg/time should be 0.5 mg per dose; IVIG at 1 g/kg 2 times per day should be IVIG 1 g/kg given twice daily.

It is not clear in the section on "Antiviral treatments" whether all patients were given ribavirin and
those with severe disease were given IVIG in addition to the ribavirin.

Pg 6 Line 4 : Is there a reference to the manufacturer's instructions on the performance of the test?

Pg 6 Line 31 : "length of stay" instead of "hospitalization duration"

Pg 6 Line 34 : Do the authors mean "treatment outcome" when they refer to "outcomes to identify"?

Pg 6 Line 36 : ..... and H test was used to compare the difference between multiple groups

Pg 7 Line 7 : None of the children required pediatric intensive care unit (PICU) care

Do the authors have a different criteria for severe HFMD cases and those who required intensive care? If so, what are the indications for intensive care?

Pg 4 Lines 47 and 52 : 
Can authors please clarify what constitutes severe and mild HFMD; i.e their definitions.
What constitutes "significant underlying disease"?

Pg 4 Line 52 : Please clarify if subjects were enrolled into study only if, in the opinion of the investigators, admissions were based on "severe HFMD" due solely to EV71 and CA-16 (subsequently confirmed by RT-PCR). Also please confirmed that if in the opinion of the investigators, if a subject has severe clinical disease but has a "significant underlying disease" deemed to contribute to the severity of disease, the subject is excluded from study.

Pg 7 Line 36 : "Laboratory tests showed that white blood cell (WBC), C reactive protein (CRP), creatinekinase MB (CKMB) were evaluated in most of those hospitalized subjects. Blood sugar (BS) and alanine aminotransferase (ALT) were evaluated in some of subjects"

Please clarify if the authors mean "elevated" rather than "evaluated"

Pg 8 Line 24 : Please explain what "critical illness" the investigators were trying to prevent with IVIG and RBV

Table 5 : The authors are comparing the "clinical and laboratory outcomes" among subjects with severe HFMD with and without treatment with IVIG. The original title of Table 5 does not reflect this objective.

Pg 10 Line 41 : In addition, the subjects with more severe symptoms which were treated with IVIG showed no statistical differences of cytokine levels with subjects without IVIG ........
Re-phrase suggested:
Among subjects with severe HFMD there was no statistical differences in their cytokine levels irrespective of whether they were given IVIG, suggesting that cytokine levels may not be an indicator for severe HFMD due to EV71 and CA-A16.

Pg 11 Line 58 : representational with respect to severity factors.

Do authors mean "several" instead of "severity" and "representative" instead of "representational"?
Authors should admit there is selection bias of cases confirmed to be caused by EV71 and CA-A16 only.

**Are the methods appropriate and well described?**
If not, please specify what is required in your comments to the authors.

No

**Does the work include the necessary controls?**
If not, please specify which controls are required in your comments to the authors.

Yes

**Are the conclusions drawn adequately supported by the data shown?**
If not, please explain in your comments to the authors.

Yes

**Are you able to assess any statistics in the manuscript or would you recommend an additional statistical review?**
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I recommend additional statistical review

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Please indicate the quality of language in the manuscript:

Not suitable for publication unless extensively edited

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