

Current knowledge about the outbreak of acute severe hepatitis of unknown origin among children

Li-Xin Pan, Guan-Yu Wang, Jian-Hong Zhong*, Xiao-Hui Fan*

*Corresponding authors

Jian-Hong Zhong

Guangxi Medical University Cancer Hospital, He Di Rd. #71, Nanning 530021, P.R. China

Xiao-Hui Fan

School of Preclinical Medicine, Guangxi Medical University

Handling editor:

Michal Heger

Department of Pharmaceutics, Utrecht University, the Netherlands

Department of Pharmaceutics, Jiaying University Medical College, Zhejiang, China

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1st Editorial decision

07-Sept-2022

Ref.: Ms. No. JCTRes-D-22-00106

Current knowledge about the outbreak of acute severe hepatitis of unknown origin among children

Journal of Clinical and Translational Research

Dear Mr Zhong,

Reviewers have now commented on your paper. You will see that they are advising that you revise your manuscript. If you are prepared to undertake the work required, I would be pleased to reconsider my decision.

For your guidance, reviewers' comments are appended below.

If you decide to revise the work, please submit a list of changes or a rebuttal against each point which is being raised when you submit the revised manuscript. Also, please ensure that the track changes function is switched on when implementing the revisions. This enables the reviewers to rapidly verify all changes made.

Your revision is due by Oct 07, 2022.

To submit a revision, go to <https://www.editorialmanager.com/jctres/> and log in as an Author. You will see a menu item call Submission Needing Revision. You will find your submission record there.

Yours sincerely

Michal Heger
Editor-in-Chief
Journal of Clinical and Translational Research

Reviewers' comments:

Reviewer #1: This is a well written documentation of what was known regarding acute severe hepatitis of unknown origin among children up to 8th July.

As this is a very rapidly evolving field, important novel information is missing and should be added. Two highly relevant papers have been submitted for publication and are available in a pre-peer reviewed form in MedRxiv: Ho et al. Adeno-associated virus 2 infection in children with non-A-E hepatitis. medRxiv preprint doi: <https://doi.org/10.1101/2022.07.19.22277425>; Morfopoulou et al. Genomic investigations of acute hepatitis of unknown aetiology in children. medRxiv preprint doi: <https://doi.org/10.1101/2022.07.28.22277963>

Reviewer #2: The authors are attempting to capture the up to date knowledge on ac.sevre hepatitis in children.

the manuscript though requires major revision:

1. the data needs to be updated to the UK HSA technical briefing 4 as in the current status the manuscript is not reflective of the current knowledge and of reduced value to your readership
2. the authors fail to highlight the association with other virus especially AAV2 which is even mentioned in the UK HSA technical briefing 3
3. the discussion needs to focus on the possibility of co-infection and immunoparesis. The comment on staphylococcus induced toxic shock in mice is not very relevant for the purpose of the manuscript.
4. overall, the analysis and discussion is not going into the necessary depth and need revision.
5. the authors should include the published work from UK paed. liver centres for more insight into the management, complications and outcome of these cases

-Clinical Spectrum of Children with Acute Hepatitis of Unknown Cause.

Kelgeri C et al.

-Outbreak of hepatitis in children: clinical course of children with acute liver failure admitted to the intensive care unit.

Deep A et al.

Minor points:

1. p3 line 47 amend to "have not presented with fever"
2. p5 line 110 use the term immunoparesis rather than immunosuppression
3. p6. line 127 amend to "only emphasise upon ..."

There is additional documentation related to this decision letter. To access the file(s), please

click the link below. You may also login to the system and click the 'View Attachments' link in the Action column.

Authors' response

Dear Editor and Reviewers:

Thank you for your letter and for the reviewers' comments concerning our manuscript entitled "Current knowledge about the outbreak of acute severe hepatitis of unknown origin among children" (ID: JCTRes-D-22-00106). Those comments are valuable for improving the quality of our manuscript. Revisions are marked in red in the manuscript. The main corrections in the paper and the responses to the reviewer's comments are as flowing:

Responds to the reviewer's comments:

Reviewer #1:

1. Response to comment: Important novel information is missing in the manuscript.

Response: Just as you mentioned in your comments, acute severe hepatitis of unknown aetiology (ASHep-UA) is a rapidly evolved disease. Thus, we integrated available information released by the World Health Organization (the report is updated as of 12 July 2022), the UK Health Security Agency (technical briefing 4 is updated as of 26 July 2022), and the Centers for Disease Control (data are updated as of 17 August 2022) to obtain the latest number of probable cases, cases required liver transplant, and death as of 25 September 2022 (p2 lines 7 and 9, p2 lines 17-18, p4 lines 25-31, and Figure 1).

We expand the section "Metagenomic sequencing of ASHep-UA" and the corresponding discussion to share our insights into the association between adeno-associated virus 2 (AAV2) and ASHep-UA after reading the two relevant papers (p4 lines 73-86, p6 lines 134-136, and p6 lines 148-p9 lines 159).

We sincerely appreciate your comments and suggestions for our manuscript.

Reviewer #2:

1. Response to comment: The data needs to be updated to the UK HSA technical briefing 4.

Response: We have updated our data based on the technical briefing 4 released by the UK Health Security Agency and the corresponding report was cited (p2 lines 38-39, p3 lines 42-45, p3 lines 65-67, p5 lines 103-104).

2. Response to comment: The association with other virus especially AAV2 was missing.

Response: We regret that we previously omitted the relevant information referring to the association between ASHep-UA and adeno-associated virus 2. Our understanding of this association was added to the manuscript, which was mentioned above.

3. Response to comment: the discussion needs to focus on the possibility of co-infection and immunoparesis. The comment on staphylococcus induced toxic shock in mice is not very relevant for the purpose of the manuscript.

Response: Due to the roles of the co-infection (adenovirus and SARS-CoV-2, adenovirus and AAV2, or even adenovirus, AAV2 and HHV-6) in the outbreak of ASHep-UA are still under investigation, we have not come up with more insights based on the available data. However, we noticed that the HLA-DRB1*04:01 allele was mentioned in the study of Glasgow and UCL, which may lead to more severe clinical outcomes for ASHep-UA cases due to the increased genetic risk (Ho et al. Adeno-associated virus 2 infection in children with non-A-E hepatitis.; Morfopoulou et al. Genomic investigations of acute hepatitis of unknown aetiology in children.). The reason for us to quote “the comment on staphylococcus induced toxic shock in mice” is that SARS-CoV-2 possesses a superantigen motif similar to that of *Staphylococcus* enterotoxin B, which possibly means the co-infection of adenovirus and SARS-CoV-2 can result in severe liver damage at least in mice (Brodin P, Arditi M. Severe acute hepatitis in children: investigate SARS-CoV-2 superantigens.).

4. Response to comment: The analysis and discussion is not going into the necessary depth.

Response: The limited depth of the analysis and discussion in the manuscript may be due to our limited understanding of the relevant report and the difficulty of obtaining raw data of the ASHep-UA. We had tried to integrate the available data about this recent outbreak as we can, and we sincerely hope that our manuscript advances the understanding of ASHep-UA.

5. Response to comment: More insight into the management, complications and outcome of ASHep-UA cases should be included.

Response: Our understanding of the study of Deep A et al. was added in p3 lines 51-53.

Thank you for your comments and advice.

Other revisions: **p3 line 47** amend to “have not presented with fever”; **p6 line 131** amend to “immunoparesis”; **p7 line 164** amend to “only emphasize on”.

Revisions not mentioned above: As the high frequency of adenovirus and human herpesvirus present in the manuscript, abbreviated forms for adenovirus (AdV) and human herpes virus (HHV) were used for readability. All revisions in our manuscript were marked in red.

Once again, thank you very much for your comments and suggestions.

2nd Editorial decision
26-Sep-2022

Ref.: Ms. No. JCTRes-D-22-00106R1
Current knowledge about the outbreak of acute severe hepatitis of unknown origin among children
Journal of Clinical and Translational Research

Dear authors,

I am pleased to inform you that your manuscript has been accepted for publication in the Journal of Clinical and Translational Research.

You will receive the proofs of your article shortly, which we kindly ask you to thoroughly review for any errors.

Thank you for submitting your work to JCTR.

Kindest regards,

Michal Heger
Editor-in-Chief
Journal of Clinical and Translational Research

Comments from the editors and reviewers: