

Reviewer #1: Dear Sir/Madam With great interest I studied the article titled (Transfusion-transmitted hepatitis E: what we know so far? Manuscript NO: 66965). In this article, authors have tried to describe transmission of hepatitis E through transfusion of blood products (Fresh frozen plasma, platelet concentrates and packed RBCs) and organ transplantation. Risks of transmission, clinical features, diagnosis, management and long term prognosis has been described in detail. This topic covers a new interesting area in field of hepatology in the current era of organ transplantation and immunosuppression. The article is comprehensive and written well in a lucid manner. However, few changes in key words, discussion and corrections in grammar should be done which I have mentioned in the attachments.

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With great interest I studied the article titled (**Transfusion-transmitted hepatitis E: what we know so far? Manuscript NO: 66965**). In this article, authors have tried to describe transmission of hepatitis E through transfusion of blood products (Fresh frozen plasma, platelet concentrates and packed RBCs) and organ transplantation. Risks of transmission, clinical features, diagnosis, management and long term prognosis has been described in detail. This topic covers a new interesting area in field of hepatology in the current era of organ transplantation and immunosuppression. The article is comprehensive and written well in a lucid manner. However, I would like to make few comments.

1. **Title-** The title reflects well the subject of manuscript. However, a lot of emphasis is given on the structure of HEV as well as extrahepatic manifestations of HEV infection which may not be relevant in the context of this review.

***Authors' response:** Details on HEV structure and genotype have been shortened. Extrahepatic manifestations have been summarized in Table 1 instead of in the main text.*

2. **Abstract-** Abstract has been written well and it summarize and reflect the work described in the manuscript
3. **Key words-**HEV and hepatitis E have been provided as key word. Both looks same. I suggest you to add acute and chronic hepatitis or only hepatitis. 'Blood' as a key word seems odd. Both transfusion and organ transplantation with underlying immunosuppressed state are key culprit of TTE. Instead of immunocompromised, immunosuppression can be used.

Authors' response: Key words have been changed according to the suggestions.

4. Background/Methods/Results/Biostatistics/Units-NA

5. Discussion-The authors have discussed well regarding TT-HEV infection including seroprevalence, screening methods, route of transmission, clinical features, diagnosis, treatment and prevention of this upcoming entity. However, I will like authors to add few more points

- a) Serological screening of donor individuals should take into account the two factors. These include the prevalence of HEV infection in particular region. In hyperendemic areas, screening of blood products should be of less importance compared to nonendemic areas. It is because in hyperendemic areas, most of the donors might have subclinical infection in past followed by viral clearance with persistent IgG antibodies. Similarly, recipients in these areas may also be seropositive without prior history of transfusion. I agree with the authors that in hyperendemic areas feco-oral transmission may play an important role in transmission of HEV. Similarly, recipient factors including immunosuppression state, underlying chronic liver disease and pregnancy predisposes individuals to develop fulminant hepatitis, ACLF or chronic hepatitis.

Authors' response: Discussion on serological screening has been added on page 16, including discussion of targeted screening of recipients' immunocompromised states.

- b) Clinical features of TT-HEV is not well described though very few small studies are available. Acute TT-HEV hepatitis generally takes the form of subclinical to intermediate illness, with no severe or fulminant cases having been reported. Transfusion recipients, a population that is variably immunosuppressed, are more vulnerable to chronic liver injury as a result of TT-HEV than the general population is as a result of foodborne infection (1).

Authors' response: We have added some discussion on the clinical features of TT-HEV and the fact that transfusion recipients are more vulnerable to chronic liver injury.

- c) Decompensated cirrhosis per se is a state of immunosuppression. Future studies are needed to look into clinical feature, course of illness and overall prognosis of these patients when exposed to HEV infection. Authors have

pointed out that these patients may develop ACLF which may not be universal. For example, in Asia, infection with genotype-1 is most common which most commonly cause acute hepatitis, fulminant hepatitis or ACLF which may not be true with other genotypes (genotype 3 or 4) which are classically known to cause chronic infection.

Authors' response: We understand that HEV genotype 1 more readily induces ACLF in patients with chronic liver disease compared with genotype 3 or 4. However, the study in Europe by Frias M et al. shows that HEV genotype 3 can still cause liver decompensation (reference 24: Frias M, López-López P, Rivero A, Rivero-Juarez A. Role of hepatitis E virus infection in acute-on-chronic liver failure. Biomed Res Int 2018; 2018: 9098535 [doi: 10.1155/2018/9098535. PMID: 30050945; PMCID: PMC6046156]), so we think that clinicians should remain vigilant to the possibility even in patients infected with less pathogenic genotypes.

6. **References-** The manuscript cites appropriately the latest, important and authoritative references in the introduction and discussion sections.
7. **Quality of manuscript organization and presentation-**The manuscript is organized and presented well. However, the emphasis on structure, genotype, clinical features including extrahepatic manifestations can be reduced
Authors' response: As suggested, we have reduced the section of the article on HEV structure, genotype and clinical features.
8. **Research methods and reporting/Ethics statement-NA**

Reviewer #2: The topic chosen by Cheung et al is unique. They have succinctly presented the review. Some minor suggestions- Place , (comma) before and in following sentences- jaundice, tea-coloured urine(.) and hepatomegaly. Many such sentences where , needs to be placed. Universal screening has been adopted in some countries after consideration of risk and resource availability etc. - delete etc. Clinical features and extrahepatic manifestations may be presented in a Table and can delete the text. The majority... may be a changed to A majority of or Most of (written in viremia paragraph, TT HEV, and treatment paragraph) Delete the last sentence in conclusions paragraph-Strategies to reduce foodborne transmission should also be emphasized.

Authors' response: Thank you for these suggestions. We have revised the punctuation and wording as the reviewer has suggested, deleted the relevant sentences and put the extrahepatic manifestations into a table (Table 1), with the text deleted.

(1) Science editor: Scientific quality: the authors stated that they aimed to review existing evidence on transfusion-transmitted hepatitis E virus, and the implications for screening of blood donations. The topic is within the scope of the WJG. Classification: Grade C; Grade A Summary of the Peer-Review Report: First reviewer stated that the authors have tried to describe transmission of hepatitis E through transfusion of blood products (Fresh frozen plasma, platelet concentrates and packed RBCs) and organ transplantation. Risks of transmission, clinical features, diagnosis, management and long term prognosis has been described in detail. This topic covers a new interesting area in field of hepatology in the current era of organ transplantation and immunosuppression. The article is comprehensive and written well in a lucid manner. However, few changes in key words, discussion and corrections in grammar should be done which I have mentioned in the attachments. Second reviewer stated that the authors he topic chosen by Cheung et al is unique. They have succinctly presented the review. Some minor suggestions- Place , (comma) before and in following sentences- jaundice, tea-coloured urine(.) and hepatomegaly. Many such sentences where , needs to be placed. Universal screening has been adopted in some countries after consideration of risk and resource availability etc. - delete etc. Clinical features and extrahepatic manifestations may be presented in a Table and can delete the text. The majority... may be a changed to A majority of or Most of (written in viremia paragraph, TT HEV, and treatment paragraph) Delete the last sentence in conclusions paragraph-Strategies to reduce foodborne transmission should also be emphasized. Format: There are 3 tables. References: A total of 218 references are cited. Self-cited references: There are no self-cited references. References recommendations: No

recommendation. Language evaluation: Classification: Grade B; Grade B Academic norms and rules: The authors provided the english language certificate. Supplementary Comments: There are many studies in the literature on this topic. It can be seen that the authors made an extensive literature review on HEV infection in this article. References should be rearranged according to WJG guideline. The PMID and DOI sections should be: [PMID: 31181848 DOI: 10.3390/v11060539] Re-Review: No- required. Recommendation: Conditional acceptance.

Authors' response: References have been revised to meet WJG guidelines. In addition, we have added a flow chart showing how to approach management of transfusion-transmitted HEV (Figure 1).