Editors-in-Chief

World Journal of Hepatology

Dear Editors,

Thank you for the information concerning the manuscript No. 51794 entitled "**Management of hepatitis C in children and adolescents during COVID-19 pandemic".**

We find the Reviewers' comments valuable and contributing to the improvement of the article. The manuscript has been reviewed accordingly and the revised paper is attached. Our answers to queries of the Reviewers and the consequent changes are described in detail below **in bold**. All changes made to the manuscript are highlighted in yellow.

Reviewer #1:

Pokorska-Śpiewak M et al. reviewed the current status of antiviral treatment of HCV for children and adolescents and recommendation of patient care for children and adolescents under the COVID-19 pandemic. This is an interesting topic and will draw the attention of the readers.

Thank you for the acknowledgement of our work.

With that being said, I would suggest a few modifications to improve the manuscript. Major comments:

1) The title "Antiviral treatment of hepatitis C in children and adolescents during COVID-19 pandemic" does not reflect the main subject of this manuscript adequately. The main idea of this manuscript is about "management" of pediatric patients during COVID-19 pandemic and not "treatment".

Thank you for this remark. We changed the title accordingly to "Management of hepatitis C in children and adolescents during COVID-19 pandemic".

2) Page 5 Line 8, The authors stated " Only three DAA regimens have been approved for use in adolescents by the European Medicines Agency (EMA) in Europe", and sofosbuvir/ledipasvir, sofosbuvir with ribavirin and glecaprevir/pibrentasvir (age between 12 to 17) come under this classification. However, after that (Line 14) , the authors mentioned that sofosbuvir/ledipasvir and sofosbuvir with ribavirin (age between 3 to 11),and sofosbuvir/velpatasvir (as young as 6 years of age or weighing at least 17 kg) are approved by FDA. In my understanding, these two kinds of regimens are approved in US but not in Europa, but this is a bit confusing. Please make them clear.

To explain this issue we added the following statement: "However, the FDA approvals are not applicable in Europe."

3) Page 7, "Management of pediatric patients with CHC during the COVID-19 pandemic" I understand that this is a review and the number of references for this topic is limited. However, suggestions/recommendations for the management/treatment specific to pediatric patients are not sufficient. For example, if you have experienced some difficulties in the management of pediatric patients under this situation, sharing such experiences will be helpful for the readers.

We added following additional recommendations for the management of CHC during the COVID-19 pandemic to this paragraph, and to Table 2, accordingly:

"It is essential to educate the patients on risk and precaution on COVID-19, especially in cases complicated by cirrhosis or end-stage liver disease, when the risk of severe course of COVID-19 exists[39]."

"In case of patients already on DAA treatment, therapy should be continued[39]"

"While planning DAA treatment, its priority should be determined. In patients with stable CHC, therapy may be safely postponed to after COVID-

19 pandemic. However, in selected cases with known advanced liver disease (e.g., with significant fibrosis – liver stiffness measurement > 7 kPa) or in patients with HIV coinfection, decision on starting therapy despite COVID-19 pandemic should be considered."

"The number of family members who accompany patients to their visits should be limited to one healthy parent or guardian[39]. All patients should be screened for symptoms of COVID-19 (e.g., fever, cough, shortness of breath, sore throat, rhinitis) and their temperature should be checked as they entry the clinical space[39]. There are currently no specific recommendations on screening for SARS-COV-2 infection in patients with CHC. As in individuals without HCV infection, children with CHC should be tested for COVID-19 in case of the presence of clinical symptoms suggesting the SARS-CoV-2 infection or having household contact with an infected family member. Our unpublished observations of over 100 pediatric patients with COVID-19 suggest that children usually acquire infection from infected close relatives. Thus, family history should be assessed in order to stratify the risk of the SARS-CoV-2 infection. In addition, testing should be considered in patients requiring hospitalization, in order to reduce a risk of spreading the infection by an asymptomatic person in the hospital setting."

"In all hospitalized COVID-19 patients, regular monitoring of aminotransferase levels is recommended, particularly in cases treated with tocilizumab or remdesivir, due to their hepatotoxicity[39]. As COVID-19 is only rarely associated with elevated liver enzymes in children, all pediatric patients with high aminotransferase levels during the SARS-CoV-2 infection should be evaluated for other etiologies and underlying liver diseases, including hepatitis A, B or C and drug-induced liver injury[39]."

Minor comments:

1) Page 4. Subtitle ”Antiviral treatment of HCV infection" does not reflect the main subject of this section.

Thank you for this remark. We changed the subtitle accordingly to “Management of HCV infection in children and adolescents”.

2) Please add references in Table 1.

We added the relevant references.

Reviewer #2:

This MS is a timely review on managing hepatitis C in children and adolescents during COVID-19 pandemic. The MS emphasized several efforts that can be made by pediatric hepatologists to prioritize patient care in children with CHC, including promoting telemedicine in the outpatient setting, using local laboratory testing for follow-up visits, and engaging in the home delivery of DAAs for patients under antiviral therapy whenever possible.

Thank you for the acknowledgement of our work.

I would like to have following comments:

1. Several professional societies, like AASLD and EASL have published their recommendations on hepatology practice during covid-19 pandemic, including hepatitis C. These should be referenced.

Thank you for this remark. The EASL-ESCMID recommendations had already been included in our manuscript (Ref. #35). We included also the American Association for the Study of Liver Diseases (AASLD) Expert Panel consensus statement as a reference No. 39: “Recent recommendations from the European Association for the Study of the Liver - European Society of Clinical Microbiology and Infectious Diseases (EASL - ESCMID) and the American Association for the Study of Liver Diseases (AASLD) Expert Panel consensus statement on the care of patents with liver disease during

the COVID-19 pandemic may also be useful for pediatricians caring for children with CHC [35, 39]" We also included these references in Table 2.

2. The session "Coronavirus disease 2019 (COVID-19) and the liver" was too brief and incomplete. For instance, mild LFTs elevation is commonly seen (37.2%; 15% to 53%) in covid-19 patients (Liver International. 2020; 40:998).

Thank you for this remark. We added a following paragraph to this section "Patients with chronic liver disease including cirrhosis may be at higher risk of death resulting from COVID-19, however, risk factors in specific liver diseases have not been defined[39]. It was revealed that SARS-CoV-2 similarly to SARS-CoV, uses angiotensin-converting enzyme 2 (ACE2) as its entry receptor [40]. Both liver and bile duct cells express ACE2. Thus, liver is a potential target for SARS-COV-2 infection[39, 40]. It results in liver injury, which is observed in 14.8% to 58% of patients, more commonly in severe COVID-19 cases[39, 40]. The incidence of liver disease in death cases of COVID-19 was as high as 58% to 78%[40]. Liver disease manifests mainly with elevated aminotransferase levels and/or slightly elevated bilirubin level[39, 40]. Liver injury is usually transient and does not require specific treatment[39]. Severe liver injury as a result of SARS-CoV-2 infection is uncommon in pediatric patients. In the rare cases of severe COVID-19 in children, increase in aminotransferase level was only mild (not exceeding 2 x upper limit of normal)[39]. There are only limited data on SARS-CoV-2 infection in patients with chronic viral hepatitis[35]. Thus, it remains unknown whether patients with chronic viral hepatitis B and/or C are more susceptible to liver injury from SARS-CoV-2[39]."

3. My main concern is several other key efforts are missing in this MS (comments 3-6). First, CHC patient education on risk and precaution on covid-19 should be included. That is patients with hepatitis C, especially complicated by cirrhosis and end-stage liver disease could be more at risk of having a bad reaction to the virus that causes COVID-19.

We added a following statement to the manuscript: "It is essential to educate the patients on risk and precaution on COVID-19, especially in cases complicated by cirrhosis or end-stage liver disease, when the risk of severe course of COVID-19 exists [39]." In addition, we added this issue in Table 2.

4. Another key question is whether CHC patients undergoing HCV treatment should be screened for covid-19 before starting DAA treatment. What are current societies recommendation?

Thank you for this remark. We added following statement to the manuscript: "There are currently no specific recommendations on screening for SARS-COV-2 infection in patients with CHC. As in individuals without HCV infection, children with CHC should be tested for COVID-19 in case of the presence of clinical symptoms suggesting the SARS-CoV-2 infection or having household contact with an infected family member. Our unpublished observations of over 100 pediatric patients with COVID-19 suggest that children usually acquire infection from infected close relatives. Thus, family history should be assessed in order to stratify the risk of the SARS-CoV-2 infection. In addition, testing should be considered in patients requiring hospitalization, in order to reduce a risk of spreading the infection by an asymptomatic person in the hospital setting."

5. Likewise, it should be addressed if we need to assess family history of ongoing covid-19, that will increase risk and possible interruption of DAA treatment.

We added a following statement to the manuscript: "It is essential to educate the patients on risk and precaution on COVID-19, especially in cases complicated by cirrhosis or end-stage liver disease, when the risk of severe course of COVID-19 exists[39]."

6. Perhaps, the priority of DAA treatment should also be determined before planning DAA treatment, as DAA treatment may be safely postponed to after covid-19 pandemic in those with stable CHC.

Thank you for this remark. The following statement was added to the manuscript: "While planning DAA treatment, its priority should be determined. In patients with stable CHC, therapy may be safely postponed to after COVID-19 pandemic. However, in selected cases with known advanced liver disease (e.g., with significant fibrosis – liver stiffness measurement > 7 kPa) or in patients with HIV coinfection, decision on starting therapy despite COVID-19 pandemic should be considered."; "In case of patients already on DAA treatment, therapy should be continued[39]".

7. In page 6, para2, line 5, "In April… " should be "In March…".

We changed this sentence accordingly.

We hope that the manuscript in this amended form conveys a clearer message and is now liable to be acceptable for publication.

Yours sincerely,

On behalf of all the coauthors,

Maria Pokorska-Śpiewak, MD, PhD
(Reviewer Number ID: 03337012)