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DEPARTMENT OF MEDICINE
Section of Gastroenterology • Center for Liver Diseases

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Subrata Ghosh, MD
Andrzej S Tarnawski, MD, PhD
Editors-in-Chief
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Dear Drs. Ghosh and Tarnawski:

We sincerely thank you for your invitation to re-submit our review article (ID# 69362) entitled “The ABCs of Viral Hepatitis” to the *World Journal of Gastroenterology* (*WJG*). We have a longstanding interest in both researching and treating patients with viral hepatitis and are pleased to share our review of Hepatitis A, B, C, D, E, and G with you. Each of the hepatitis viruses has a unique and fascinating history and poses a distinct diagnostic and therapeutic scenario to the treating clinician.

Since the discovery of each of these viruses, there has been extensive research with regards to epidemiology, infection transmission, virologic and biochemical properties of the viruses, and the natural clinical history of both acute and chronic infections. Research of the natural history has yielded fascinating discoveries about host immunologic responses to both acute and chronic viral infections, and combined with virologic data, has led to vaccines to prevent Hepatitis A, B, and E and highly effective antiviral therapies for chronic Hepatitis B and C. These recent therapeutic breakthroughs are transforming the fields of transplant medicine and global health. Most notably, these exciting developments have recently led to the ambitious goal of eliminating chronic viral hepatitis on a global scale. While this goal is attainable, there are many barriers to achieving global elimination, many of which are being actively researched in basic science and clinical labs on the local, national, and global levels.

In this review, we provide a historical perspective while also providing pertinent clinical information and recent organizational guidelines for each of the individual hepatitis viruses. Finally, we synthesize this information with the latest research to focus on exciting future directions. We believe that this review will be of high interest to the readership of the *World Journal of Gastroenterology*.

After email discussion with Lin-Yutong Wang, we have decided to re-submit our manuscript to *World Journal of Gastroenterology* with the recommended revisions detailed at the end of this cover letter.

Once again, thank you for considering our manuscript for publication in the *World Journal of Gastroenterology*. We hope that you share our enthusiasm for this area and look forward to your comments.

Best regards,

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The University of Chicago Medicine

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OUR RESPONSES TO THE REVIEWERS ARE BELOW IN BOLD:

Reviewer #1: It is an interesting review article discussing latest clinical information and organizational guidelines for hepatitis viruses including Hepatitis A, B, C, D, E, and G, focusing on epidemiology and natural history of infection and clinical course as well as prevention/diagnosis/treatment. Furthermore, for each hepatitis virus, the authors bring known information together with current investigations to target on future directions. In particular, in Hepatitis B virus, there is a "Future Therapies Under Investigation" section discussing the novel direct-acting antiviral therapies such as gene editing via clustered regularly interspaced short palindromic repeats (CRISPR-Cas9) technology with the potential to promote a true cure. The manuscript is well written in English and directly relevant to the clinical application. There are only minor suggestions as follows. 1.Table 1 lacks the title, and there is no explanation of abbreviations like HBIG, IVDU, etc. 2.A Conclusion section is needed at the end of this manuscript.

Response to reviewer #1:

Thank you for your thoughtful review of our manuscript and your suggestions for improvement. We have taken your comments into account as follows:

1. ***Table #1:***
    a. ***We have now titled the table: "Overview of epidemiology, symptoms, natural history and clinical management of viral hepatitis infections."***
    b. ***We have put a legend to explain the following abbreviations used in the table***
        i. ***Abbreviations: HAV (Hepatitis A virus), HBV (Hepatitis B virus), HCV (Hepatitis C virus), HDV (Hepatitis D virus), HEV (Hepatitis E virus), HGV (Hepatitis G virus), WHO (World Health Organization), IVDU (Intravenous drug use), HCC (hepatocellular carcinoma), HBIG (Hepatitis B immunoglobulin)***

Reviewer #2: This manuscript systematically introduces Epidemiology, Natural History of Infection & Clinical Course, Prevention, Diagnosis, and Treatment of hepatitis A, B, C, D, E, G. Furthermore, the author introduced the future therapies under Investigation including CRISPR-CAS-9, siRNA, ASO in the hepatitis B virus infection, and the application of hepatitis C positive donors in solid organ transplantation. Overall, this article is very interesting and useful in virus hepatitis, but I hope that the author can add more of his own views on the prevention and diagnosis of viral hepatitis in the manuscript, in addition, they should summarize at the end of the manuscript and put forward his own opinions and prospects.

1. ***We have now added 1-2 sentences with our own viewpoints at the end of each section on prevention and diagnosis throughout the manuscript.***
    a. ***HAV:***
        i. ***"In summary, while effective HAV vaccines are available, we believe that the available data support the current practice of targeted vaccination in areas where patients who are more prone to more severe symptoms from HAV are more likely to be exposed rather than vaccinating all individuals in endemic areas. For those who are exposed, it will be interesting to see if further improvements can be made to already good predictive models to***

determine the clinical trajectory of patients with acute, fulminant HAV to determine whether liver transplant will be needed. Finally, we will be eagerly watching for further data on currently investigational liver support devices, which hold promise to provide supportive care through fulminant HAV and obviate the need for liver transplantation."

- ***b. HBV:***
  - ***i. In sum, the most promising method for prevention of primary HBV infections is early, universal vaccination, and we are hopeful that aggressive vaccination campaigns already underway will substantially reduce the burden of HBV in the coming decades. Fortunately, highly active antivirals are capable of controlling the virus and reducing the burden of advanced liver disease from HBV; however, there remains no cure for HBV. In the next section, we discuss many exciting experimental approaches aimed at curing HBV via multiple different mechanisms.***
- ***c. HCV:***
  - ***i. At the moment, prevention of HCV infection is dependent upon behavioral risk reduction (e.g. clean needle programs), which is unfortunately being overpowered by a surge of new cases with the ongoing opioid epidemic in the United States. While a vaccine would be ideal, there are various obstacles to overcome, as detailed above. Fortunately, widespread screening and treatment programs are underway on a global scale, and we are hopeful that these will achieve the goal of elimination of chronic hepatitis .***
- ***d. HDV:***
  - ***i. The impressive ongoing global efforts to eliminate chronic viral hepatitis – including HBV – should also significantly reduce the burden of HDV.***
- ***e. HEV:***
  - ***i. Efforts to bring clean drinking water to all parts of the world should reduce the burden of HEV, and we are hopeful that the vaccine for HEV may be approved outside of China for further HEV prevention.***

2. We have also added a final, summary paragraph at the end of the manuscript:

- ***a. As a group, viral hepatitis represents an ongoing global health concern. Acute viral hepatitis infections – HAV and HEV – tend to be self-limited infections with little-to-no long-lasting effect, and both vaccines and improved sanitation conditions will decrease the burden of disease over time. Moreover, ever-improving understanding of the risk factors for acute liver failure from acute hepatitis and experimental supportive care options will aid in further reducing the impact of acute viral hepatitis. Chronic viral hepatitis infections – HBV and HCV – on the other hand, often result in cirrhosis and death if left untreated. While vaccination for HBV is highly effective in reducing transmission, and treatments for HBV are effective in reducing HBV viral load and progression of liver disease, an effective cure for HBV remains elusive. Conversely, an effective vaccine for HCV has not been achieved, but highly effective treatments cure HCV in nearly 100% of cases and are now revolutionizing the fields of transplant medicine. Despite unique barriers, there are ongoing global efforts to eliminate chronic viral hepatitis, and given substantial progress, we are hopeful that this ambitious goal will be realized.***

Minor comments

1. Punctuation is missing in several places in the manuscript.
    a. ***Thank you for pointing out this mistake. We have now added appropriate punctuation to the end of every sentence.***
2. In the section of hepatitis A virus, the references are too old and needs to be updated accordingly. Such as the author cited a reference of 2006, to explain the risk factors related to death from Fulminant HAV (14. Taylor, R. M. et al. Fulminant hepatitis A virus infection in the United States: Incidence, prognosis, and outcomes. Hepatology 44, 1589–1597 (2006)), newer reference should be cited (A Model to Predict 1-Month Risk of Transplant or Death in Hepatitis A-Related Acute Liver Failure.Hepatology. 2019 08; 70 (2), 621-629.), and the paragraph needed to be updated.
    a. ***Thank you for bringing our attention to this updated reference. We have included it in this paragraph and have commented that this is a new and superior prediction model. The paragraph now reads as follows:***
    b. ***"In 2006, the ALFSG study group designed a prognostic model based on clinical features at presentation (alanine transaminase (ALT) < 2,600 IU/L, creatinine (Cr) > 2.0 mg/dL, intubation, and vasopressors) that predict the likelihood of death and need for transplant with high accuracy.[14] Subsequently, an refined scoring system was derived from a cohort of 294 Korean patients with fulminant hepatitis A to predict the likelihood of death or need for liver transplant.[15] This scoring system takes multiple objective values (age, INR, bilirubin, ammonia, creatinine, and hemoglobin) at the time of HAV-associated ALF into account, and compared to the ALFSG study group, this new model better predicted the likelihood of death or need for transplantation in both the Korean discovery cohort and international validation cohorts.[15] These scoring systems are useful in determining the level of care that a patient with acute HAV infection should receive. Nevertheless, there is an unusually high rate of recovery for HAV-related acute liver failure, and given this, auxiliary transplantation and artificial liver devices have been proposed as therapeutic bridges to native liver recovery and regeneration.[16] However, these are not commonly used in clinical practice."***

3. The author indicated that hepatitis B was mainly transmitted via exposure to infected blood or bodily fluids, the most common being intravenous drug injection, sexual contact or vertical transmission, but in endemic areas, vertical transmission between mother and child and horizontal transmission among young children are the most common routes of HBV infection, we recommend that the author add the route of vertical transmission between mother and child.
    a. ***This section now clarifies that vertical transmission is from mother to child:***
    b. ***"It is transmitted via exposure to infected blood or bodily fluids, most commonly from intravenous drug use, sexual contact, or vertical transmission from mother to child.[21] The burden of HBV is declining in the developed world due to vaccination,[22] but HBV prevalence is still quite high in endemic areas primarily due to vertical transmission between mother and child and early life exposures.[23]"***

4. In section Natural History of Infection & Clinical Course of HBV, the sixth paragraph. We feel that this description is unreasonable "current antivirals can help clear HBsAg", because until today antiviral drugs cannot effectively eliminate HBsAg.
    a. ***Thank you for your careful read of this and recommendation. This was a mistake and has been corrected to read as follows:***
    b. ***"While current antivirals can help improve liver histology, decrease hepatic decompensation, and improve long-term survival, achieving a functional cure (i.e. HBsAg loss) is an uncommon event with unknown predictive factors."***

5. The author indicated that chronic hepatitis B has four distinct phases, but did not find a complete introduction to the 4 stages in this section.
    a. ***The 4 phases – immune tolerant phase, immune active phase, inactive carrier state, and reactivation – were previously in italics throughout this paragraph. We have now put this more clearly at the beginning of the paragraph and left each phase in italics at the beginning of the sentence describing the phase in more detail. The first sentence of this paragraph now reads:***
    b. ***"Chronic hepatitis B has four distinct phases: the immune tolerant phase, immune active phase, inactive carrier phase, and reactivation."***
6. Because HCV infection can remain asymptomatic for years, and during this time many infections go undiagnosed while patients suffer from sustained liver damage; but the author have not introduced the the diagnosis of HCV infection,
    a. ***Thank you for this suggestion. We have changed the title of this section to: "Diagnosis and Treatment" and have started the section with the following paragraph:***
    b. ***"As briefly discussed above, Hepatitis C is almost universally a chronic, asymptomatic disease until it ultimately causes advanced fibrosis and cirrhosis, when it has symptoms that overlap with a variety of advanced liver diseases. As such, diagnosis relies entirely on serologies. Given the frequency of HCV in the general population, the asymptomatic nature of early HCV, and the ease of treatment (discussed more below), it is recommended that all adults in the United States be screened for HCV at least once and that high-risk individuals be screened more frequently[101]. In most patients, diagnostic testing consists of a hepatitis C antibody test with a reflex to HCV RNA viral load if the antibody test is positive. Alternatively, in high-risk patients, some physicians may choose to send an HCV RNA level regardless of antibody result. If any test yields a positive result, further characterization of liver function – including a fibrosis assessment – will help direct further treatment and screening procedures."***

7. Please write the title consistently "Natural History of Infection & Clinical Course" and "Natural History of Infection & Clinical Course.
    a. ***We have changed "and" to "&" within this section header. All section heads now read:***
    b. ***"Natural History of Infection & Clinical Course"***