To:

Editorial Board of World Journal of Hepatology

RE: Manuscript ID: **19178**

Highlights Title:
Advances in Cirrhosis: Optimizing the Management of Hepatic Encephalopathy

We would like to express our appreciation to the reviewers and editor for spending time and effort to improve our manuscript. Your suggestions were valuable to help us strengthen our work.

Reviewer(s)' Comments to Author:

Reviewer: 1

Thank you for the opportunity to review your manuscript. Even though the manuscript is well written and structured I believe that data regarding the pathogenesis of HE should be added.

> **RESPONSE**: We agree with the reviewer that it is important to include additional information on the pathogenesis of HE. We have added the following section:

"Pathogenesis of Hepatic Encephalopathy

Cerebral dysfunction in liver failure is a varied phenomenon that can is termed hepatic encephalopathy. Numerous, complementary mechanisms have been stipulated to underlie HE. Ammonia and other toxins, typically filtered by the liver, play a role in conjunction with altered blood-brain transport of neurotransmitter precursors, metabolism of amino acid neurotransmitters, and cerebral glucose oxidation.[17, 18, 19] These alterations result in propagation of inhibitory signals, mediated by gamma-aminobutyric acid and serotonin, and inhibition of excitatory signals, mediated by glutamate and catecholamines.[20, 21] The overall effect is neural inhibition. Other contributing mechanisms include neuroinflammation and altered gut flora.[22, 23]"

When describing the clinical trials, the strengths as well as limitations of the studies should be described/criticized in order to improve the quality of the review.

> **RESPONSE**: We agree with the reviewer and have added strengths and limitations of key studies mentioned in the article to improve the manuscript.

Reviewer: 2

This is a well written review about hepatic encephalopathy and provides useful information for clinicians. However, the authors should more discuss about BCAA treatment.

> **RESPONSE**: We agree with the reviewer that it is important to more deeply discuss BCAA therapy. We have added the following to the *Acute Overt Hepatic Encephalopathy* section:

"Branched-chain amino acids (BCAA) have been studied as therapeutic agents targeting HE. Randomized controlled trials have evaluated the use of BCAA-rich parenteral nutrition in patients with HE.[41, 42] Based on a meta-analysis, patients receiving BCAA-rich infusions demonstrated superior mental recovery compared to controls.[43] The impact on mortality was mixed among the constituent trials, with three suggesting improved survival and two suggesting worse survival. Data regarding oral BCAA supplements is controversial. Whereas some trials have demonstrated significant benefit in mental performance with oral BCAA dietary supplementation, others have not revealed consistent benefit.[44, 45] A recent meta-analysis including 16 randomized controlled trials of both intravenous and oral BCAA supplementation determined that BCAA had a clinically beneficial effect on OHE (RR 0.73, 95% CI 0.61 to 0.88); however, there was no impact on mortality, quality of life, or nutritional parameters.[46] Increased risk of nausea and vomiting was noted. Les et al. found improvement in performance on neuropsychometric tests and an increase in mid-arm muscle circumference in patients randomized to BCAA.[45] The design of this study was limited by its inability to discriminate between the effects of the quantity and quality of nitrogen intake. Marschesini et al. found

improved benefits of BCCA in average hospital admission rate, nutritional parameters and liver function tests.[47] The major limitation of this study was the withdrawal of a significantly greater number of patients form the BCAA arm compared to control study, primarily due to a combination of adverse effects and noncompliance."

Reviewer: 3

Well written review but some changes has to be made before this paper is acceptable. A section for the pathogenesis of PSE has to be added for better understanding of its management.

> **RESPONSE**: We agree with the reviewer that it is important to include additional information on the pathogenesis of HE. We have added the corresponding section as noted above in the response to Reviewer 1.

In the management of PSE more discuss is needed with the use of BCAA and some other options like peg products. The authors have to mention also the use a lactilol as an alternative to lactulose.

> **RESPONSE**: We appreciate the reviewer's suggestion regarding the need for discussion of BCAA therapy and other options, including PEG products and lactitol as an alternative to lactulose. We have added additional discussion about BCAA therapy as noted above in the response to Reviewer 2. We have also added discussion pertaining to PEG and lactitol to the *Acute Overt Hepatic Encephalopathy* section of the manuscript as follows:

"Polyethylene glycol (PEG), a cathartic agent best known for management of constipation, results in increased fecal ammonia excretion. In a randomized controlled trial, PEG was compared head-to-head with lactulose among inpatients with HE. Among patients who were randomly assigned to four liters of PEG over four hours, there was greater improvement in HE after 24 hours compared to those who were given three or more doses of lactulose, each 20 to 30 g, over 24 hours. Furthermore, median time to resolution of HE was shorter in the PEG cohort.[48] The study was limited by its single-center design and lack of blinding."

"Lactitol, a second-generation unabsorbed dissacharide, is an alternative with an analogous mechanism of action to lactulose in the management of HE. Lactitol, which is formulated as a powder that can be dissolved in water for administration, is known to have superior taste properties and a defined laxative threshold. In addition, lactitol has demonstrated comparable efficacy with lactulose.[38, 39]"

Reviewer: 4

Thank you for the opportunity to review your manuscript. There is a significant amount of work that still needs to be done that will improve this manuscript: 1. You do not discuss any peg products despite there being data to support in overt HE and emerging data in maintenance 2. There is a lack of critique of the trials discussed, they each have some limitations that should be addressed.

RESPONSE:

1. We agree with the reviewer that it is important to discuss PEG products to strengthen the manuscript. We had added related discussion to the manuscript as detailed above in the response to Reviewer 3.
2. We agree with the reviewer that critique of the key trials, including discussion of limitations, is important to enhance the review. We have added discussion regarding the limitations of the major studies discussed in our manuscript.

Reviewer: 5

The review manuscript written by Liu et al. summarizes the reports on the management of hepatic encephalopathy. Hepatic encephalopathy is a serious complication of cirrhosis, and its management is important for maintaining the QOL of the patients. The review is well written and provides important information on the therapy for hepatic encephalopathy. However, there are some concerns that need to be addressed. Minor points, 1. The treatment option of hepatic encephalopathy using branched-chain amino acids is not mentioned, although there have been many reports supporting the effect. 2. In addition, it would be better to add the chapter describing the pathogenesis of hepatic encephalopathy, because the treatment strategy depends on the pathogenesis

RESPONSE:

1. We agree with the reviewer that it is important to discuss BCAA therapy in the manuscript. We had added related discussion to the manuscript as detailed above in the response to Reviewer 2.
2. We agree with the reviewer that discussion of the pathogenesis of hepatic encephalopathy adds an important dimension to the review. We have added related information as detailed in the response to Reviewer 1.

Once again, we appreciate the time that the reviewer and the editor have spent in bringing these points to our attention. We believe that the manuscript is now much improved, and we hope that the response has been adequate. We again appreciate your consideration for publishing this manuscript in *World Journal of Hepatology*.

Sincerely,

Aijaz Ahmed, MD