July 7, 2015

To:

Editorial Board of World Journal of Gastroenterology

RE: Manuscript ID: 19943

Highlights Title: Advances in Alcoholic Liver Disease: An Update on Alcoholic Hepatitis

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

Comments to authors: The manuscript entitled “Advances in Alcoholic Liver Disease: An Update on Alcoholic Hepatitis” by Liang R. et al. is an excellently written comprehensive review about the current understanding of the pathogenesis, natural course and therapy of this distinct acute manifestation of alcoholic liver disease. The publication of this review article on this very important topic should have high priority. Alcoholic hepatitis is a severe complication of alcohol abuse still having a high mortality rate. For adequate therapeutic measures it is crucial to understand the pathophysiology of the disease and to diagnose it promptly. Furthermore controversy about the best therapeutic strategy in addition to the essential abstinence from alcohol exists. Recently, several clinical trials with different therapeutic strategies have been conducted to shed light on this controversial subject. Especially the question about the evaluation of these patients for liver transplantation is highly controversial. The submitted manuscript by Liang R. et al. covers these issues in an excellent There are only minor concerns: 1. The different scoring systems for evaluating the severity of the disease and response to therapy (DF, MELD, GAHS and Lille score) are somewhat confusing especially for readers who are not that familiar with the subject. Therefore a short description of these scores- either in the text part of the article or in a short table is recommended. Understanding the scoring systems is important to evaluate the results of past and future clinical

> **RESPONSE**: We agree with the reviewer that it is important to include information about different scoring systems regarding severity of disease and response to therapy in alcoholic hepatitis. A new Figure 1 has been added that briefly highlights differences between Maddrey’s discriminant function, Model for End-Stage Liver Disease, Glasgow alcoholic hepatitis score, and Lille score. Figure 1 now reads:

Figure 1. Scoring Systems for Evaluating Severity of Alcoholic Hepatitis

Scoring System	
Maddrey DF	The DF, based on the prothrombin time and total bilirubin, is most commonly used in the decision to treat AH. The DF is a prognostic model at baseline, or static model, similar to MELD and GAHS.
MELD	The MELD score, calculated from creatinine, total bilirubin, and international normalized ratio (INR), is classically used for liver transplantation waitlist prioritization but can also be applied as a prognostic indicator in AH.
GAHS	The GAHS is calculated based on age, white blood cell count, blood urea nitrogen, total bilirubin, and prothrombin time. The GAHS is another static model that can identify patients at high risk for short-term mortality.
Lille score	The Lille model is a dynamic model, which includes the baseline total bilirubin level and the total bilirubin seven days into treatment. Other variables included in the model are age, albumin, creatinine, and prothrombin time. The Lille model is most accurate among these scoring systems in identifying the degree of response to therapy in AH.[103]

AH = Alcoholic Hepatitis; DF = Discriminant Function; MELD = Model for End-Stage Liver Disease; GAHS = Glasgow alcoholic hepatitis score

2. For non-Anglo-American readers it would be useful to give the critical amounts of alcohol intake also in International System units e.g. in milliliters.

RESPONSE: We agree with the reviewer that it is important to include units in International System units as well in order to improve accessibility to non-American readers. The Introduction (Paragraph 1, Sentence 5) now reads: *"While reports vary, current consensus is that patients with AH typically ingest over 100 to 120 grams of ethanol on a daily basis for 10 to 20 years, with a standard drink equal to 14 grams of pure alcohol, which is equivalent to 12 ounces* ***(354.88 mL)*** *of beer, 5 ounces* ***(147.87 mL)*** *of wine, 1.5 ounces* ***(44.36 mL)*** *or a "shot" of 80-proof liquor.[2-5]"*

3. A short description of the role of increased gut permeability and subsequent endotoxemia and the link to the activation of proinflammatory cytokines should be included in the article. The understanding of these pathways could possibly lead to future therapies early in the disease process.

> **RESPONSE**: We agree with the reviewer that discussion of the role of increased gut permeability and subsequent endotoxemia in alcoholic hepatitis is important. The Pathophysiology of Alcoholic Hepatitis section (Paragraph 2) now reads: *"The importance of an alcohol-induced increase in gut permeability as a mechanism underlying endotoxemia leading to activation of inflammatory cytokines is increasingly being recognized.[12] Whether the increase in gut permeability is primarily gastroduodenal or intestinal remains under debate. However, evidence suggests that the increase in gut permeability following acute alcohol ingestion is longer lasting among patients with advanced liver disease, compared to normal controls.[12]"*

4. The clinical trials to evaluate the use of anti-TNFα-antibodies should be discussed a little more in detail.

> **RESPONSE**: We agree with the reviewer that additional details regarding the clinical trials to evaluate the use of anti-TNFα-antibodies in alcoholic hepatitis would be valuable. There is now a new section entitled, ***Anti-TNF-α Antibodies***, which reads: *"Anti-TNF-α antibodies were considered among the most promising potential therapies for alcoholic hepatitis. Levels of the cytokine correlated strongly with severity of disease in AH and low levels were associated with liver regeneration.[89] Based on a feasibility study in 20 patients with biopsy-proven severe AH, anti-TNF-α therapy in addition to prednisone was associated with significant reduction in Maddrey's DF at day 28 compared to prednisone alone.[90] However, two larger randomized controlled trials evaluating anti-TNF-α therapy failed to demonstrate benefit and even suggested harm.[91, 92] Therefore, use of anti- TNF-α therapy in AH to date remains investigational."*

Reviewer: 2

In this manuscript submitted by Liang et al, the authors aimed to review Advances in Alcoholic Hepatitis. The quality of the manuscript's presentation and readability is satisfactory. The review is correctly developed with a suitable order, and it summarizes the relevant approaches. Consequently, the article is suitable for publication in its present form. Regards

> **RESPONSE**: We appreciate the reviewer's positive feedback.

Reviewer: 3

I agree with most of the points emphasized by the author in this comprehensive review. I have some minor revisions to suggest.

- In "Clinical Manifestation of AH",
  - I think that the statement (p. 7): *"The patients report drastic drastic increase in their alcohol consumption"* is too assertive. To my knowledge, there is no data in the literature to support it. In my own experience, a recent increase in alcohol consumption is far from constant. Perhaps the sentence could be attenuated (e.g. "Some patients" or "The patients often report").

> **RESPONSE**: We appreciate the reviewer's suggestion regarding the statement regarding alcohol consumption being too assertive. We have followed the reviewer's advice and the Clinical Manifestations of Alcoholic Hepatitis section (Paragraph 1, Sentence 5) now reads: *"Some patients report drastic increase in their alcohol consumption secondary to recent life stressors such as a divorce, death of a loved one, and loss of employment."*

  - p. 8: "*The presence of fever…antibiotic treatment."* Although I acknowledge that AH could be a cause of fever, infection is also highly prevalent in that context. As a consequence, I would not stress (like the author does) on the fact that the search for an infection could be "unnecessary" in those patients. My position is rather that attributing fever to the AH itself could only be done after that infection has been ruled out. On the topic of infection and AH, I am a little surprised that the author doesn't discuss the important work of Louvet *et al.* (Louvet A, Wartel F, Castel H, Dharancy S, Hollebecque A, Canva-Delcambre V, Deltenre P, Mathurin P. Infection in patients with severe alcoholic hepatitis treated with steroids: early response to therapy is the key factor. Gastroenterology. 2009 Aug;137(2):541-8.)

> **RESPONSE**: We appreciate the reviewer's suggestion regarding the topic of fever in alcoholic hepatitis. We have followed the reviewer's advice, added commentary related to the suggested reference, and the Clinical Manifestations of Alcoholic Hepatitis section (Paragraph 1, Sentences 13-15) now reads: *"While it is worthwhile to rule out infectious sources given degree of immunosuppression from malnutrition, it is also important to understand that fever and leukocytosis may be commonly seen in the presentation of alcoholic hepatitis. Nevertheless, the importance of evaluating for infection among patients with AH cannot be understated as at least a quarter of patients have coexistent infections.*[26] *Specifically, nonresponse to steroids is most predictive of infection and worse survival in this patient population.*[26] *"*

- In "Behavioral treatment" "abstinence":
  - p. 11-12: "*A few studies…from alcohol use are poor*." I think that the author is a little bit severe for the works that has been done to evaluate the interventions to reduce alcohol consumption in heavy drinkers. Perhaps the word "few" could be removed.

> **RESPONSE**: We appreciate the reviewer's suggestion regarding the topic of reducing alcohol consumption. We have followed the reviewer's advice and the Behavioral Treatment section (Paragraph 2, Sentence 2) now reads: *"Studies have suggested that there is a small but significant beneficial effect; the actual benefit*

of these interventions is unclear as data on abstinence maintenance from alcohol use are poor.[35] ”

- p. 12: “*Nalmefen has demonstrated…higher selectivity…opiates receptors*.” This statement is not perfectly exact: nalmefen action has not a higher selectivity than naltrexone but, on the contrary, a broader action as it also links to kappa receptor.

RESPONSE: We appreciate the reviewer’s suggestion regarding the mechanism of action for nalmefene. We have modified the text in the Behavioral Treatment section (Paragraph 2, Sentence 9) which now reads: *“Nalmefene has demonstrated several favorable properties compared to naltrexone including longer duration of action, absence of dose-dependent liver injury, and broader action on central nervous system opiate receptors.*[41-44] ”

- p. 12: “*Baclofen… alcohol craving.*” The author should mention the study by Addolorato *et al.* which is the only one to date to have evaluated an anticraving medication in a context of severe liver disease (Addolorato G, Leggio L, Ferrulli A, Cardone S, Vonghia L, Mirijello A, Abenavoli L, D'Angelo C, Caputo F, Zambon A, Haber PS, Gasbarrini G. Effectiveness and safety of baclofen for maintenance of alcohol abstinence in alcohol-dependent patients with liver cirrhosis: randomised, double-blind controlled study. Lancet. 2007 Dec 8;370(9603):1915-22.)

RESPONSE: We agree with the reviewer that it is important to include information about the trial published in the Lancet relating to baclofen. The Behavioral Treatment section (Paragraph 2, Sentence 11) now reads: *“Baclofen is the only anti-craving medication to date that has been studied in the context of advanced liver disease.*[46] ”

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 Gastroenterology.

Sincerely,

Aijaz Ahmed, MD