

ANSWERING REVIEWERS



January 15, 2014

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 6465-review.doc).

Title: Cirrhosis and its Complications: Evidence Based Treatment

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Name of Journal: *World Journal of Gastroenterology*

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The manuscript has been improved according to the suggestions of reviewers:

1 Format has been updated

2 Revision has been made according to the suggestions of the reviewer

Reviewer 1

- 1) In introduction the authors state that cirrhosis is “generally thought to be irreversible”. This, although somewhat controversial, is false to me. It has been demonstrated that at-least in the setting of HBV and HCV-related liver disease, cirrhosis can be reverted by complete viral response.

We agree newer evidence favors that cirrhosis is a reversible phenomenon. We have made changes to the introduction to reflect the same.

- 2) At page 5, last 2 lines of section “Treatment of Underlying Etiology”, the authors state that “Cases of cirrhosis due to causes other than alcohol, hepatitis B, and autoimmune hepatitis are less reversible by the time ascites is present.[12]”. As even in the setting of HCV-related liver cirrhosis a complete viral eradication is associated with a decrease in decompensation rate, HCC development, this reviewer would rather state that in case of HCV-related decompensated cirrhosis, antiviral treatment is contraindicated. The authors should refer to these papers that can be included in reference list - Braks RE, et al. Effect of sustained virological response on long-term clinical outcome in 113 patients with compensated hepatitis C-related cirrhosis treated by interferon alpha and ribavirin. *World J. Gastroenterol.* 2007; 13: 5648-5653. - Morisco F. Sustained virological response: a milestone in the treatment of chronic hepatitis C. *World J Gastroenterol.* 2013; 19: 2793-8. - Tsuda N, et al. Long-term clinical and virological outcomes of chronic hepatitis C after successful interferon therapy. *J. Med. Virol.* 2004; 74: 406-413. - Gentile I, et al. Surrogate endpoints and non-inferiority trials in chronic viral hepatitis. *J. Hepatol.* 2010; 52: 778. - Bruno S, et al. Sustained virological response to interferon-alpha is associated with improved outcome in HCV-related.

We appreciate the reviewers input and agree that studies have shown slower rate of disease progression and decrease in rate of decompensation in patients who achieve SVR but treatment of hepatitis C is beyond the scope of our review. In addition treatment of hepatitis C is evolving rapidly and hopefully in the coming few months to years decompensation might not be a contraindication to treatment. He however did make changes to reflect that its treatment will improve clinical outcomes.

- 3) For secondary prophylaxis, norfloxacin is usually give at a dose of 400 mg once daily and not twice daily as the authors state at page 10.

We appreciate reviewers input and have made changes to reflect the above.

- 4) At page 10, last 2 lines of HRS the authors state: "The incidence of hepatorenal syndrome (HRS) after development of cirrhosis is 18% and 39% at one and five years". It should be added that these figures refer to cirrhosis with ascites and not generically to cirrhosis!

We have made changes as per reviewer's suggestions.

- 5) At page 14, in the section "Screening" the authors should provide more details on the different date of varice detection in different stages of the diseases. They should use and cite these papers: - Zaman A, et al. Risk factors for the presence of varices in cirrhotic patients without a history of variceal hemorrhage. Arch Intern Med. 2001 Nov 26;161(21):2564-70 Gentile I et al. Noninvasive prediction of oesophageal varices: as simple as blood count? Liver Int. 2010 Sep;30(8):1091-3. Burton JR, et al. Validation of a multivariate model predicting presence and size of varices. J Clin Gastroenterol. 2007; 41: 609-15. Gentile I, et al. A simple noninvasive score predicts gastroesophageal varices in patients with chronic viral hepatitis. J Clin Gastroenterol. 2009 ; 43: 81-7 Ng FH, et al. Prediction of oesophagogastric varices in patients with liver cirrhosis. J Gastroenterol Hepatol. 1999;14:785-90.

We agree factors like severity of liver disease, thrombocytopenia, increasing age and hypoalbuminemia can predict presence of varices but accuracy of these remain limited and AASLD recommends endoscopic evaluation at the time of diagnosis. We have made changes to reflect the same.

- 6) In the treatment of hepatic encephalopathy a first-line treatment is lacking. This is the diagnosis and possible resolution of the trigger cause (e.g. infection). A careful evaluation of the possible causes must be performed in every case of hepatic encephalopathy.

We have made changes to reflect importance of recognition and treatment of precipitating facts.

- 7) English language needs a minor polishing (e.g. at page 10, "The criteria used to define hepatorenal renal syndrome was updated in 2007" should read: "The criteria used to define hepatorenal renal syndrome were updated in 2007".

Thank you for identifying this typographical error. We have corrected this in the manuscript.

Reviewer 2

- 1) Though there is FDA warning about tolvaptan, this drug should still be briefly mentioned in the section of refractory ascites.

Based on the suggestion of our reviewer we have added a paragraph hyponatremia and vaptans

- 2) The role of transient elastography to predict varices and HCC should be briefly discussed. **We appreciate the suggestion and have provided data about use of TE for screening of varices and predictor of HCC.**

Reviewer 3

- 1) They referred only one manuscript for each subject, and there is no discussion on selection from several candidate treatment methods. There is either no discussion on controversial ideas of mechanism of diseases.

We appreciate the reviewers input. We have referred to more than 150 studies. Within the space constrains we have tried to discuss treatment options. Based on the suggestion from the reviewers we have added information on compensated cirrhosis, how cirrhosis is now considered a reversible phenomenon, optimal diuretic therapy for ascites, TIPS for refractory ascites and variceal bleeding.

Reviewer 4

- 1) This is a comprehensive review of the evidence-based treatment of cirrhosis and its complications. However, there are some aspects that would merit specific attention, but have not been addressed or have been marginally addressed by the authors. I understand that space constraint may have induced to skip some issues. If so, I wonder whether the paragraphs dedicated to hepatocellular carcinoma could be omitted in favour of other aspects. In my view, the topics that should not be missed in a review dedicated to the treatment of cirrhosis and its complications are: - A paragraph dedicated to compensated cirrhosis, with emphasis on etiologic treatments; - TIPS for refractory ascites - Hyponatremia in cirrhosis with ascites - Early TIPS in variceal bleeding - Bacterial infections other than spontaneous bacterial peritonitis (including the relevance of MDR bacteria

We have made changes as per the reviewer's suggestions and have added a paragraph on compensated cirrhosis, hyponatremia, TIPS for refractory ascites and Bacterial infections

- 2) Introduction, 1st paragraph. "Its complications" is repeated

Thank you for identifying the typographical error. We have corrected this.

- 3) 2) Introduction, 3rd paragraph. "Portal hypertension can lead to ... functional and biochemical abnormalities ...". Please clarify.

We have added information so as to clarify these terms

- 4) Page 4, 2nd paragraph. "Salt restriction ... are the backbone of first-line therapy". Indeed, salt restriction is currently not seen as important as it was in the past. Controlled salt intake would sound more appropriate. See also EASL Guidelines for the treatment of ascites.

We have made changes accordingly

- 5) Page 4. Bed rest. "... this theory is not supported by clinical trials ...". It is true that there are not controlled clinical trials demonstrating the clinical usefulness of bed rest. However, evidence that upright posture aggravates sodium retention and impairs response to diuretics in patients with cirrhosis and ascites has been provided (Bernardi et al, Gut 1985; Ring-Larsen et al, Br Med J 1986).

We have made changes to manuscript as per the reviewer's suggestions

- 6) Page 4. Salt restriction. A marked reduction in sodium intake not only does not add efficacy to diuretic treatment, but also favours the occurrence of diuretic-induced renal failure and hyponatremia (Reynolds et al, Gut 1978).

We have added changes as per the reviewer's suggestion

- 7) Page 5. First-line diuretics. It could be commented that most patients included in the study by Santos et al (ref 15) had a recent onset ascites, and therefore, had fairly preserved renal function. A subsequent study by Angeli et al (Gut 2010), which enrolled patients with long standing-ascites, many of whom with a significant impairment of renal perfusion, showed that the combination of therapy could be preferred. This study must be cited and its results discussed in view of those obtained by Santos et al.

We have tried to discuss the results of these important studies.

- 8) Page 5. Hypokalemia. Citation 20 refers to patients with acute alcohol intoxication and/or patients with alcohol withdrawal syndrome, but not to patients with acute alcoholic hepatitis.

Holding furosemide in event of hypokalemia has been suggested by AASLD we have cited the guidelines instead

- 9) The study by Stanely et al (#17) enrolled 299 patients (and not 3860) assigned to either standard medical treatment or Leveen shunt. In addition, they were stratified into three groups according to the severity of cirrhosis and the presence of renal impairment. Its citation here is not entirely appropriate.

We have discussed combination therapy versus single agent earlier in the manuscript and have deleted this paragraph

- 10) Page 6. Albumin infusion. The study by Gentilini et al (J Hepatol 1999) on the effect of albumin administration to in-patients with ascites should be cited here.

We have discussed this study

11) Page 7. Refractory ascites. The occurrence of refractory ascites is 5% per year. This paragraph should be supported by a reference (Planas et al, Clin Gastroenterol Hepatol 2006)

We have added the reference as per the suggestion

12) Page 7. Refractory ascites. The evidence supporting the effectiveness of Midodrine in refractory ascites is very weak. I would use more caution in suggesting that its use, and, in any case, to the best of my knowledge, no study reported an improvement in survival. The relevant citations should be reported.

We have provided more detail to reflect that the studies were small and evidence is weak at this time.

13) Page 9. Prevention of recurrence. The commonly recommended dose for Norfloxacin prophylaxis is 400 mg/day.

We have corrected this in the manuscript

14) Page 9. The reported incidence of HRS is in patients with cirrhosis and ascites.

We have made changes to reflect this.

3 References and typesetting were corrected

Thank you again for publishing our manuscript in the *World Journal of Gastroenterology*.

Sincerely yours,

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