

Porto Alegre, 03 may 2014

Dear Editor

Please find enclosed the edited manuscript in Word format (file name: multiresistant bacteria in SBP - 01-05-2014 – review).

Name of journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: 10297

Columns: EDITORIAL

Title: Multiresistant bacteria in the Spontaneous Bacterial Peritonitis: a new step in management?

Authors: Angelo Alves de Mattos, Ane Micheli Costabeber, Livia Caprara Lionço, Cristiane Valle Tovo

We are most thankful for the suggestions made by the four reviewers who have accepted the article for publication.

They have indeed shown great knowledge in this field and have remarkably contributed for the improvement of this manuscript to be published in such well-recognized journal.

We have followed all the suggestions, as follows:

Reviewer 1

This is a mainly well-written editorial on the current management of cirrhotic patients with Spontaneous Bacterial Peritonitis (SBP) Comments;

1. Please include 3 Tables:
 1. on the diagnosis definitions of SBP;
 2. summarizing the studies evaluating the treatment efficacy/outcomes (mortality, etc) and
 3. on the suggested treatment management/algorithm

Answer: A Table with the diagnosis definitions of SBP was included (Table 1 - Line 143). The suggestion to use an algorithm regarding the treatment management was also accepted (Line 287 - Figure 1). Otherwise, considering that many studies about the treatment efficacy and outcomes depends on the bacterial flora and that they have been performed previously to the bring of multiresistant bacteria, we understand that with the present algorithm the proposed Table (summarizing the studies evaluating treatment efficacy/outcomes) lose power.

2. Please include a conclusion section highlighting the expert opinion

Answer: The modification was accepted (Line 353)

Reviewer 2

In this manuscript, Mattos et al. reviewed the current status of spontaneous bacterial peritonitis, especially in the diagnosis and management of those induced by multi-resistant bacteria. It is relevant to the scope of the Journal. However, some concerns need to be addressed:

1. The English needs to be polished. Some sentences are too long to be understood. I suggest the author to use simple and short sentence to present the contents. Some grammatical errors are also present, e.g. "studies have been published that show changes in..." should be "studies have been published that showed changes in..."; "It is believe that this fact is due to..." should be "It is believed that this fact is due to..."

Answer: The English style was reviewed and some modifications were done to become more suitable to read (highlighted in the text). The modification in the grammar was accepted (Line 94 and Line 166)

2. Page 4: "when admitted to the hospital" change to "when admitted to a hospital"; "varies from 10 to 30%" change to "varies from 10% to 30%"

Answer: The modification was accepted (Line 76-77).

3. Page 6: "When the PMN number is higher than 250/ cells/mm³" change to "When the PMN number is higher than 250 cells/mm³"

Answer: The modification was accepted (Line 118)

4. Page 7: "(66% x 10%)" change to "(66% vs. 10%)"

Answer: The modification was accepted (Line 147)

5. Page 9: "once that a study performed in the United States showed a high rate of resistance (45%) to cephalosporins in patients with SBP [32]." and "After 48h from the beginning of treatment, control paracentesis diagnostic is recommended, where a reduction of at least 25% in the number of SBP should be observed" I cannot understand these two sentences.

Answer: The modification was accepted (Line 196 and Line 213)

6. Page 10: "...and should be treated with specific antibioticotherapy." What is "specific antibioticotherapy"? It should be defined.

Answer: The modification was accepted and the paragraph structured to better understanding (Line 231).

7. Page 11: "...the use of intravenous albumin in the dose of 1,5 g/Kg of body weight in the first day and..."It was 1.5g/kg rather than 1,5g/kg in the original publication.

Answer: The modification was accepted (Line 269)

8. Page 12: "norfloxacin (400 mg bid for 7 days) has been used more commonly." Application of norfloxacin 800mg daily is a large dosage and is uncommonly used in clinical practice. The author should present evidences to support the usage of such a big dosage.

Answer: This is the correct dosage to prevent bacterial infections in cirrhotic patients with gastrointestinal hemorrhage, as recommended in the AASLD guideline (Runyon B. Hepatology 2013), on page 18, recommendation 34.

9. Page 13: "In patients with levels of proteins in ascitic fluid lower than 1,5 g/dL and advanced hepatic disease (Child-Pugh score higher than or equal to 9 with total serum bilirubin higher than or equal to 3 mg/dL) or renal dysfunction (serum creatinine higher than or equal to 1.2 mg/dL, BUN higher than or equal to 25 mg/dL or serum sodium concentration lower than or equal to 130 mEq/L), the administration of prophylactic norfloxacin resulted in a reduction of probably in one year from the occurrence of SBP and hepatorenal syndrome, and in the increase of survival rate in three months and in one year [50]." This sentence is too long and I cannot understand it. In addition, proteins in ascitic fluid lower than 1,5 g/dL or 1.5g/dL should be addressed.

Answer: The modification was accepted (Line 323).

10. Page 14: "Several proposals exist, but for the sake of reflection, starting from the premise that proton pump inhibitors favor enteric colonization; the occurrence of bacterial overgrowth and, ultimately, the bacterial translocation among individuals with cirrhosis, after systematic review and meta-analysis, it was suggested an association of this medication with higher incidences of SBP." I cannot understand this long sentence. "The distinction between community-acquired infectious episodes, healthcare-associated infections or nosocomial, and the identification of risk factors for multi-resistant germs assist in the decision-making regarding the empirical antibioticotherapy choice." This long sentence is incomplete.

Answer: The modification was accepted (Line 340).

11. References: Some of the references are not published in English and cannot be accessed by international readers.

Answer: Although the comment is relevant, the references not published in English refers to the expertise of the authors, and it should be necessary to

divulge the local experience in national journals. We must emphasize that both journals cited (GED and Arq Gastroenterol) are indexed in some database, as Lilacs, Scopus, Embase, Latindex, or Pubmed/Medline.

The journal's names in the references are not in uniform. Some of them were present in abbreviation while some were in full.

Answer: The references citation were reviewed and modified to be uniform.

Reviewer 3:

Maybe a table showing a several reports and frequent bacteria found can be applied in the manuscript body

Answer: We understood in this comment that the reviewer let us the decision, and although this is an interesting suggestion, as we already added one Table (Table 1) and one Figure (Figure 1) in the text, maybe another Table could let the text too long to read.

Reviewer 4:

The review well investigated a very hot topic in modern Hepatology: the role of multiresistant bacterial in spontaneous bacterial peritonitis. However, the Authors performed a descriptive review. Studies are not cited according to their relevance, nor the degree of evidence / the strength of recommendation are reported. Furthermore, there are not tables and several minor problems.

1. Title The title refers to "a new step". This is not well discussed in the review. The title chosen by the Authors is appropriate for an Editorial, written in order to introduce a innovative leading study. I suggest to evaluate these two options: "Management of multiresistent bacteria in the spontaneous bacterial peritonitis" or "Multiresistent bacterial in the spontaneous bacterial peritonitis: evolution in the diagnosis, treatment, prophylaxis"

Answer: The title chosen was firstly submitted and accepted by the Editor, and the Reviewer must consider that this manuscript is exactly an Editorial, and not just a Review. However, we have nothing against to change the title if the Editor think it is necessary. In this case, we prefer the second option.

2. Evidences

a. Evidences regarding the “evolution in the management of spontaneous bacterial peritonitis should be hopefully summarized in a table (year, Author, N of patients, % of success, evidences, relevance, strength of recommendation) (table # 1).

b. A further table (table # 2) should hopefully summarize the key points in the treatment and the prophylaxis.

Answer: We understand that the algorithym proposed (Figure 1) shows the evolution of the management of patients with SBP, and could attend the idea of the present reviewer.

3. Implications

a. The implications of the management in the scope of liver transplantation should be better elucidated. The possible evolution to plastic peritonitis (which is a contraindication to liver transplantation), should be considered. The differential diagnosis with massive ascites due to portal thrombosis and to spread of hepatocellular carcinoma should be at least mentioned.

Answer: The short survival after a SBP episode was now highlighted and the need of liver transplantation emphasized in the text (Line 289).

b. The advantages and drawbacks of paracentesis should be reported.

Answer: The indication of paracentesis in cirrhotic patients with ascites is well established in the text (Line 109). Although the suggestion regarding the inserting a topic with advantages and drawbacks of paracentesis is

interesting, this is not the focus of the present Editorial, and could become a long and tiresome manuscript to read.

4. Authors opinion. Authors should hopefully distinguish evidences from the literature from the personal opinion.

Answer: Considering that is an Editorial, the opinion of the authors is wellcome, and all of them are embased in personal experience published in national journals. Moreover, the opinions presented in this Editorial are not against the literature published.

5. Limitation paragraph A limitation paragraph with identification of shadows should be hopefully included before the conclusion paragraph.

Answer: The suggestion was accepted (Line 353).

6. Take home message A 5-6 point take-home message should be hopefully reassumed in a separate table (table # 3) or in the conclusion paragraph.

Answer: The use of "take-home message" is not a common practice in the WJG, and not a demand. For this reason, we understand that the insertion of a limitation paragraph for the "conclusions" is enough.

7. References

a. The recent multicentre study on albumin supplementation in severe sepsis and septic shock (Caironi et al., NEJM march 2014) and the related correspondence in press should be cited. The NEJM paper gives the impression that patients with liver disease and severe sepsis, only a small number of which were included (n=27, 1.5% of study population), do not benefit from albumin. Withholding albumin in settings where albumin supplementation has been proven to be effective, would be an unfortunate and unintended, but not unlikely, consequence of the study.

Answer: Although this is an important contribution, this is not the focus of the presente manuscript, because we did not included patients with

sepsis. Thus, we understand this is not appropriate to include this study. Otherwise, a recent metanalysis (40) observed a beneficial effect of albumin in patients with SBP.

b. Please also consider the inclusion of: Ponziani FR et al. *Transplant Rev (Orlando)*. 2014 Apr;28(2):92-101.

c. Please also consider the inclusion of: Pompili M et al. *World J Gastroenterol*. 2013 Nov 21;19(43):7515-30

Answer: We appreciate the suggestion, but this is not the focus of the study, and was not included. Otherwise, the references referring to liver transplantation were included in the text as suggested by the present reviewer (Line 289).

8. Minor issues

a. The word prevalence (INTRODUCTION paragraph) could be changed in incidence.

Answer: The modification was accepted (Line 76).

b. The English style of the paper would benefit from a revision (native English speaker).

Answer: The English style was reviewed and some modifications were done to become more suitable to read (highlighted in the text).

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

Sincerely yours,

The authors