



BAISHIDENG PUBLISHING GROUP INC

8226 Regency Drive, Pleasanton, CA 94588, USA

Telephone: +1-925-223-8242 Fax: +1-925-223-8243

E-mail: bpgoffice@wjgnet.com <http://www.wjgnet.com>

Name of journal: *World Journal of Hepatology*

ESPS Manuscript NO: 21253

Manuscript Type: MINIREVIEWS

Answering reviewers

Response to the editor:

Changes made according to editor's comments. Signed pdf file for "conflict-of-interest" provided. Key words modified properly. Audio core tip provided. Acknowledgements added. Format of the text modified when needed. PMID and DOI (according to CrossRef) provided for references. Figure (modified) provided in powerpoint. References in table modified according to editor's comments.

Additional notes:

-Unfortunately, we the authors of the manuscript *or* our institution, do not have a subscription for *iThenticate*. Instead of it, we performed a check of our revised manuscript for plagiarism using free software available on the internet (*The Pensters*, *Plagscan*) and we provide screenshots in a pdf file (*plagiarism check.pdf*). Additionally, we provide screenshots of the final title using *Google Scholar* in a separate pdf file (*google scholar.pdf*).

-According to statement 3.1 "....If you believe that the language of your manuscript has reached or exceeded Grade A without the need for employing a professional editing service, you may choose to sign a personal guarantee for the language presentation of your manuscript." in "**Guidelines and Requirements for Manuscript Revision: Minireviews**", we did not provide a language editing certificate, but, instead of it, a signed personal guarantee for the language presentation of our manuscript, in a separate pdf file (*language guarantee.pdf*).

Response to reviewer 69827:

Although, it's a fairly well written review and analysis some new markers of bacterial translocation in cirrhosis but basically the article covers the same theme as the recent publication of french group in World J Hepatol: Di Martino V, Weil D, Cervooni JP, Thevenot T. New prognostic markers in liver cirrhosis. World J Hepatol. 2015 May 28;7(9):1244-50. doi:10.4254/wjh.v7.i9.1244. Review. PubMed PMID: 26019739; PubMed Central PMCID: PMC4438498. I would suggest the other journal for publication of this paper because the topic is of some interest to the readers. Perhaps, to make a more comprehensive review and include topics analysed by the french group.

Answer: We thank the reviewer. We agree that some overlap between ours and other reviews is inevitable. Nevertheless, it is our opinion that our review is substantially different in that it is specifically focused on markers of bacterial translocation and not on *prognostic* markers in *cirrhosis* in general (C-reactive protein, Copeptin, Vitamin D, Serum free cortisol, Von Willebrand factor antigen) as does the article by Di Martini *et al* (World J Hepatol. 2015 May 28;7(9):1244-50) to which the reviewer refers.

Response to reviewer 3373179:

Congratulation on a such beautiful piece of art. Generously referenced and well-written.

Answer: We thank the reviewer for his positive comment.

Response to reviewer 2548745:

The present paper reviews markers of BT in cirrhosis. This reviewer finds the review relevant, comprehensive, concise, balanced and well written.

Answer: We thank the reviewer.

I have a few minor points, which may improve the paper:

1) Abstract states that BT refers to the passage of bacteria/products thorough the intestinal wall. Through the intestinal epithelium may be more precise. Answer: Following the reviewer's suggestion, we changed "Wall" to "epithelium".

2) Figure 1: The figure indicates bacteremia secondary to SBP. I would state BT-> Spontaneous bacteremia -> SBP to be the general understanding of how BT causes SBP. In the legend: "systematic" should be "systemic".

Answer: We have modified the Figure according to reviewer's comment.

3) Table 1. (bDNA) One "Con" of bDNA, as stated in the text, is that results seem to depend on the exact methodology used. Consider adding this to the cons section1)

Answer: We followed the reviewer's suggestion and added this comment to "cons" section of bDNA of the table.

Response to reviewer 2539632:

This review by Koutsounas and colleagues summarizes which markers for bacterial translocation (BT) are commonly used so far and discusses their advantages and disadvantages. BT is generally an important complication (or even cause) of liver pathologies and good markers for this event are indeed still needed. Therefore this review should be of general interest to the field of hepatologists.

Answer: We thank the reviewer for his positive reviews.

Specific criticism:

- *since this review does not only address BT in cirrhosis but more general in severe liver disease (even including hepatic encephalopathy and hepatorenal syndrome), I would suggest to replace "cirrhosis" in the title by a more broad term – "end-stage liver disease" (?)*

Answer: We have changed the title as suggested.

- *"Alternatively, breath tests have been used as sensitive and simpler tools for diagnosis of bacterial overgrowth" – please be more precise: what exactly was measured in the breath? bacterial DNA?*

Answer: We thank the reviewer. We have provided an answer in our revised manuscript.

- *"... are found to have a significant immune and haemodynamic derangement, which is ameliorated by norfloxacin." – what does it mean? What does norfloxacin do? –*

Answer: We thank the reviewer. We have provided an explanation in our revised manuscript.

"... showing either improvement of minimal encephalopathy in cirrhotic patients receiving rifaximin,..." – which points to what? What does rifaximin do? – "...

Answer: We thank the reviewer. We have provided an explanation in our revised manuscript.

was always associated with its simultaneous presence in MLNs." – what does MLN stand for? –

Answer: "MLNs": mesenteric lymph nodes. Explanation added earlier in the text.

in the chapter about LPS it is stated that LPS can enhance hepatic stellate cell activation and their production of inflammatory mediators. Although this is correct and important, the more well known LPS-responsive cell type of the liver is the Kupffer cell, the resident macrophage of the liver, and it is well described that LPS acts pro-inflammatory via affecting these cells but they are not mentioned at all.

Answer: We have added new text to address the reviewer's comment.

I have the impression that a lot of background information is missing. For example, CD14 – it is not mentioned that CD14 is a co-receptor for TLR-4; on which cell types are CD14/TLR4 expressed? soluble CD14 is mentioned but it is not explained how and why this is generated.

Answer: We have added new text to address the reviewer's comment.

"The presence of bacteria triggers the production of LBP..." – be more precise; do really bacteria themselves trigger LBP synthesis? Or does instead LPS do this? In which cells and via which mechanism?

Answer: We have added new text to address the reviewer's comment.

-citation 77 is a manuscript in German – it would be better to cite only English manuscripts.

Answer: citation 77 and relative text were omitted and paragraph was modified properly. Additionally, citation [82] (*Montalto et al*) was added.

figure 1 seems a bit too "quick and dirty" – only boxes and arrows, many spelling errors, no explanation of the abbreviations in the figure legend... Please improve this figure. Include more details (involved organs, cell types, etc.?).

Answer: We have modified the figure and figure legend according to reviewer's comments.