

ESPS Peer-review Report

Name of Journal: World Journal of Gastroenterology

ESPS Manuscript NO: 9724

Title: THE GUT MICROBIOTA IN ALCOHOLIC HEPATITIS: PATHOGENETIC ROLE AND THERAPEUTIC PERSPECTIVES

Reviewer code: 00001263

Science editor: Gou, Su-Xin

Date sent for review: 2014-02-26 09:01

Date reviewed: 2014-02-28 03:03

| CLASSIFICATION | LANGUAGE EVALUATION | RECOMMENDATION | CONCLUSION |
|--|---|-------------------------------------|--|
| <input type="checkbox"/> Grade A (Excellent) | <input type="checkbox"/> Grade A: Priority Publishing | Google Search: | <input type="checkbox"/> Accept |
| <input type="checkbox"/> Grade B (Very good) | <input checked="" type="checkbox"/> Grade B: minor language polishing | <input type="checkbox"/> Existed | <input type="checkbox"/> High priority for publication |
| <input checked="" type="checkbox"/> Grade C (Good) | <input type="checkbox"/> Grade C: a great deal of language polishing | <input type="checkbox"/> No records | <input type="checkbox"/> Rejection |
| <input type="checkbox"/> Grade D (Fair) | | BPG Search: | <input type="checkbox"/> Minor revision |
| <input type="checkbox"/> Grade E (Poor) | <input type="checkbox"/> Grade D: rejected | <input type="checkbox"/> Existed | <input type="checkbox"/> Major revision |
| | | <input type="checkbox"/> No records | |

COMMENTS TO AUTHORS

The authors summarized the gut microbiota in alcoholic liver disease. Major points:

1. In the paper, the authors discussed the gut microbiota in alcoholic liver disease, not just alcoholic hepatitis. Thus, the authors should change “alcoholic hepatitis” to “alcoholic liver disease” in the title.

We have changed the title

2. On page 4, the authors discussed the acetaldehyde and liver injury. A recent study from ALDH2 knockout mice should be discussed and included. (Kwon et al: Aldehyde dehydrogenase 2 deficiency ameliorates alcoholic fatty liver but worsens liver inflammation and fibrosis in mice. Hepatology. 2014 Feb 3. doi: 10.1002/hep.27036. [Epub ahead of print] **We have included the suggested study**

3. Too many short paragraphs. The authors should combine these short paragraphs. **We combine the several short paragraphs.**

4. Intestinal microflora section is difficult to follow and needs to be modified. **We have modified the section**

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| CLASSIFICATION | LANGUAGE EVALUATION | RECOMMENDATION | CONCLUSION |
|--|--|-------------------------------------|--|
| <input type="checkbox"/> Grade A (Excellent) | <input checked="" type="checkbox"/> Grade A: Priority Publishing | Google Search: | <input type="checkbox"/> Accept |
| <input type="checkbox"/> Grade B (Very good) | <input type="checkbox"/> Grade B: minor language polishing | <input type="checkbox"/> Existed | <input type="checkbox"/> High priority for publication |
| <input checked="" type="checkbox"/> Grade C (Good) | <input type="checkbox"/> Grade C: a great deal of language polishing | <input type="checkbox"/> No records | <input type="checkbox"/> Rejection |
| <input type="checkbox"/> Grade D (Fair) | | BPG Search: | <input type="checkbox"/> Rejection |
| <input type="checkbox"/> Grade E (Poor) | <input type="checkbox"/> Grade D: rejected | <input type="checkbox"/> Existed | <input checked="" type="checkbox"/> Minor revision |
| | | <input type="checkbox"/> No records | <input type="checkbox"/> Major revision |

COMMENTS TO AUTHORS

this manuscript reviews the main findings on gut microbiota and alcoholic liver disease. Overall, the paper is well written and presents the actual findings and perspectives.

I suggest that 3 additional references should be listed in the revised manuscript.

Zhu L, et al. Hepatology 2013; 57(2), 601-

Rao RK et al. AJPhysiol 2004; 286(6), G881-

Mutlu EA et al. Am J Physiol 2012; 302 (9): G966-

We have added the 3 references

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ESPS Manuscript NO: 9724

Title: THE GUT MICROBIOTA IN ALCOHOLIC HEPATITIS: PATHOGENETIC ROLE AND THERAPEUTIC PERSPECTIVES

Reviewer code: 00005218

Science editor: Gou, Su-Xin

Date sent for review: 2014-02-26 09:01

Date reviewed: 2014-03-04 01:14

| CLASSIFICATION | LANGUAGE EVALUATION | RECOMMENDATION | CONCLUSION |
|--|---|-------------------------------------|--|
| <input type="checkbox"/> Grade A (Excellent) | <input type="checkbox"/> Grade A: Priority Publishing | Google Search: | <input type="checkbox"/> Accept |
| <input type="checkbox"/> Grade B (Very good) | <input checked="" type="checkbox"/> Grade B: minor language polishing | <input type="checkbox"/> Existed | <input type="checkbox"/> High priority for publication |
| <input type="checkbox"/> Grade C (Good) | <input type="checkbox"/> Grade C: a great deal of | <input type="checkbox"/> No records | <input type="checkbox"/> Rejection |
| <input type="checkbox"/> Grade D (Fair) | language polishing | BPG Search: | <input checked="" type="checkbox"/> Rejection |
| <input checked="" type="checkbox"/> Grade E (Poor) | <input type="checkbox"/> Grade D: rejected | <input type="checkbox"/> Existed | <input type="checkbox"/> Minor revision |
| | | <input type="checkbox"/> No records | <input type="checkbox"/> Major revision |

COMMENTS TO AUTHORS

General: The major problems with this manuscript include lack of quantitative specificity for mechanisms of intestinal bacteria, which ones are involved in production of endotoxin, poor structure throughout, lack of diagrams, and lack of critical evaluation of many of the data.

Many specific issues include the following:

p.3: Provide reference for statement that gut derived endotoxin results from bacterial translocation. Please address the question whether colonic bacteria are exposed to significant concentrations of ethanol, which is predominantly absorbed in the proximal small bowel. **In the revision we have modified this part and the statement was deleted**

p. 4: last para: Clarify site and which cells are responsible for production of NO. **We specify where iNOS and production of NO happen.**

p5, intestinal microflora: please relate CFU to numbers of bacteria present in terminal ileum and colon. **We relate CFU to number of bacteria present in the intestine**

P5. Clarify whether you are referring just to colonic bacteria or more proximal intestine. **We refer to gut microbiota, in other words to all human normal flora in the intestine (colon and proximal intestine)**

P5: statement that portal blood carries bacteria is inconsistent with prior statement that bacteria are lodged in mesenteric lymph nodes (bottom p 3). **We eliminate prior statement.**

P6, 2nd para: these are all very general statements; provide quantitative levels and fold-differences in colonic bacteria generated by alcohol consumption. **We reported the types of colonic bacteria influenced by alcohol consumption.**

P7: Provide quantitative dimension to “bacterial overgrowth”. Which bacteria are most affected, and by how much are they reproduced? **We have indicated the dimension of bacterial overgrowth and which bacteria are most affected** Which bacteria are most likely to translocate to mesenteric lymph nodes and produce LPS? Is LPS produced also in the lumen for translocation? **We eliminate this part in the reconstruction of the paragraph**

P7: 3rd para: Toll-like, not Tool-like. **We corrected it** Define PAMP. **We defined it**

P7, last para: does alcohol itself induce an inflammatory response? seems unlikely, since the accepted mechanism is LPS activation of TLRs. **Alcohol also induces a direct inflammatory response.**

P7: Recommend a figure to show differences in liver cell types and their receptors. **In a figure we indicated liver cells and the correspondent receptors**

P8, second line: “TLR4 which binds” what?? **We eliminate “and binds”**

P9: top: Specify whether and which antibiotics are proven to promote liver healing and how. Which mechanisms described in this paragraph are improved by antibiotic treatment? **We explained the role of antibiotic to promote liver healing**

P9 prebiotics: what are the mechanisms by which prebiotics may improve ALD, and what is evidence for their benefit? This is all inconvincing. **We have specified the role of prebiotics**

P10, probiotics: All of these statements are generalized, and actual proof of efficacy is not convincingly shown. **We have modified the paragraph following your indications**

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Reviewer code: 02539632

Science editor: Gou, Su-Xin

Date sent for review: 2014-02-26 09:01

Date reviewed: 2014-03-10 22:27

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| | | <input type="checkbox"/> No records | |

COMMENTS TO AUTHORS

This review by Malaguarnera et al. summarizes current knowledge about the role of the gut microbiome in ALD. Overall this article somehow appears unfinished.

There is a lot of repetitions and many citations seem not fitting well or citations are missing at all. **We correct it**

There is not a single figure or scheme for illustration. **We added figure and tables**

In the chapter "Intestinal permeability" - do the authors really suggest that the acetaldehyde produced by the bacteria is causing gut leakyness? If so, where is the connection then to ingested alcohol? **Acetaldehyde is a metabolite of alcohol ingested. It is formed by the action of alcohol dehydrogenase and its accumulation could be due to low efficiency of bacterial aldehyde dehydrogenase**

Many abbreviations are not explained with first use. **We have checked the abbreviations**

The language style and grammar needs improvement. **We have corrected grammar errors.**