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# PEER-REVIEW REPORT

**Name of journal:** World Journal of Gastroenterology
**Manuscript NO:** 36534
**Title:** Rifaximin ameliorates hepatic encephalopathy and endotoxemia without affecting the gut microbiome diversity
**Reviewer's code:** 02822816
**Reviewer's country:** Romania
**Science editor:** Ze-Mao Gong
**Date sent for review:** 2017-10-05
**Date reviewed:** 2017-10-07
**Review time:** 2 Days

| CLASSIFICATION | LANGUAGE EVALUATION | SCIENTIFIC MISCONDUCT | CONCLUSION |
|---|---|---|---|
| [ ] Grade A: Excellent | [ Y] Grade A: Priority publishing | Google Search: | [ ] Accept |
| [ Y] Grade B: Very good | [ ] Grade B: Minor language polishing | [ ] The same title | [ Y] High priority for publication |
| [ ] Grade C: Good | [ ] Grade C: A great deal of language polishing | [ ] Duplicate publication | [ ] Rejection |
| [ ] Grade D: Fair | [ ] Grade D: Rejected | [ ] Plagiarism | [ ] Minor revision |
| [ ] Grade E: Poor | | [ Y ] No | [ ] Major revision |
| | | BPG Search: | |
| | | [ ] The same title | |
| | | [ ] Duplicate publication | |
| | | [ ] Plagiarism | |
| | | [ Y ] No | |

## COMMENTS TO AUTHORS

To the authors, I read with interest your work. I have no comments. Congratulations.

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# PEER-REVIEW REPORT

**Name of journal:** World Journal of Gastroenterology
**Manuscript NO:** 36534
**Title:** Rifaximin ameliorates hepatic encephalopathy and endotoxemia without affecting the gut microbiome diversity
**Reviewer's code:** 00182114
**Reviewer's country:** Japan
**Science editor:** Ze-Mao Gong
**Date sent for review:** 2017-10-05
**Date reviewed:** 2017-10-08
**Review time:** 2 Days

| CLASSIFICATION | LANGUAGE EVALUATION | SCIENTIFIC MISCONDUCT | CONCLUSION |
|---|---|---|---|
| [ ] Grade A: Excellent | [ Y] Grade A: Priority publishing | Google Search: | [ ] Accept |
| [ ] Grade B: Very good | [ ] Grade B: Minor language polishing | [ ] The same title | [ ] High priority for publication |
| [ Y] Grade C: Good | [ ] Grade C: A great deal of language polishing | [ ] Duplicate publication | [ ] Rejection |
| [ ] Grade D: Fair | [ ] Grade D: Rejected | [ ] Plagiarism | [ Y] Minor revision |
| [ ] Grade E: Poor | | [ Y ] No | [ ] Major revision |
| | | BPG Search: | |
| | | [ ] The same title | |
| | | [ ] Duplicate publication | |
| | | [ ] Plagiarism | |
| | | [ Y ] No | |

## COMMENTS TO AUTHORS

Antibiotics have been administered in the treatment of HE, usually employed as second-line therapy. The mechanism is thought to relate to decreased colonic deaminating bacteria that produce nitrogenous compounds (i.e. ammonia) by metabolism of urea. The most common antibiotics used on a historic basis for HE include neomycin and metronidazole. Neomycin is approved as adjuvant therapy in hepatic coma. Metronidazole is not approved for HE. Neomycin is better studied than metronidazole . There are several controlled trials involving neomycin. Most studies, including those with metronidazole, are small and uncontrolled. Few support the use of either antibiotic for treatment of HE. Furthermore, long-term use of neomycin is limited by ototoxicity and nephrotoxicity Rifaximin is a poorly absorbed, oral antibiotic . It is derived from rifamycin and has a broad spectrum of activity against Gram-positive and

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Gram-negative, aerobic and anaerobic, enteric bacteria. It is thought to diminish deaminating enteric bacteria to decrease production of nitrogenous compounds that are subsequently absorbed and cause HE. I ask some questions to author. 1. Therefore, please comment the mechanism for the decreased NH3 with Rifaximin from the point of Gram-positive and Gram-negative, aerobic and anaerobic, enteric bacteria. 2. I think decreased endotoxin was due to improvement of intestinal tight junction by Rifaximin. Therefore ,please comment intestinal barrier function parameter with Rifaximin. 3. How about amino acid level with Rifaximin?

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# PEER-REVIEW REPORT

**Name of journal:** World Journal of Gastroenterology
**Manuscript NO:** 36534
**Title:** Rifaximin ameliorates hepatic encephalopathy and endotoxemia without affecting the gut microbiome diversity
**Reviewer's code:** 03253490
**Reviewer's country:** Turkey
**Science editor:** Ze-Mao Gong
**Date sent for review:** 2017-10-05
**Date reviewed:** 2017-10-15
**Review time:** 10 Days

| CLASSIFICATION | LANGUAGE EVALUATION | SCIENTIFIC MISCONDUCT | CONCLUSION |
|---|---|---|---|
| [ ] Grade A: Excellent | [ ] Grade A: Priority publishing | Google Search: | [ ] Accept |
| [ ] Grade B: Very good | [ Y] Grade B: Minor language polishing | [ ] The same title | [ ] High priority for publication |
| [ Y] Grade C: Good | [ ] Grade C: A great deal of language polishing | [ ] Duplicate publication | [ ] Rejection |
| [ ] Grade D: Fair | [ ] Grade D: Rejected | [ ] Plagiarism | [ Y] Minor revision |
| [ ] Grade E: Poor | | [ Y ] No | [ ] Major revision |
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| | | [ ] Duplicate publication | |
| | | [ ] Plagiarism | |
| | | [ Y ] No | |

## COMMENTS TO AUTHORS

The study is investigating 'the impact of rifaximin on the endotoxin activity and gut microbiota identified by 16S ribosome RNA (rRNA) gene sequencing in patients with decompensated cirrhosis.New studies /reviews suggest that ' Rifaximin may have beneficial actions beyond its direct antibiotic activity. Rifaximin's clinical activity may be attributed to effects on metabolic function of the gut microbiota, rather than a change in the relative bacterial abundance'.The discussion part may be updated by adding new reviews and studies focused on this topic.

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# PEER-REVIEW REPORT

**Name of journal:** World Journal of Gastroenterology
**Manuscript NO:** 36534
**Title:** Rifaximin ameliorates hepatic encephalopathy and endotoxemia without affecting the gut microbiome diversity
**Reviewer's code:** 03567380
**Reviewer's country:** United States
**Science editor:** Ze-Mao Gong
**Date sent for review:** 2017-10-05
**Date reviewed:** 2017-10-16
**Review time:** 11 Days

| CLASSIFICATION | LANGUAGE EVALUATION | SCIENTIFIC MISCONDUCT | CONCLUSION |
|---|---|---|---|
| [ ] Grade A: Excellent | [ ] Grade A: Priority publishing | Google Search: | [ ] Accept |
| [ ] Grade B: Very good | [Y] Grade B: Minor language polishing | [ ] The same title | [ ] High priority for publication |
| [Y] Grade C: Good | [ ] Grade C: A great deal of language polishing | [ ] Duplicate publication | [ ] Rejection |
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| [ ] Grade E: Poor | | [Y] No | [ ] Major revision |
| | | BPG Search: | |
| | | [ ] The same title | |
| | | [ ] Duplicate publication | |
| | | [ ] Plagiarism | |
| | | [Y] No | |

## COMMENTS TO AUTHORS

The case control study by Kaji et al. describes the use of rifaximin for the management of HE that results from decompensated liver cirrhosis. The authors describe an improvement in ammonia, endotoxin and neurocognitive assessments in subsets of patients without a significant change in the composition of the gut microbiome. The authors perform the study well and acknowledge a significant area of concern due to the low number of patients. That being said, there are a few areas the authors should address to improve this report which are listed below: 1) How many patients were included in the analysis with the high endotoxin activity (>0.4), delayed NCT and the high ammonia groups? Are these the same patients? The number of patients of each group should be included in the results and figure legends. This information (regarding the split of the groups) should be included in the methods or results. 2) Table

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1 should include the scores after the 4 weeks of rifaximin treatment (or it could be included as a second table). Any significant differences should be discussed in the text.