

PEER-REVIEW REPORT

Name of journal: *World Journal of Hepatology*

Manuscript NO: 85923

Title: Evaluation of a protocol for rifaximin discontinuation in critically ill patients with liver disease receiving broad-spectrum antibiotic therapy

Provenance and peer review: Unsolicited Manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 05238521

Position: Peer Reviewer

Academic degree: MD, PhD

Professional title: Assistant Professor

Reviewer's Country/Territory: Croatia

Author's Country/Territory: United States

Manuscript submission date: 2023-07-08

Reviewer chosen by: AI Technique

Reviewer accepted review: 2023-07-12 18:13

Reviewer performed review: 2023-07-22 20:15

Review time: 10 Days and 2 Hours

Scientific quality	<input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Very good <input type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
Novelty of this manuscript	<input checked="" type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Good <input type="checkbox"/> Grade C: Fair <input type="checkbox"/> Grade D: No novelty
Creativity or innovation of this manuscript	<input checked="" type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Good <input type="checkbox"/> Grade C: Fair <input type="checkbox"/> Grade D: No creativity or innovation

Scientific significance of the conclusion in this manuscript	<input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Good <input type="checkbox"/> Grade C: Fair <input type="checkbox"/> Grade D: No scientific significance
Language quality	<input checked="" type="checkbox"/> Grade A: Priority publishing <input type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
Conclusion	<input type="checkbox"/> Accept (High priority) <input type="checkbox"/> Accept (General priority) <input checked="" type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input type="checkbox"/> Rejection
Re-review	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
Peer-reviewer statements	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous
	Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

SPECIFIC COMMENTS TO AUTHORS

The subject of the research is clinically relevant and interesting. The title is appropriate for the study. The abstract summarizes the study and the key words describe it appropriately. The manuscript is well organized. The introduction section explains the rationale of the research. Study protocol and methods are well described. The results are clearly presented. In the discussion, the authors explain the main findings, compare the results with similar studies and state the limitations of the study as well as open questions for future research. The main problem of the study are rather robust primary and secondary outcomes of the study, small patient groups and short duration of the study, but these limitations have been explained in the discussion. The findings of the study are provoking and relevant for clinical practice. I would suggest the authors to reconsider the terms “pre- and post- protocol” groups, and maybe replace them with experimental and control (historical) group. Several times throughout the abstract and the manuscript the authors stress that this is a pharmacist-driven protocol, however, it is not clear how does it reflect to the study? I would also suggest the authors to consider adding the analysis of the results according to the antibiotic regimen used, as this might

also play a role in the outcomes.

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Reviewer's code: 03755068

Position: Peer Reviewer

Academic degree: MD

Professional title: Consultant Physician-Scientist

Reviewer's Country/Territory: Italy

Author's Country/Territory: United States

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Reviewer chosen by: Geng-Long Liu

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Reviewer performed review: 2023-08-08 08:11

Review time: 1 Day and 15 Hours

Scientific quality	<input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Very good <input type="checkbox"/> Grade C: Good <input checked="" type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
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	Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

SPECIFIC COMMENTS TO AUTHORS

This was an interesting single center study which explored rifaximin withdrawal in patients with cirrhosis admitted to the ICU and receiving broad spectrum antibiotic therapy. The Authors compared a group of patients who received rifaximin together with antibiotics in 2019 (retrospective cohort) with a group of patients who received antibiotics only. The primary outcome (days alive and free of delirium and coma to day 14) was similar between groups. The aim of the study is of interest, and I congratulate the Authors. However, I think that the indication to rifaximin use was not so clear, and that there is a wide spectrum of variables (e.g., response to sepsis, severity of sepsis, super-infection, different indication to ICU admission) which may influence the primary endpoint. I think that results provided by this study are perhaps difficult to replicate.

Major comments - The Authors said that in most cases rifaximin is administered as a continuation of home therapy. However, according to Table 1, less than half patients received pre-ICU rifaximin. - What was the indication of rifaximin in patients who had low HE grade according to WH criteria? - The best option to evaluate the role of rifaximin withdrawal in such a cohort would be a randomized trial. - The number of



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patients who met the primary endpoint was very low in both group (3 vs. 2 patients).

Minor points - Patients receiving low dose of rifaximin may be excluded - I suggest to change the term primary biliary cirrhosis with primary biliary cholangitis