

Reviewer #1:

Scientific Quality: Grade D (Fair)

Language Quality: Grade B (Minor language polishing)

Conclusion: Rejection

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.

- Thank you for taking time to provide a thoughtful review of our manuscript.

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.

- We agree that objective and explicit identification of the indication for rifaximin was challenging to obtain with retrospective data collection in a diverse cohort. We agree that illness-specific factors may have influenced the primary outcome which were not explicitly recorded in the present study. The discussion section has been updated to more completely address this limitation (page 14, line 24-28).

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 frequency of pre-hospital rifaximin use was determined based on insurance records available in the electronic medical record. The manuscript does not contain a statement that “most” patients received rifaximin pre-hospital. The statement in the introduction reads “In many cases of infection, patients also receive rifaximin either as a continuation of home therapy or newly initiated treatment.” (page 6, line 6-7). There does exist a possibility that patients were identified as new starts when they were receiving rifaximin for preventative therapy in the outpatient setting. Unfortunately, due to the nature of manual, retrospective data collection, we could not definitively record the indication of rifaximin in patients with low HE grade according to WH criteria. We recognize this as a limitation and adjustments were made to the discussion section for clarity (page 14, 1-5)

- The best option to evaluate the role of rifaximin withdrawal in such a cohort would be a randomized trial. - The number of patients who met the primary endpoint was very low in both group (3 vs. 2 patients).

- We agree that a randomized trial would be the optimal way to address this research question and hope that such a study will be completed in the future. We also agree that the number of

patients who achieved the primary outcome was very low which further emphasizes the need for larger follow-up studies to be completed. This is addressed in the conclusion section (page 15, line 19-23).

Minor points - Patients receiving low dose of rifaximin may be excluded

- Regarding low-dose rifaximin, patients prescribed low-dose rifaximin would be receiving off-label therapy for hepatic encephalopathy treatment or prevention. However, in our study, no patient was excluded based on rifaximin regimen (and no patients received low dose therapy) therefore this limitation would not apply.

- I suggest to change the term primary biliary cirrhosis with primary biliary cholangitis

- Primary biliary cirrhosis has been revised to primary biliary cholangitis (page 21, Figure 2).

Reviewer #2:

Scientific Quality: Grade B (Very good)

Language Quality: Grade A (Priority publishing)

Conclusion: Minor revision

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.

- Thank you for taking time to provide a thoughtful review of our manuscript.

I would suggest the authors to reconsider the terms “pre- and post- protocol” groups, and maybe replace them with experimental and control (historical) group.

- Because the study was not fully prospective, we hesitate to use the term “experimental.” The reviewer’s intent in simplifying group terminology is noted. The manuscript has been updated to use “control” and “protocol” for group titles throughout.

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?

- The protocol was pharmacist-initiated, pharmacist-led, and manually applied with significant multidisciplinary support which differs from a standing or provider-driven protocol. Emphasizing this element provides representation and a resource for other pharmacists looking for strategies to reduce medication costs and improve antibiotic stewardship efforts. The discussion section

has been updated to draw a clearer connection between this element of the study design and the conclusions (page 13, line 17-23).

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.

- While a subgroup analysis based on antibiotic regimen, or including this variable in the multivariable analysis, would have been interesting, the large number of potential antibiotic regimens, frequent modification of regimens for each patient, and very low rate of event days does would not allow the development of a statistically stable model. What may also be compelling is accounting for the appropriateness of antibiotics based on culture data. It is the authors' hope that a larger, controlled study will be conducted to confirm our findings, and this would certainly be a valuable consideration for design of such a study.