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**Revision reviewer:**

**Specific comments to authors**

I re-reviewed the article, and the authors needed to clarify the last changes made in the text. Therefore, it isn't easy to judge the differences compared with the initial draft specifically. The article has improved, and the authors added A new table 1

Dear peer reviewers

First of all, we want to thank you for your review, which we consider of great value to improve the article. Please find enclosed a complete copy of the manuscript entitled: "Challenges and recommendations when selecting empirical antibiotics in patients with cirrhosis" and a point-by-point response to your suggestions and observations.

**Reviewer ID 02539765**

-Comment 1: It is a well written article, and I have no major critical comments. Minor language polishing is needed. Response: The article was reviewed by a native speaker after the first submission, according to your suggestion.

-Comment 2: This paper might benefit from a brief discussion of bacterial infection in cirrhosis. Response: Thanks for this comment. We have discussed in the initial section of the manuscript the prevalence, type of bacterial infections, associated risk factors, and prognosis in patients with cirrhosis. We believe that increasing the length of the discussion regarding this topic would be inappropriate since the central topic is the rationale for using empirical antibiotics. There is a word limit for this review, so the reader could consider it somewhat out-of-focus.



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-Comment 3: A table or image illustrating the clinical implications of bacterial infection in cirrhosis might enhance this work. Response: Thanks for this comment. We definitely agree with your suggestion of incorporating a table. Taking together the other reviewers' suggestions, we decided to incorporate a table comparing American and European recommendations for empiric antibiotic use in patients with cirrhosis since, after an extensive review of the literature, that table was never published before and could be very useful for readers.

#### **Reviewer ID 06151472**

-Comment 1. The choice of antibiotic prophylaxis should be made according to the patient care setting, in my opinion. Prophylaxis in a patient who is admitted for variceal bleeding and prophylaxis in a patient who bleeds while on ongoing antibiotic therapy in the ICU probably may not be the same. Second, this paper does not deal with type of antibiotics, according to the source of infection.

Response: Thanks for raising this issue. Based on your observation, we discussed this issue under the title "Antibiotic prophylaxis in patients with acute gastrointestinal bleeding" (last paragraph) with particular mention of the clinical scenario you portrayed.

-Comment 2: There are some new antibiotic drugs, or innovative measurement of antibiotic effectiveness in patients with cirrhosis (e.g., ascitic concentration of antibiotic) that should be mentioned. Response: We prefer to focus on the central theme, which is the difficulty of rationally using empirical antibiotics. This review has a word limit, so the reader could consider it somewhat out-of-focus.

-Comment 3: I agree with the Authors when they said that empiric antibiotic therapy should be considered in patients with cirrhosis that deteriorate their clinical status without any known precipitating event. I also agree when they said that cultures are often available after 48 h. Therefore, I think that a rapid institution of empiric antibiotic therapy, with early de-escalation/stop when cultures are negative may be a reasonable option. Is this the key message the Authors want to address? Otherwise, do they advise on wait for cultures? - The Surviving Sepsis Campaign 2021 recommend to start empirical antibiotic therapy in patients with high suspicion of sepsis. The lack of high suspicion (according to SIRS criteria, or to lab test) is the key point that differentiates the patient with cirrhosis. - There are several biomarkers beyond WBC, CRP, procalcitonin that have been investigated in patients with cirrhosis (IL-6, presepsin, etc). Response: thank you for this remark. As pointed out, we state that the rapid institution of antibiotics is key in the management of patients with cirrhosis and suspected infections. It is mentioned in the paragraph that begins with the phrase, "When a bacterial infection is suspected in patients with cirrhosis, the immediate initiation of antibiotics is key to improving prognosis." In this setting, waiting for cultures would be opposite to the rapid institution of empiric therapy. Several biomarkers as surrogates for sepsis in cirrhosis are detailed.

-Comment 4: The MDRO challenge is a serious problem for patients with cirrhosis. MDRO patients are often those who underwent previous antibiotic therapies, and/or those who had previous (often prolonged) hospitalizations. There is some evidence that previous rectal colonization by MDRO can be useful to predict further MDRO invasive infection. Response: Thank you for this comment. Accordingly, we have added a paragraph mentioning current evidence regarding the role of rectal colonization and MDRO infections in patients with cirrhosis.

-Comment 5:- I fully agree with the Authors when they said that local epidemiology is of paramount importance. Nevertheless, this is a Gordian knot. Indeed, also the local epidemiology can rapidly change (as demonstrated in studies from Europe on the CANONIC cohort), and the local epidemiology can reflect only culture positive infection, which account for nearly 50% infection in patients with cirrhosis. Response: We definitely agree with your observation. In fact, one of the key messages of the review is that more commitment is needed to implement and maintain surveillance programs.

-Comment 6 : The paper deals with antibiotic prophylaxis, therefore, this should be mentioned in the title. Response: we agree with your observation. That is why the title mentions “empirical antibiotics” without specifying “therapeutic” or “prophylactic” .

-Comment 7: Are there Guidelines that suggest different antibiotic approaches according to organ failure(s), or ACLF? Response: No, no specific guidelines are focusing on ACLF or organ failures.

#### **Reviewer ID 00504581**

Comment 1: We need help to find any news on these topics. However, this report should revise other items. We were referring to the discussion of the appropriate empirical treatment of pneumonia (community or nosocomial), bacteremia, sepsis of unknown origin, cutaneous or brain infections (meningitis), or even articular infections is necessary. Response: Thanks for your comment. This review has a word limit, therefore, considering your observation, we included a table comparing European and American recommendations of empirical antibiotics for various bacterial infections.

Comment 1: Something needs to state about the need for antibiotic prophylaxis in viral pneumonia. Response: Unfortunately, after an extensive revision of the literature and consulting specialists in infectious diseases, there are no practical recommendations that could be incorporated into this mini-review regarding this issue.

Yours sincerely,

Sebastián Marciano (on behalf of all co-authors)

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