

## PEER-REVIEW REPORT

**Name of journal:** *World Journal of Hepatology*

**Manuscript NO:** 81280

**Title:** Challenges and recommendations when selecting empirical antibiotics in patients with cirrhosis

**Provenance and peer review:** Invited manuscript; Externally peer reviewed

**Peer-review model:** Single blind

**Reviewer's code:** 06151472

**Position:** Peer Reviewer

**Academic degree:** MD

**Professional title:** N/A

**Reviewer's Country/Territory:** Italy

**Author's Country/Territory:** Argentina

**Manuscript submission date:** 2022-11-12

**Reviewer chosen by:** AI Technique

**Reviewer accepted review:** 2022-11-13 14:41

**Reviewer performed review:** 2022-11-13 20:02

**Review time:** 5 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 Grade E: Do not publish
Language quality	<input type="checkbox"/> Grade A: Priority publishing <input checked="" 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 type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input checked="" type="checkbox"/> Rejection
Re-review	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

<b>Peer-reviewer statements</b>	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

This was an interesting minireview about empirical antibiotic therapy in patients with cirrhosis. The Authors briefly described the prevalence and the prognostic role of bacterial infection in patients with cirrhosis. Then, they remarked the importance of a timely introduction of the empiric antibiotic therapy when bacterial infection is suspected. Finally, they discussed about the challenges on antibiotic prophylaxis (namely prophylaxis during variceal bleeding and primary and secondary prophylaxis for spontaneous bacterial peritonitis). The paper is easy to understand, but it does not discuss in depth some important challenges Hepatologists face every day in clinical practice. First, 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. 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. Major comments. - 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



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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). - 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. - 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. Minor comments. - The paper deals with antibiotic prophylaxis, therefore this should be mentioned in the title - Are there Guidelines that suggest different antibiotic approaches according to organ failure(s), or ACLF?

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**Reviewer's code:** 00504581

**Position:** Editorial Board

**Academic degree:** MD, PhD

**Professional title:** Associate Chief Physician, Associate Specialist, Attending Doctor, Doctor, Medical Assistant, Staff Physician

**Reviewer's Country/Territory:** Spain

**Author's Country/Territory:** Argentina

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**Reviewer chosen by:** AI Technique

**Reviewer accepted review:** 2022-11-12 10:56

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**Review time:** 4 Days and 1 Hour

<b>Scientific quality</b>	<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
<b>Language quality</b>	<input type="checkbox"/> Grade A: Priority publishing <input checked="" type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
<b>Conclusion</b>	<input type="checkbox"/> Accept (High priority) <input type="checkbox"/> Accept (General priority) <input type="checkbox"/> Minor revision <input checked="" type="checkbox"/> Major revision <input type="checkbox"/> Rejection

<b>Re-review</b>	[ <input checked="" type="checkbox"/> ] Yes [ <input type="checkbox"/> ] No
<b>Peer-reviewer</b>	Peer-Review: [ <input checked="" type="checkbox"/> ] Anonymous [ <input type="checkbox"/> ] Onymous
<b>statements</b>	Conflicts-of-Interest: [ <input type="checkbox"/> ] Yes [ <input checked="" type="checkbox"/> ] No

## SPECIFIC COMMENTS TO AUTHORS

For this paper's review, we considered the article's title, which reveals in some way the final author's goal "Challenges and recommendations when selecting empirical antibiotics in patients with cirrhosis." This report described a group of facts that, on the other hand, are very well-known in the literature, such as the influence of bacterial infections and their severity on the survival of the cirrhotic patient and their evident relationship with the development of acute on chronic liver failure and mortality) I.e, "Impact of bacterial infections in patients with Cirrhosis." Moreover, the authors pointed out the difficulties in the early diagnosis of these infections (i.e., "Challenges on timely diagnosis and treatment of bacterial infections," and stressed the importance of the early use of empirical antibiotics accordingly to the possible source of the infection, and with antibiotics strong enough to be able to cover more than 85% of the potential bacteria involved in that particular infection, This article contains general points and statements that are very well-known for hepatologists. The relevant infections considered and discussed in this report were the empirical antibiotic treatment of SBP, Upper gastrointestinal bleeding antibiotic prophylaxis, and urinary tract infections. The authors only added and stressed an attention, call for studying bacterial resistances at the local level to fit the Guideline indications with the particularities of each country or region. 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. Something needs to state about the need for antibiotic prophylaxis in viral pneumonia. After all, the article made a limited revision on this topic, based on facts already known and clearly established on the international guidelines, without any novelty, and only stressing the importance of the local investigation on bacterial resistance, rarely available in many places of the world.

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**Peer-review model:** Single blind

**Reviewer's code:** 02539765

**Position:** Peer Reviewer

**Academic degree:** MBBS, MD

**Professional title:** Additional Professor

**Reviewer's Country/Territory:** India

**Author's Country/Territory:** Argentina

**Manuscript submission date:** 2022-11-12

**Reviewer chosen by:** AI Technique

**Reviewer accepted review:** 2022-11-12 01:22

**Reviewer performed review:** 2022-11-21 11:08

**Review time:** 9 Days and 9 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
Language quality	<input type="checkbox"/> Grade A: Priority publishing <input checked="" 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 checked="" type="checkbox"/> Accept (General priority) <input type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input type="checkbox"/> Rejection
Re-review	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No



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<b>Peer-reviewer statements</b>	Peer-Review: [ <input checked="" type="radio"/> ] Anonymous [ <input type="radio"/> ] Onymous
	Conflicts-of-Interest: [ <input type="radio"/> ] Yes [ <input checked="" type="radio"/> ] No

#### **SPECIFIC COMMENTS TO AUTHORS**

In this mini-review, authors have discussed infection in the patients with liver cirrhosis and the challenges while selecting empirical antibiotics in such patients. It is a well written article, and I have no major critical comments. Minor language polishing is needed. For example, the sentence “Therefore, is of paramount importance to know the local epidemiology in order to propose tailored guidelines” looks incomplete. Some of my other suggestions are: 1. This paper might benefit from a brief discussion of the pathogenesis of bacterial infection in cirrhosis. 2. A table or image illustrating the clinical implications of bacterial infection in cirrhosis might enhance this work.



## RE-REVIEW REPORT OF REVISED MANUSCRIPT

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**Reviewer's code:** 00504581

**Position:** Editorial Board

**Academic degree:** MD, PhD

**Professional title:** Associate Chief Physician, Associate Specialist, Attending Doctor, Doctor, Medical Assistant, Staff Physician

**Reviewer's Country/Territory:** Spain

**Author's Country/Territory:** Argentina

**Manuscript submission date:** 2022-11-12

**Reviewer chosen by:** Jing-Jie Wang

**Reviewer accepted review:** 2022-12-30 14:56

**Reviewer performed review:** 2023-01-01 19:10

**Review time:** 2 Days and 4 Hours

<b>Scientific quality</b>	<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
<b>Language quality</b>	<input type="checkbox"/> Grade A: Priority publishing <input checked="" type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
<b>Conclusion</b>	<input type="checkbox"/> Accept (High priority) <input checked="" type="checkbox"/> Accept (General priority) <input type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input type="checkbox"/> Rejection



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<b>Peer-reviewer statements</b>	Peer-Review: [ <input checked="" type="checkbox"/> ] Anonymous [ <input type="checkbox"/> ] Onymous Conflicts-of-Interest: [ <input type="checkbox"/> ] Yes [ <input checked="" type="checkbox"/> ] No
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#### **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