Dear Editors and Reviewers,

Thank you for taking the time to review our manuscript. We appreciate your insightful comments and are grateful for the opportunity to improve our work. Our point-by-point response is provided below.

Reviewer 1

Reviewer Comment: "Although this is a review, the authors are encouraged to add a Materials and Method section to better and clearly explain the type of review (descriptive, systematic, etc.), how many RCTs were considered, timespan, what databases were used for interrogation, inclusion and exclusion criteria of RCTs, etc. For a systematic review the PRISMA checklist must be followed. For a descriptive review, a more relaxed structuring can be followed, such as classical IMRAD construction."

> **Author Response:** Thank you for taking the time to evaluate our manuscript, which is designed to be a narrative review. Our piece is descriptive in nature and follows the guidelines set forth by the *World Journal of Hepatology* and the scientific community in general. It is not a systematic review, and a PRSIMA checklist is not applicable. Additionally, an IMRaD format is also not applicable in this context. Specifically, it would be atypical to include a materials and methods section since our work did not incorporate any pre-defined methodology. Relevant citations were selected at the authors' choice. They were not chosen based on a structured search or selection process (or any other specific criteria). We feel like the addition of a materials and methods section may create confusion for readers as the other narrative reviews in this publication do not usually include such a section. However, if the editors feel like this would be helpful, we would be happy to include a brief methods section.

Reviewer Comment: "After clarifying the type of review, the title should be modified to better reflect the study."

> **Author Response:** We believe that our title adequately portrays the content of our review. The type of manuscript will be clearly depicted on the title page per journal format, so including it again in the title is repetitive.

Reviewer Comment: "A section dedicated to the limitations of the study is also recommended."

Author Response: As noted, this is not a study. This narrative review carries the inherent limitations of any descriptive piece, including bias based on the authors' non-structured choice of citations. We have attempted to clearly highlight knowledge gaps pertaining to this subject matter.

Reviewer 2

Reviewer Comment: "I read with interest the paper by Dr. Jimenez and collaborators regarding the emerging concepts on septic shock in patients with cirrhosis. The paper overviews on many aspects of the topic, including pathophysiology, diagnosis and management. The manuscript is well written and easy to read. Figures are informative. I have only few comments for the Authors.**"**

Author Response: Thank you for taking the time to review our manuscript and for providing encouraging remarks. We are delighted that you enjoyed reading our review.

Reviewer Comment: "I appreciate the comment about the poor reliability of hypoperfusion according to a fixed MAP value in patients with cirrhosis. This is a good point for the everyday clinical practice, in my opinion."

Author Response: Yes, we agree. The use of a fixed MAP value may not be applicable in some patients with cirrhosis as discussed in our review. Thank you for the comment.

Reviewer Comment: "Impairment of mental status can be another important sign in patients with cirrhosis and sepsis. Very often, altered mental status has been considered an unreliable tool in cirrhosis because of hepatic encephalopathy. Nevertheless, I think that acute alteration of mental status, especially in a hospitalized patient with negative blood ammonia levels, should be taken into account as a tool for sepsis."

Author Response: We generally agree with Reviewer 2 regarding the importance of the neurological window in the assessment of septic shock.

Nonetheless, its interpretation is complicated, especially among patients with hepatic encephalopathy.

The application of ammonia levels in an encephalopathic patient with cirrhosis and suspected sepsis is controversial and potentially unreliable. This is largely due to the technical aspects of specimen collection and processing and possible confounding factors for hyperammonemia. This is further compounded by the observation that normal ammonia levels may be commonly found in grade 1 or 2 hepatic encephalopathy. Therefore, the presence or absence of hyperammonemia may not necessarily help in the diagnosis of hepatic encephalopathy in some patients. In turn, the absence of hyperammonemia in an encephalopathic patient is not necessarily a reliable predictor of sepsis and shock. However, we agree with Reviewer 2 that the lack of alternative inciting factors for hepatic encephalopathy should raise the suspicion for infection as the cause for altered mental status, especially among critically ill patients. We have added the following sentence in our manuscript: “In patients with new or unexplained HE, there should be a high index of suspicion for sepsis with or without shock.”

Reviewer Comment: “Lactate is a very useful tool, in my opinion, to diagnose septic shock in patients with cirrhosis, where other signs of sepsis are often poorly represented. Therefore, I would encourage the Authors to give the Reader more precise indication about lactate. For instance, would the Authors prefer arterial vs venous lactate levels? Is there a concordance between levels in cirrhosis? Is there a fixed diagnostic threshold of lactate serum levels for diagnosis of sepsis? Have lactates been incorporated in any diagnostic or prognostic score for patients with cirrhosis?”

Author Response: We agree that lactate is a useful marker in the diagnosis and management of shock. Studies have generally demonstrated a close correlation between venous and arterial lactate levels. Although this finding has not been specifically validated in patients with cirrhosis, we believe that venous levels are appropriate in this context, especially because most laboratory blood samples are venous. However, in patients who have arterial lines (which are often accessed for lab samples when present), the use of arterial lactate levels is also acceptable. As is the case with most clinical markers in critically ill patients, the interval change in values before and after interventions is often more useful than isolated absolute values.

In patients with compensated cirrhosis, a cutoff > 2 mmol/L should be used in the diagnosis of shock, albeit with the considerations specifically stated in the "Manifestations of Shock in Cirrhosis" section (i.e. recent alcohol intake, medications etc). However, in patients with decompensated cirrhosis, there is evidence for the use of higher levels (>4 mmol/L). This is now stated in our manuscript as follows: "Venous lactate levels > 2 mmol/L should raise suspicion for shock, but a multimodal approach that accounts for other signs and symptoms of organ hypoperfusion is warranted. In decompensated cirrhosis, a higher threshold (>4 mmol/L) may be considered[36]."

Finally, we thank Reviewer 2 for bringing up the application of lactate in prediction scores such as the MELD-LA score. Interestingly, the validation of the MELD-LA in critically ill patients with end-stage liver disease discriminates values of 4 mmol/L among survivors and non-survivors, supporting the previously noted cutoff for lactate levels in decompensated cirrhosis. Therefore, we have included the following text in the manuscript: "Mortality prediction models such as the MELD-LA score have demonstrated that lactate values have prognostic significance."

Reviewer Comment: "What is the role of terlipressin in noradrenaline-refractory septic shock in cirrhosis. Any available evidence in such a setting?"

Author Response: Reviewer 2 highlights an interesting aspect of vasopressor trials and the quality of the evidence for our daily practice. The evidence for second- and third-line vasopressors in septic shock is scarce. Randomized controlled trials testing both terlipressin and vasopressin for septic shock used a direct comparison of vasopressors (norepinephrine versus terlipressin and norepinephrine versus vasopressin) plus open label add-ons. Although there are small studies testing the addition of terlipressin, the results of Liu´s study (reference 70) demonstrated safety concerns with the use of terlipressin. Therefore, even in patients with cirrhosis, the evidence favors the use of vasopressin over terlipressin as a second agent (and the vasopressin analogue of choice in septic shock). We now cite these studies and explicitly state the preference for vasopressin over terlipressin given the current evidence: "Though it may be reasonable to consider vasopressin analogues such as terlipressin in some patients with cirrhosis, there is currently insufficient data to support their use over vasopressin[78-80]."

Reviewer Comment: "I appreciate the section about antibiotics, and the need of a rapid broad-spectrum coverage, in order to decrease mortality. However, I think that rapid diagnosis of strains responsible for infection is of paramount importance, too, in order to de-escalate antibiotic therapy and/or to shift empiric therapy to targeted therapy. I suggest to briefly discuss emerging diagnostic tools (e.g., array panels) that should improve the diagnostic process in patients with cirrhosis. I think that, given the peculiarities of sepsis in patients with cirrhosis and CSPH, these arrays should be made available once sepsis is suspected, not only in the ICUs but also in the regular ward. Culture negative infections represent 40-50% infection in hospitalized patients with cirrhosis (pneumonia, SBP). This should be briefly discussed, in my opinion."

Author Response: Reviewer 2 brings up the relevant role of advanced molecular diagnostics in the identification of sepsis. We agree that this is a relevant topic. Therefore, we have briefly discussed this subject in our manuscript as follows: "Unfortunately, up to 50% of cases of sepsis are associated with insufficient or negative culture data, which complicates both antimicrobial de-escalation and the detection of resistant strains[112]. Rapid diagnostic techniques which rely on molecular methods such as polymerase chain reaction, are now available for the identification of pathogens and resistance genes. They have been shown to be efficient and effective in isolating the cause of sepsis[113]. Their use is associated with improved antibiotic selection, decreased antimicrobial use[114], shortened hospital stays, and in the case of bloodstream infections, improved mortality[115]. When available, these techniques should be used to optimize precision in the diagnosis and treatment of sepsis."

Reviewer Comment: "Emerging concepts about the pharmacokinetics of antibiotics have been developed in cirrhosis, for instance, in patients with spontaneous bacterial peritonitis, where penetration of molecules into ascites has been questioned. I think that a brief comment would be valuable."

Author Response: We incorporated a comment regarding this important pharmacologic concept as follows: "Furthermore, patients with ascites have an increased volume of distribution, which may result in decreased peak concentrations of antibiotics, especially those which distribute extracellularly[121]. In the case of spontaneous bacterial peritonitis, a common source of sepsis among hospitalized patients with cirrhosis, peritoneal antibiotic

penetration is an essential concept. While some agents like cephalosporins, fluoroquinolones, and meropenem[122-124] achieve high concentrations in ascitic fluid, others such as aminoglycosides and tigecycline have reduced penetration[125,126].”