Dear Editor

We would appreciate your consideration of the enclosed revised manuscript, entitled "Spontaneous Fungal Peritonitis: Epidemiology, Current Evidence and Future Prospectives" (ESPS Manuscript NO: 25838) for publication in the World Journal of Gastroenterology. Our point-by-point responses appear below.

**Reviewer 1**

Spontaneous bacterial peritonitis (SBP) is common complication of advanced liver cirrhosis with well defined impact on kidney function and mortality. Spontaneous fungal peritonitis (SFP) has lower incidence, but it is probably underdiagnosed. Authors wrote review containg epidemiology, current evidence and future prospectives of SFP. Review is well written, but paper needs revision. Major changes: 1)To decribe pathogenesis of SFP in liver cirrhosis and the differences between SBP and SFP. 2) To describe assocation between SFP and other infectious complications (especially fungal infection) 3) To describe in detail impact of SFP on kidney function. 4) To summarize assciation between SFP and mortality in special table. Minor changes: 1) Citation 4) Was SFP found in 9 or 11 patients? 2) Authors make conclusions about SBP without presentation of SFP data. 3) To summarize impact of antimycotic treatment on course of liver cirrhosis. 4) Figure 1) High risk factors for SFP start antibiotic and antifungal therapy - please to clarify Without clinical improvement: add-on antifungal therapy - please to clarify 5) To add recommendation, how to improve diagnosis of SFB. 6) Text needs grammar revision.

*We have very appreciated the comments of the first reviewer.*

Major changes

1) *We have described the possible pathogenesis of SFP and the differences between SBP and SFP (highlighted in green) in the first and second paragraph dedicated to the current evidence (reference 15)*.

2) *We have described the association between SFP and SBP in Table 1 (polymicrobial infections). We have not found studies that associate the SFP to other foci of infection*.

3) *In the studies reported there is not a sub-analysis of the impact of SFP on kidney function. New prospective studies that asses the different impact on kidney function between SBP and SFP are needed*.

Minor changes

1) *SFP was found in 9 patients (the number corrected is highlighted in green)*.

2) *In the third paragraph of the future prospects we emphasized the concept that in cirrhotic patients with septic shock secondary to SBP have high mortality (80%). Each hour of delay in appropriate antimicrobial therapy was associated with a 1.86 times increase in hospital*

*mortality. Unfortunately, it is not possible to extrapolate from this study the subgroup of SFP, but we can assume that septic shock has a worse outcome (highlighted in green)*.

3) *There are no studies that compare empiric antifungal treatment versus standard (not antifungal) treatment. First, we want to point out that in the study of Piano et al. (reference 19), for the first time, an antifungal agent was proposed in an empirical treatment protocol for SBP. Indeed, even in the most recent guidelines on management of infections in cirrhosis, antifungal treatment has not been suggested in non-responders to broad-spectrum antibiotics (reference 21)*.

4) *High risk factors for fungal infections are: Total parenteral nutrition, Fungal Colonisation, Renal replacement therapy etc. summarized in reference 32, highlighted in green*.

5) *To improve diagnosis of SFP the clinicians should immediately perform ascitic/blood culture (figure 1)*.

6) *Text grammar revision was performed*.

**Reviewer 2**

Spontaneous bacterial peritonitis (SBP) is a well-known complication of cirrhosis; however, spontaneous fungal peritonitis (SFP) is less well-recognized and described. In this review, the author provided an overview of the current evidence-based information on the epidemiology, characteristics, and optimal empirical antifungal therapy. This review is described in detail, which, as a valuable information, could help the readers that have better understand the first-hand knowledge of this topic to start novel studies. This review is recommended to be published in the journal.

*We are enormously proud of the comments of the second reviewer and we want to thank him that understand the difficulty of writing about a topic scarcely considered in the scientific literature.*

**Reviewer 3**

This is an interesting review of a relevant topic (spontaneous fungal peritonitis) scarcely considered in the scientific literature. Accordingly, this review is welcome, specially if it can be useful to guide future treatment of patients. However, some corrections are necessary to clarify the text: - In the introduction section (third line) authors describe the diagnosis of SFP when in fact is the diagnosis of SBP. - In the description of the study from Hwang et al. (Epidemiology section. Asia. Reference 1) the number of patients with SFP and nosocomial peritonitis and the mean value of Child-Pugh score should be indicated. - In the description of the study from Li YT et al. (Epidemiology section. Asia. Reference 4) authors state "Nine patients were positive for fungi (2.9%); there was significant difference regarding fungi distribution between nosocomial (7.1%, 9 patients) and non-nosocomial (0.9%, 2 patients) cases (P = 0.004) [4].". How many patients had fungal infection? 9 or 11. - In the description of the study from Piroth L et al (Epidemiology section. Europe. Reference 7) authors state

"Bacterascites seems be considered a serious condition given the mortality rate (close to 20%). The authors concluded that bacterascites is probably a surrogate marker of advanced liver disease [7]." But this conclussion concerns the bacterascites. What about the SFP?. Was the mortality in patients with bacterascites related to the existence of SFP?, This paragraph must be clarified. - In the description of the study from Friedrich et al. (Epidemiology section. Europe. Reference 9) authors state "Interestingly, there was no significant difference regarding Candida spp. distribution between nosocomial (9.0%, 8 patients) and non-nosocomial (4.1%, 2 patients) cases (P = 0.287) [9].". Why interestingly? The number of patients is so small that any statistical analysis is underpowered. However, there are twice as many cases with nosocomial SFP and this is not analyzed. - In the description of the study from Karvellas et al. (Epidemiology section. North America/Miscellaneous. Reference 14) authors state "The authors concluded that cirrhotic patients with septic shock secondary to SBP have high mortality (80%). Each hour of delay in appropriate antimicrobial therapy was associated with a 1.86 times increase in hospital mortality.". Again, authors make statements about SBP without SFP data. Information about SFP cases must be given. - The title "FUTURE POSPETIVES" is wrong - Authors must develop in detail (in a new section) the underlying mechanisms to fungal infections in cirrhosis. Is specially important to take in consideration the relationship between immunosuppression and fungal infections, the mechanism involved in the association between bacterial polymicrobial infections and fungal infections and the influence of liver impairment in the development of fungal infections. - A general review of grammar and verb tenses is recommended

*We have appreciated the comments of the third reviewer.*

Major changes

1) *We use for SFP the definition used by Hwang SY et al. (reference 1).*

2) *We indicated the number of patients with SFP and nosocomial peritonitis and the mean value of Child-Pugh score end of first paragraph highlighted in green.*

3) *In the description of the study from Li YT et al. (Epidemiology section. Asia. reference 4) authors state 9 patients had fungal infection highlighted in green.*

4) *In the description of the study from Piroth L et al (Epidemiology section. Europe (reference 7) "Bacterascites seems be considered a serious condition given the mortality rate (close to 20%). We do not suppose that the mortality in patients with bacterascites is related to the existence of SFP, we clarify in the area of uncertainty (fourth paragraph of future prospectives) that Fungalascites has higher mortality rates than bacteriascites.*

5) *In the description of the study from Friedrich et al. (reference 9) we state "Interestingly, there was no significant difference regarding Candida spp. distribution between nosocomial (9.0%, 8 patients) and non-nosocomial (4.1%, 2 patients) cases (P = 0.287). We emphasize at the end of second paragraph of current evidence that the number of patients is so small that any statistical analysis is underpowered so a meta-analysis of observational studies could*

*clarify the fungi distribution between nosocomial and non-nosocomial infections because we suppose that this review can be useful to guide future epidemiological studies.*

6) *In the description of the study from Karvellas et al. (reference 14) we state "The authors concluded that cirrhotic patients with septic shock secondary to SBP have high mortality (80%). Each hour of delay in appropriate antimicrobial therapy was associated with a 1.86 times increase in hospital mortality." We emphasize in the third paragraph of future prospectives that unfortunately it is not possible to extrapolate from this study the subgroup of SFP, but we can assume that septic shock has a worse outcome.*

7) *We have described the possible pathogenesis of SFP and the differences between SBP and SFP (highlighted in green) in the first and second paragraph dedicated to the current evidence (reference 15).*

8) *Text grammar revision was performed.*