

Format for ANSWERING REVIEWERS

September 22, 2014

Dear Editor,



Please find enclosed the edited manuscript in Word format (file name: 13762-review.doc).

Title: Invasive candidiasis in critical care setting, recommendations from 'Invasive Fungal Infections-Clinical Forum' (IFI-CF), Iran

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Name of Journal: *World Journal of Critical Care Medicine*

ESPS Manuscript NO: 13762

Thank you and the reviewers for the thoughtful evaluation of our work. We were very pleased with the review as well as the opportunity to resubmit. The critiques were both informative and constructive.

Revised/added parts are highlighted in yellow in the present version.

The manuscript has been improved according to the suggestions of reviewers. Below, kindly find the point-to-point response to reviewers.

Reviewer's comments:

1. This is an important effort to draw a pathway how to apply the international guidelines to country or area specific clinical practice. I will suggest to add some recommendations about fundoscopic examination, catheter removal, frequency of blood cultures after the initiation of antifungal therapy, a pathway for the patients without clinical response and subtype specific antifungal therapy.

Response: Thanks very much for suggesting to add these points. The IFI-CF's recommendations have covered such points. The panel refocused on these issues and concurred on the related statements to be added to the manuscript.

- a) With respect to the clinical manifestations of suspected IFIs in the ICU and routine clinical evaluations, fundoscopic examination needs to be done by an intensivist. However, this examination has a low negative predictive value against IFIs and treatment should be based on a wider risk stratification and assessment.
- b) In case of a documented IFI, catheter removal becomes mandatory since eradicating the infection without removing the device looks unlikely. The challenge will arise in the context of suspected IFIs in the presence of permanent catheters, pace makers, implantable cardioverter defibrillator (ICD) or cardiac resynchronization therapy (CRT), etc. where some expert recommend a "device salvage trial"

for successful outcome. Taken together, the general recommendation is to remove catheters the soonest possible.

- c) The duration of antifungal therapy depends mainly on both response to treatment and status of blood culture at the beginning of IFI therapy. Normally, 72 to 96 h of treatment duration is adopted with a repeated blood culture after IFI therapy was started. The treatment will usually be stopped after 14 days since the first negative blood culture. If the therapy was started empirically (no positive blood culture), the duration of therapy is 14 days provided the patient's condition is improving on treatment. Repeated blood culture will prove whether the fungal infection is resolved.
- d) Drawing a clinical pathway for non-responding patients may be difficult but still possible. Lack of response may be due to an alternative diagnosis, either non-fungal or additional microbial infections which have not been properly covered in the current therapy. Either way, a review has to be done to detect the possible source of infection and necessary investigations including standard blood cultures, non-culture based assessments, if available, and possible imaging studies such as high-resolution computed tomography (HRCT) and advanced ultrasound should be considered to diagnose a possibly-disseminated IFIs or resistant organisms not fully sensitive to the current therapy. In challenging, non-responding IFI cases, the treatment should be adjusted with the possibility of combination antifungal therapy. Finally, lack of response may be due to inappropriate source control including devices, foreign bodies, and surgically-accessible factors like collections which require appropriate interventions. One should always bear in mind that the lack of response may be due to non-infectious causes which also need to be well-explored.
- e) Based on the risk and severity assessment, empirical approach allows the timely management of IFIs. According to the evidence highlighted in this report, moderate- to high-risk patients for severe infections require echinocandins. Streamlining depends on response and the culture results. Meanwhile, mild infections in stable patients can still be treated with FCZ. Suspected *Aspergillus* requires VCZ, whereas the emerging and rare fungal infections would still require AmB. Furthermore, the possibility of combination antifungal therapy should be considered.

The above justifications are now included in the manuscript under: [The panel's position on the management of IC in critically-ill patients], second paragraph.

2. Taking into account the actuality and quality of the research work, the manuscript should be considered for publication after minor revision. Below some suggestions are listed to improve the quality of the present manuscript: - *Candida* (in Italic) species (in Italic) - *Candida*(in Italic) species (not in Italic) - spp (in Italic)- spp (not in Italic) - *Candida* spp. - *Candida* (in Italic)spp. - *Candida albicans* - It could be abbreviated as *C. albicans* - spp - spp. - non-*albicans* spp.(in Italic) - non-*albicans* spp. (not in Italic) - protetive - protective - Please, abbreviate the fluconazole as FCZ, voriconazole as VCZ, caspofungin as CFG, echnicandin as ECH, etc. - "...identification of candida in the blood.." - identification of *Candida* (in Italic) spp. in the blood - "...of different candida species rather than..." - of different *Candida* (in Italic) species rather than - "...fluconazole-resistant candida species..." - "fluconazole-resistant *Candida* (in Italic)species - "7. Approach to Invasive Candidiasis in Intensive Care Unit" - Please, do not begin all words with Capital letter. - non-*albicans* candida isolation - non-*albicans* *Candida* (in Italic) isolation - "...illustrated in figure 2..." - illustrated in Figure 2 - Please, indicate the abbreviations in the figure and table legends where it is needed.

Response: Thanks for the meticulous attention to typesetting with regard to fungi and medication names. These points were taken and required corrections were made throughout the manuscript.

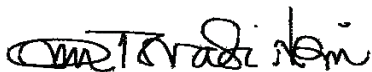
Abbreviations were inserted and detailed where necessary.

1. Format has been updated.
2. The title was squeezed not to exceed the word limit: "Invasive candidiasis in critical care setting, recommendations from 'Invasive Fungal Infections-Clinical Forum' (IFI-CF), Iran".
3. References and typesetting were corrected. A native English speaker with biomedical background rechecked the manuscript's language for accuracy and needed corrections. The English is now believed to be up to the required grade A standards.
4. Both figures are now presented in decomposable form.
5. Legends which are now presented at the end of the manuscript include detailed abbreviations

Thank you again for publishing our manuscript in the *World Journal of Critical Care Medicine*.

Sincerely yours,

On behalf of the IFI-CF, Iran



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