Author's response to reviews

Title: Risk factors for fatal candidemia caused by Candida albicans and non-albicans Candida species

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Author's response to reviews: see over
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To whom it may concern,

I am sending the revised manuscript MS5727355235859146 entitled “Risk factors for fatal candidemia caused by Candida albicans and non-albicans Candida species” accommodating the comments and suggestions of the reviewers.

Best regards,

Sincerely yours,

Hsiu-Jung Lo, Ph.D.
Corresponding author

For Dr. Arnaldo L. Colombo

1. Paper is not well written
   We have asked help from English native speakers.

2. I am not sure that Candida spp are the pathogens most frequently implicated in invasive fungal infection, as stated by the authors. …. 
   We have deleted “most” in the text according to the suggestion.

3. I do not agree with the authors when they say that candidemic patients often present clinical picture of slow deterioration……
   We have deleted this statement.

4. The study may be biased by the fact that only 130 cases out of the 415 episodes of candidemia reported in that particular medical center were evaluated during the investigation. The authors do not justify the criteria that they used for selecting the cases.
   To investigate the rate contributing to mortality of candidemia caused by different species and the risk factors for C. albicans and NAC infections, 130 patients including 68 and 62 patients infected with C. albicans and NAC, respectively, met the inclusion criteria of having at least one positive blood culture for Candida species within one month prior to fatal outcome. We have added this to the section of Methods.

5. In the methodology section is missing important definitions of the potential risk factors that were evaluated. In order to characterize the clinical relevance of the variables that were considered in the identification of risk factors for acquiring non-albicans candidemia, a clear definition of some topics systemic drugs? Did the authors consider immunosuppressed a patient who received only 3 days of 20 mg of prednisone? …..
   We have revised the text by adding the definition of “immunosuppression”, which is
accounted to prior use of steroids.

6. Statistical analysis: the authors must clarify the criteria used to select variables included in the multivariate analysis, as well as the particular tool and software that they used to perform the analysis.

The risk factors with p-values smaller than 0.1 in the univariate analysis were placed in a multivariate analysis. We used the multiple logistic regression package in the SAS system for Windows V8. Confidence limit of 95% means that the confidence interval interval (limit) contains the true value of odds ratio with probability of 0.95.

We have added this in the section of Methods.

7. There is no single information in the manuscript about the methods they used to perform blood cultures and yeast identification.

*Fedi* species were isolated from blood using BACTEC 860 system (Becton Dickinson, INC, Sparks, MD). The species were identified using API-32C system (bioMerieux Vitek, Inc, St. Louis, MI).

We have revised by adding the information for blood cultures and yeast identification in the section of Methods.

8. The study was not designed to validate any specific antifungal treatment strategy……

We have revised according to the comment.

For Dr. John Baddley

Major compulsory revisions

1. Background: I would disagree that candidemia presents with clinical picture of slow deterioration…..

   We have modified the text by deleting this statement.

3. Statistical analysis section: more explanation of the logistic regression model is needed…..

   The risk factors with p-values smaller than 0.1 in the univariate analysis were placed in a multivariate analysis. We used the multiple logistic regression package in the SAS system for windows V8. Confidence limit of 95% means that the confidence interval interval (limit) contains the true value of odds ratio with probability of 0.95.

   We have added this in the section of Methods.

4. Results: Does the term “urinary tract infection” used in Table 1 refer to bacterial, fungal, or both? Was this infection present before or after diagnosis of candidemia?

   The “urinary tract infection” refers to bacterial infection before the diagnosis of candidemia. We have revised the text by adding this information.

5. The authors state that leucopenia and thrombocytopenia are “risk factors” for NAC. Were these lab tests drawn before or after the diagnosis of candidemia?…..

   These tests were done within seven days before the diagnosis.

6. What does “immunosuppression” in table 1 mean?…..

   We have revised the text by adding the definition of “immunosuppression”, which is accounted to prior use of steroids.

7. The last sentence of the results states that “patients without ICU stay was the risk factor for NAC infections. This is not correct. Should be changed to “medical ward stay”…..

   We have modified as suggested.

8. Discussion says that “patients with NAC were more likely to require higher doses of fluconazole
to achieve clinical cure”. There was not evident from the data presented in the paper.

We have modified this statement by adding our previously published work regarding the drug susceptibilities of these isolates as a reference.

9. Page 7, second paragraph states “patients without ICU stay” was a risk factor. This is not shown in data. Should be changed to “medical ward stay”.

We have modified as suggested.

10. Page 8, last paragraph. NAC have higher MICs than C. albicans, but the point should also be made that clinical correlation of MICs to outcomes in patients with candidemia is not well established.

We have modified this statement as suggested.

Minor essential revisions
1. Please give a title to table 1 and 2. Explain for the readers what white blood cells refer to table 2. Confidence limits?

   We have revised as suggested in the section of Methods.

2. Table 1-how is ANC defined. It is confusing to read this in the data.

   We have revised to clarify this.