Author's response to reviews

Title: Candidemia in the Critically Ill: Initial Therapy and Outcome in Mechanically Ventilated Patients

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Author's response to reviews: see over
To the BMC Anesthesia Editorial Team,

On behalf of my co-authors, Marcela A. Ferrada, Andrew A. Quartin, Daniel H. Kett, I thank you for your recent response to our submission of the manuscript “Candidemia in the Critically Ill: Initial Therapy and Outcome in Mechanically Ventilated Patients.”

In response to your query, the University of Miami/Jackson Memorial Hospital was a participating center in the PATH registry. Investigators were encouraged to submit research projects utilizing the data collected. We submitted a specific request for access to data from patients entered in the database who required mechanical ventilatory support.

We have revised the manuscript, with changes shown in track changes in the submitted Word document. A detailed response to the reviewers’ comments is included in this letter. All authors have approved this version for resubmission.

**Reviewer's report:**
As previously written, some potential confounders were not taken into account. I believe that important variables such as the adequacy of initial antifungal treatment and severity scores are lacking and must be integrated in the statistical analysis.

The purpose of this study was to evaluate the adequacy of initial antifungal therapy. Clearly, the variable under study cannot also be a confounder. A severity score (TIRT) is incorporated in the statistical analysis.

The authors answered that “PATH was not ICU registry, but collected from entire hospitals. ICU scoring systems were not employed, quite reasonable as prognoses of non-ICU patients may be poorly described by these tools.” First, if PATH registry was not ICU registry, we could wonder why the authors focused the present work on mechanically ventilated patients.

Authors of Candida treatment guidelines have suggested that perhaps the choice of fluconazole or an echinocandin as initial therapy should be based on whether or not the patient is severely ill. We selected mechanical ventilation as a marker of critical illness. A clarification has been added to the Materials and Methods section.
Second, I am quite sure that ICU scores could be retrospectively found.

The PATH registry is a very broad based multicenter study. A uniform ICU severity score was not available. This information was not part of the PATH database and cannot be retrospectively determined. However, we have constructed an ICU severity score, the TIRT, which discriminates equivalently to other models commonly employed in this sort of analysis. This is expounded upon in the text of the manuscript.

Third, I believe that, at least, adequacy of initial antifungal therapy could be reported and included in prognostic analysis.

The primary focus of the manuscript is the adequacy of initial antifungal therapy, as measured by association with survival.

Finally, I do not understand the two following sentences which could appear contradictory.

‘Proportional hazards modeling found no significant interaction between initial therapy choice, whether or not therapy was changed within two days, and survival (P=.79 for interaction).’ and ‘Initial therapy with fluconazole remained a predictor of better outcome, irrespective of whether therapy was changed early.’

There is no contradiction between these sentences. The first sentence states precisely that the relationship between initial therapy and survival was not contingent upon whether or not therapy was changed within 2 days. The second sentence is a less statistically focused exposition of the same statement.

Thank you again for considering this manuscript for publication in BMC Anesthesiology.

Kind regards,

Michele I. Morris, M.D.