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
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Dear Editor:

This original manuscript, *Candidemia in the Critically Ill: Initial Therapy and Outcome in Mechanically Ventilated Patients*, has been extensively revised to address the reviewer comments. We appreciate the efforts of your editorial staff, and believe that the revisions we have provided, including an additional statistical analysis now summarized in the new Figure 5, should address the questions raised. We have attempted to answer the reviewer queries as outlined below. We hope that you will now find our manuscript acceptable for publication.

Reviewer number: 1

The authors present a unique proposal, that initial antifungal choice may influence 28-day mortality. While this is an interesting proposition, the approach taken by the authors suffers from some significant flaws:

1.) Virtually every predictive marker for poor response or severity of illness was biased against the echinocandins (immunosuppressed, dialysis, neutropenia, diabetes, transplant, prior antifungal therapy, time to initiation of therapy). It is difficult to put full confidence in the author's conclusions, regardless of what statistical adjustments they employ. What ends up happening is the reader is left wondering whether other statistical approaches would have garnered different results. Another aspect that calls into question the validity of the results are the findings that delayed time to initiation of therapy and solid organ transplantation were associated with reduced risk of mortality.

   The paper does not state that solid organ transplantation is associated with a reduced risk of mortality. In fact, the mortality among the 47 patients with solid organ transplants was 46%, compared with 40% among non-transplanted patients. The negative coefficient associated with transplant in a multivariate model means that transplantation is associated with a reduced risk when considering all other factors in the model, not when considered in isolation. In this case, the TIRT includes immunosuppressive therapy, hepatic dysfunction, and hyperbilirubinemia, among other terms. A transplanted patient (particularly liver transplant) presenting with some or all of these risk factors might indeed be “healthier” than a medical patient satisfying the same criteria.

One way to enhance confidence in their findings is if the authors included a compilation score of severity of illness, such as APACHE II. Would inclusion of this score have accurately reflected the higher overall baseline mortality risk in the EC group and thus overwhelmed the fluconazole finding? The Andes CID 2012 review that the authors discuss found APACHE II to be significantly associated with mortality on multivariable analysis. If the authors do not have APACHE data available, then they should at the least temper the confidence in their overall conclusions.
The TIRT is a compilation score, and it performs quite well – at least as well as APACHE II does when used similarly. We had not included diagnostics of the TIRT in the manuscript previously because it was not our principal focus, but we believe, based upon reviewer comments, that inclusion of this material may be helpful.

The performance of the TIRT is best appreciated graphically (now Figure 5 in the revised manuscript). TIRT predicted mortality rates range from 10% in the lowest decile of risk to nearly 80% for the highest decile. The c statistic for the model is 0.74, in the range expected for APACHE II when used to stratify infected patients in ICU populations, calibration is good, and outcomes trend with TIRT predictions in both treatment groups. The addition of vital sign data would not be expected to appreciably improve model performance.

The reviewer is not incorrect in stating that echinocandin treated patients appeared sicker at the time of treatment initiation. The TIRT anticipates a 6% absolute increase in mortality in the echinocandin patients, based on non-treatment factors. However, this is not sufficient to explain the observed difference in mortality, which was substantially larger.

2.) I would argue that a minimum duration of therapy with the initial antifungal regimen should be an inclusion criterion. Per the authors current methodology, a patient could get 1 dose of fluconazole, convert to an echinocandin for 13 days, and be counted in the fluconazole group. Perhaps the authors should only include patients who had received at least 3 consecutive days of the same therapy as their initial therapy. This would somewhat alleviate the significant concern with 24% of fluconazole patients changing therapy, often after only one day of identification of candidemia.

We disagree. There is at this point a substantial body of literature highlighting the importance of initial therapy for treatment of life-threatening infections. Most of this literature considers delays in terms of hours, not days.

The following is a minor critique:

1. The authors do not include fluconazole susceptibility results in their analysis. Were fluconazole outcomes worse in patients infected with resistant isolates? If so, the authors should discuss how to identify patients at risk for resistance so that those patients are not initiated on fluconazole.

Susceptibility testing of Candida isolates is not necessarily routine in clinical practice, and was even less so at the time this registry was compiled. The clinical utility of these tests is still the subject of some debate. However, outcomes with therapy vary with species as one might expect: mortality was lower with echinocandin therapy among patients infected with glabrata and krusei, species associated with in vitro resistance.
Reviewer number: 2

The authors retrospectively studied 689 patients from the PATH registry. These mechanically ventilated patients had candidemia treated initially with an echinocandin (n=315) or fluconazole (n=374). They demonstrated that patients receiving fluconazole as initial monotherapy were significantly more likely to survive than those treated with an echinocandin. This difference persisted after adjustment for non-treatment factors.

Such a result is very interesting. However, as underlined by authors, it was in contrast with recent recommendations and guidelines that favour the use of an echinocandin.

In order to ensure robustness of results, the authors performed a sophisticated statistical analysis taking into account demographic data, risk factors and Candida species.

However, some potential confounders were not taken into account. The authors discussed about the fact that the absence or the presence of septic shock was not recorded in the PATH database. I believe that some other important variables are lacking and must be integrated into the statistical analysis.

1- As underlined by the authors, “inadequate initial antimicrobial therapy for bloodstream infections and pneumonia is strongly associated with increased hospital mortality”. Nevertheless, no data about the adequacy of initial antifungal treatment (fluconazole vs. echinocandin) were reported.

Assuming the choice of initial antifungal therapy is important at all, the adequacy of initial therapy should ultimately be reflected by outcome. This is the main focus of the study.

2- Recent guidelines proposed different empiric antifungal therapy according to the severity of illness. Although the authors reported that “The PATH registry captures data on several organ dysfunctions associated with mortality in critically ill septic patients and typically incorporated into acuity models: respiratory (present in all patients included in this analysis), renal, and hepatic. These data were included in the development process for the TIRT and propensity models.” I believe that severity scores such as SAPS, APACHE or/and SOFA scores are lacking in this study. It could be interesting to compare such scores in patients treated with fluconazole vs. echinocandin and perform an analysis of treatment outcomes according to different values of these scores.

As noted in the response to Reviewer 1, the TIRT functions as a composite severity score similar to SAPS and APACHE (SOFA is not really intended as a composite score), and performs as well as these other scores typically have when used to stratify severely ill patients with life-threatening infections.
Although the study is considered interesting there are according to my opinion major issues to be discussed:

a) There are no additional data on concurrent infections which might affect the outcome of the patients

We would not expect these data to be impactful. All of the studied patients had candidemia, an infection already associated with a higher mortality than any bacterial blood stream infection, and there is no guidance regarding anti-fungal therapy we are aware of that is dependent upon non-fungal infections. Infectious or otherwise, all of these patients had life-threatening co-morbidities, as evidence by their universal requirement for ventilatory support. As noted in the response to other reviewers, the TIRT effectively adjusted for the severity of these conditions.

b) There is not a clear evident association between the outcome and empirical or definite treatment

We presume, as has been documented repeatedly with other life-threatening infections, that the effectiveness of initial therapy is reflected by outcome. If this is not the case, guidelines should remain silent regarding the choice of initial therapy.

c) All the administered treatments were considered appropriate?

We prefer the terms “active” and “reasonable” to “appropriate”, since the determination can only be made after speciation. As was noted in the manuscript, there were patients initially treated with fluconazole who were subsequently found to have either 
krusei
or
glabrata
as the infecting organism, and patients initially treated with echinocandins subsequently found to have
parapsilosis
as the infecting species. The initial therapy in these cases may have been reasonable but not active.

d) What about the time between the obtained culture and the administered treatment in each arm (statistically significant against echinocandins in TIRT and univariate analysis). The same, regarding the modification of the treatment the 2nd day (is not clear if there is included in TIRT and other regressions analyses).

Unlike antibacterial agents, antifungal agents are not as a general rule included in empiric regimens. With antibacterial agents the delay between obtaining cultures and administering antibiotics should be no more than a few hours. The time scales here, with antifungal therapy, are an order of magnitude larger, and the differences in delay to initial therapy consequently relatively small. Of note, the TIRT accounts for delay of initial therapy as a risk factor.

e) The reported mortality is attributable?
Attributable mortality is virtually impossible to determine in any study of critically ill patients.

f) There are limitations in this study?

Limitations are addressed in depth in the discussion of the manuscript.

Thank you for reviewing this revised manuscript.

Sincerely,

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