Reply to Anaissie and Nucci and to Cisneros et al

TO THE EDITOR—We thank Drs Anaissie and Nucci for their interest in our presentation of the patient-level analysis of data from major candidemia and invasive candidiasis treatment trials [1]. They object to the interpretation of the study observation regarding the impact of central venous catheter (CVC) management. We applaud their attempts over the years to carefully assess the impact of this treatment strategy. In fact, analysis of the current data was based largely upon their prior editorials suggesting the importance of patient severity of illness and other potentially confounding disease factors in interpreting the impact of this strategy [2]. The data from this analysis found that removal of the CVC was associated with a >10% reduction in mortality and clinical success across a wide range of APACHE II scores. Furthermore, sensitivity analyses did not identify an interaction of CVC and other cofactors of importance for determining outcome.

Our colleagues provide a list of additional critiques of the analysis and on this basis conclude the data are insufficient to consider a recommendation for CVC removal in many patients. First, they note a different result from their recent analysis of CVC removal among 2 of the studies used in our investigation [3]. They suggest this is due to the lack of timing information linked to CVC removal. They hypothesize that CVC removal beyond 24–48 hours will not favorably impact patient outcome. We have some concern that our colleagues did not identify the impact of CVC removal because of the smaller sample size and the grouping of patients with CVC removal beyond 24–48 hours in the “CVC not removed” portion of the analysis. In fact, more than a quarter of the patients counted in the “catheter not removed” group indeed underwent catheter removal, but the device was extirpated after 48 hours of diagnosis. This misclassification bias potentially diluted an effect on outcome. These points are thoughtfully discussed in an accompanying editorial [4]. Additionally, similar analysis of the identical database found catheter removal linked to favorable outcome [5].

The basis for their theory regarding early removal has not been presented, but they state the time constraint is consistent with the Infectious Diseases Society of America (IDSA) candidemia guidelines [6]. They would be advised to read the guidelines more carefully. Nowhere in the most recent version of the IDSA treatment guidelines for candidiasis is there a reference to “early removal” of CVCs. These guidelines do emphasize that clinicians need to strongly consider CVC removal in all patients (both nonneutropenic and neutropenic) with candidemia, but they also state explicitly that these decisions are to be individualized using the best available information and taking into consideration all clinical circumstances [6]. However, we agree with our colleagues on 2 points. First, it would be useful to analyze the impact of the timing of CVC removal, but we acknowledge we did not have access to complete timing data. Second, it is reasonable to posit that an early intervention may be favorable for outcome.

The authors provide a list of other data and analysis concerns. We apologize if this information was not presented clearly in the original manuscript; however, each of the critiques can be addressed by careful analysis of the text and tables. Because of space constraints, we direct readers to these sections of the manuscript for their major concerns [1]:

- **Endpoints.** We provide a strong rationale for selection of mortality as the primary endpoint (ie, lack of investigator bias). In addition, we do consider the composite clinical endpoint. Analysis interpretation is identical for both endpoints (page 2 of Methods and Table 4).
- **Disease sites.** We considered the aggregate disease sites in the primary analysis, as the goal was to test the impact of numerous factors (not only CVC removal) on outcome. Only those patients with candidemia were considered in the CVC removal logistic regression analysis (page 6).
- **Sample size.** The current logistic regression analysis is the largest published (nearly 1000 patients). It is not uncommon to have patient subsets fall out of analyses when important information for factors of suggested relevance in univariate analyses are missing for the logistic regression cohort [7].
- **Sensitivity analysis and treatment of missing data.** The analyses were appropriately completed and the treatment of missing data was defined a priori (pages 2 and 6). Furthermore, the analyses were consistent with accepted statistical analysis norms [8, 9]. Additionally, the analyses were undertaken twice by independent experts in biostatistics and further reviewed by the Mycoses Study Group steering committee.
- **Consort flow diagram.** A Consort flow diagram was not displayed owing to space constraints. However, it is possible to track patient numbers via the detailed information provided in the tables.
- **Candida parapsilosis infections.** We agree it is interesting that the impact of CVC removal was not identified in this group. We hypothesize this may be due to the relatively small sample size of this species cohort, and the relatively low
virulence of this species as demonstrated in animal model and clinical studies, making it more difficult to discern the impact of other disease and treatment variables [10, 11].

In the absence of a randomized trial of CVC management, we note in the original publication and agree with our colleagues that this issue remains contentious for some practitioners. However, it is unlikely that a trial with this design will ever be undertaken, largely because of cost and ethical concerns. Our observations regarding the impact of CVCs are not novel, but add to the extensive literature upon which the IDSA guidelines base their consensus recommendation [5, 12–15]. Our interpretation of the data and recommendation for clinicians remains congruent with the current IDSA candidemia and vascular catheter infection guidelines: most patients with candidemia should have their CVCs removed if at all possible [6, 16]. Finally, Anaissie and Nucci’s observation that “complex medical conditions deserve more than a cookie-cutter approach” is self-evident to all who practice thoughtful clinical medicine, and at no point do we state otherwise.

We also thank Dr Cisneros and his colleagues for their interest in the study [17]. The group noted 3 potential issues regarding interpretation of the antifungal treatment impact. First, the authors point to the potential for heterogeneity across studies. We agree this is always a potential problem in analysis of multiple investigations. However, the designs of the studies in question were remarkably similar despite the fact that they were conducted over a period of almost 2 decades. Furthermore, we explored heterogeneity by using the widely accepted approach of assessment for study effect. This investigation did not identify a study effect. Adjustment for multiple confounders was also undertaken. Second, our colleagues underscore the possibility of impact of other changes in care over the study period. We agree that there is a potential for other study advances over time to improve outcome in these patients. Unfortunately, the current analysis suggests this is not the case based upon nearly identical mortality rates across all studies. Finally, the group suggests analysis of only trials in which an echinocandin was utilized. We did not a priori hypothesize that any particular class of antifungal therapy would be optimal and thus included the largest number of randomized patients for which to undertake analysis.

Note

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All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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