Letter to the Editor

Lessons from uncertainty on antifungal treatment in ICU

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We read with great interest the Editorial from Moghnieh *et al.* on the EMPIRICUS trial and antifungal use in intensive care unit (ICU) (1). Authors described nicely the trial and some background evidence on untargeted antifungal treatment in non-neutropenic critically ill patients in ICU (2,3). However, we believe that some points may be further clarified. First, it may be useful to cite the study from Knitsch *et al.* among those evaluating empiric antifungal treatment in ICU (4). Knitsch *et al.* enrolled 252 critically ill patients with localized/generalized intra-abdominal infection either of community or of nosocomial origin requiring emergency surgery. They were randomized to receive micafungin or placebo. Interestingly, the study was unable to provide any significant difference in terms of invasive candidiasis or mortality between groups. The absence of difference in invasive fungal infections (IFI) is in contrast with the results from Timsit *et al.* and the overall evidence from Cochrane systematic review (5,6). The evidence from this trial may partially overcome, for a global overview, the limited number of surgical patients enrolled in the EMPIRICUS trial. Second, Moghnieh *et al.* stated that the antifungal treatment of the trial from Timsit *et al.* should be considered as preemptive. Although it may be useless to discuss about definitions (7), the most appropriate definition seems to be "empiric" because the trial enrolled septic patients with multiple organ failure. In this case, the administration of antifungal agents depicts an empiric treatment, even though the selected population had a high risk of IFI based on known risk factors (i.e., broad spectrum antibiotic therapy, multi-site Candida colonization) (8). The enrolled population had a high level of critical illness (at the admission mean SOFA score 8, mean SAPS II 48) and this may lead to consider the timing of empirical antifungal treatment as "too late", potentially explaining the lack of effect on mortality (9). Third, other explanations about the paradoxical association between the reduced incidence of IFI and the absence of effect on mortality observed in the EMPIRICUS and other major trials on antifungal treatment may be interesting for the readers. In clinical words, many non-neutropenic critically ill patients with IFI die despite of effective antifungal agents, which do their job leading to a reduction in identifiable fungi in sterile sites by microbiological cultures. Nowadays, there is evidence supporting altered immunological functions in patients with IFI, definable as "immunoparalysis". Interestingly, this occurs in patients without neutropenia or other known factors classically describing the clinical picture of immunosuppression. It may be speculated that the impaired immunological response has a causative role on the lack of benefit in terms of mortality in patients treated with highly effective antifungal drugs (10). An insight for future research might be to evaluate immunomodulation therapy for patients at risk of IFI or with established fungal infection.

Lastly, we have now established evidence to support the fact that classic "old" antifungal strategies, such as prophylaxis and empiric treatment, are not associated with improved survival in critically ill non-neutropenic patients. Moreover, we have also evidence describing the increasing rate of resistance to antifungals, even echinocandins, when used widely (9). We agree with Moghnieh *et al.* on the need of a better selection of patients and a better timing

for antifungal treatment. Biomarkers, such as β-D-glucan, alternative techniques for identification (e.g., polymerase chain reactions assays, T2, mass spectrometry—MALDI-TOF), risk factors, prediction scores, combined together, might be a good way to improve our antifungal strategies. Before starting to evaluate new therapeutic algorithms we should focus on data trying to interpret them and understand what they are telling us. Concerning antifungal treatment, it is simple possible that, as clinicians, we have to do what guidelines suggests based on "good clinical judgment", knowing that, lack of effect is behind the corner.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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