Antifungal Treatment Strategies in the ICU: Beyond Meta-analysis

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We appreciated the efforts made by Cortegiani et al. in updating the previous review (1, 2) and providing additional evidence for the clinicians facing the suspicion of fungal infection in critically ill, non-neutropenic patients. The group takes into account recent findings including 22 studies - 10 newly identified - pointing out that untargeted antifungal treatment did not significantly reduce or increase the all-cause mortality (moderate grade evidence), but might reduce the risk of proven invasive fungal infection (low grade evidence) and fungal colonization (risk significantly reduced but low quality of evidence) (1).

The issue of antifungal treatment in non-neutropenic, critically ill patients may or may not be analyzed by the results of a meta-analysis that included a 20-year period, with significant dissimilarities and results of the studies considered (1, 2). For example, the first review included 12 trials and presented homogeneous results across all trials despite considerable heterogeneity in clinical and methodological characteristics (2, 3). Almost all trials of fluconazole and ketoconazole separately showed a non-significant risk reduction with prophylaxis. When combined, fluconazole/ketoconazole reduced total mortality by about 25% and invasive fungal infections by about 50%. On the contrary, studies published in the last five years did not find any evidence of utility of untargeted treatment and only four studies were performed with echinocandins that are recommended for treatment according to the US and European guidelines (4, 5).

However, we believe that the scientific and the practical debate cannot easily be solved with a meta-analysis, which is a powerful tool but has no universal agreement on the theoretical validity and its interpretation (6). Furthermore, the main question is about its practical application, since prophylaxis, empiric, pre-emptive and perhaps presumptive treatment strategies may not immediately be changed with an untargeted antifungal treatment approach (1, 2, 7). While recognizing the scientific rigor and agreeing on the need for new and comprehensive randomized controlled trials, a practical approach may be more useful and applicable especially as facing the complexity of the debate on a daily work setting. For these reasons, we prefer to focus on treatment strategies and *de-escalation* of antifungals, to help clinicians, to avoid expensive and prolonged treatment and perhaps to prevent the emergence of antifungal resistance.

In conclusion, we really acknowledge the efforts and the results of the meta-analysis of our colleagues but we believe that treatment strategies cannot be immediately translated into untargeted antifungal treatment approach.

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