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EDITORIAL

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On track to limit antifungal overuse!

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Invasive candidiasis (IC) has emerged as a main cause of morbidity and mortality among critically ill patients. *Candida* colonization at multiple sites promoted by prolonged exposure to antibiotics, intravascular devices for parenteral nutrition or renal replacement therapy, and complicated abdominal surgery are associated with the development of IC [1]. The gastrointestinal tract and endovascular catheters are thus the most common sources of IC [2].

Early recognition and appropriate management of IC are crucial for outcome [3, 4]. However, the sensitivity of conventional blood cultures remains limited. The utility of fungal blood markers such as beta-(1,3)-D-glucan or mannan/antimannan and PCR testing for the early diagnosis of IC needs to be confirmed in the ICU setting [5, 6]. Pending the conclusion on ongoing investigations and on the role of composite clinical scores which may improve the prediction of IC, therapeutic decisions remain essentially based on the clinical risk profile [7]. This approach results in a low threshold for starting antifungals (prophylactic, pre-emptive or empirical treatment) and in a high number needed to treat to target a single IC episode [8, 9].

It has been suggested that the epidemiological shift from *Candida albicans* to species intrinsically resistant (*Candida krusei*) or with decreased susceptibility to azoles (*Candida glabrata*) observed in some institutions is a consequence of an overuse of antifungals [10, 11]. While the efficacy of fluconazole as first-line therapy of IC is being challenged, well tolerated but expensive alternative broad-spectrum antifungal agents are now available and will be recommended in the updated IDSA guidelines for the management of IC [11–14]. These new drugs are expected to impact positively on the outcome of IC; however, the economical and ecological consequences of their increasing use are difficult to predict [15, 16]. Despite an improved therapeutic armamentarium, there is thus an urgent need for new management strategies for better targeting the use of antifungal agents.

This is the aim of the paper published by Pérez-Para et al. [17] in the current issue of the Journal, in which a frequent not evidence-based trigger for starting antifungal therapy is challenging. In a retrospective analysis the authors suggest, in contrast to the common opinion, that a central venous catheters (CVC) tip culture positive for *Candida* spp. is not synonymous of IC or of increased risk for developing IC. Among 215 non-neutropenic critically ill patients with a positive CVC culture at a single academic institution, a subgroup of 58 patients (27%) with negative blood cultures drawn within 7 days before and 7 days after catheter removal was analyzed. Twenty patients received antifungals and only one developed IC (i.e., 2% of the cases),

suggesting that the number needed to treat a single IC episode would be substantial. Independent predictors of poor outcome were a McCabe score corresponding to ultimately fatal underlying disease and the presence of severe sepsis, septic shock or multiorgan failure. The authors concluded that antifungal treatment did not impact on the clinical outcome in these patients [17].

In patients with bloodstream infection removal of the CVC has been suggested in previous investigations to accelerate the clearance of bacteremia or fungemia. In critically ill patients with sepsis and no documented infectious focus it is common practice to promptly remove and/or exchange the indwelling intravascular devices. In the absence of concomitant positive blood cultures, the clinical signification of a catheter tip culture positive for *Candida* spp. remains to be determined [18]. Nevertheless, in order to avoid acute and late complications of IC, many clinicians start antifungal therapy in this setting. The study by Pérez-Para et al. suggests that this subgroup of patients should not receive antifungal therapy.

However, many questions remain unanswered. The reason for CVC removal and culture are not specified. Did these patients present a sepsis of unknown origin or was the device removed for end of use and routinely sent for culture despite absence of any symptoms and signs of infection? [18]. The cut-off value of one colony forming unit used for defining catheter colonization may have selected a subgroup of patients with an extremely low level of CVC colonization: whether a higher colony count is associated with an increased risk of IC remains unknown. The significance of a positive catheter culture for *Candida* spp. in the absence of candidemia and of clinical signs of infection may differ according to the presence or absence of a colonization at other sites. Although the dynamics of colonization assessed semi-quantitatively by the colonization index has been shown to predict the risk of IC, this information is lacking in the present study [8, 9, 12]. Simultaneous sampling of blood cultures from a catheter line and by peripheral venipuncture is recommended. Results of blood cultures obtained through the colonized device have, however, not been reported. Whether a positive result or other clinical characteristics did influence the decision to start an antifungal therapy remains unknown. Further, blood cultures were drawn within 7 days before or after CVC removal: is such a large time window reasonable to exclude candidemia in a patient with a positive CVC culture? Finally, one may challenge the decision to a priori exclude from the analysis the 64 patients with a concomitant candidemia, the 44 patients in whom no blood cultures have been drawn and the 26 children. These selection criteria might have biased the retrospective assessment of the target population [17].

Beyond these major limitations, these data suggest that a catheter tip culture positive for *Candida* spp. in the absence of candidemia should not be automatically considered as an IC or a condition at high risk for developing IC. This observation suggests a reduction of the undiscriminated use of antifungal agents in this setting. However, this conclusion needs to be confirmed in prospective investigations assessing in which subset of patients with a positive CVC tip culture withholding or de-escalating antifungals is safe. These should be designed by defining the underlying conditions (risk factors, colonization, clinical signs of infection), by standardizing the diagnostic procedures (CVC cultures, blood cultures) and by distinguishing the type of intervention (i.e., prophylactic or pre-emptive/empirical antifungal therapy).

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