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Invasive fungal infections in critically ill patients: Different therapeutic options and a uniform strategy

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Summary

The high morbidity, mortality, and healthcare costs associated with the invasive fungal infections, especially in the critical care setting, is of importance since the prophylactic, empiric, and pre-emptive therapy interventions, based on early identification of risk factors, is of common occurrence. In the last years alone there have been important developments in antifungal pharmacotherapy. Evidence-based studies using new antifungal agents are now emerging as important players in the pharmacotherapy of invasive fungal infections in seriously ill and difficult patients. However, data on critically ill patients are more limited and usually recovered from general studies. This study shows the benefits obtained by the new antifungal agents on different clinical situations in critical care units. The increasing number of non-*C. albicans* species and the high mortality rates in these settings suggest that the application of early de-escalation therapy in critically ill patients with fungal infection should be mandatory. The possibility of using antifungal combination therapy in these types of patients should be considered.

Key words ICU, Invasive mycosis, Non neutropenic patients, Treatment, Antifungal

Infección fúngica invasora en el paciente crítico: diferentes opciones terapéuticas y una misma estrategia

Resumen

La elevada morbi-mortalidad y los altos costes sanitarios asociados con la infecciones fúngicas invasoras, en especial en las Unidades de Cuidados Intensivos (UCIs), hacen necesarias intervenciones profilácticas, empíricas y preventivas basadas en la identificación precoz de los factores de riesgo. En los últimos años, ha habido importantes avances en farmacoterapia antifúngica. Los estudios basados en la evidencia utilizando nuevos agentes antifúngicos están adquiriendo un papel importante en el tratamiento de las infecciones fúngicas invasoras. Sin embargo, los datos en pacientes críticos son más limitados, siendo generalmente recogidos a partir de estudios generales. Esta revisión muestra los beneficios logrados por los nuevos agentes antifúngicos en pacientes ingresados en UCIs en diferentes situaciones clínicas. El aumento de la incidencia de infecciones fúngicas invasoras por especies de *Candida* no *Candida albicans* y las elevadas tasas de mortalidad en estas Unidades indican que la aplicación en enfermos críticos con infección fúngica de una estrategia terapéutica basada en la desescalada debería ser imperativa; asimismo, debería considerarse la posibilidad de utilizar una terapia antifúngica combinada en este tipo de pacientes.

Palabras clave UCI, Micosis invasora, Paciente no neutropénico, Tratamiento, Antifúngicos

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Critical care medicine has advanced greatly in the past few decades. Patients with complex medical and surgical disorders are surviving longer due to equally complex medical and surgical interventions, which often involve "collateral damage" of avoiding normal body defensive mechanisms.

Approximately 10.4 % of the episodes of infection in an Intensive Care Unit (ICU) are related to a species of *Candida*, the majority of them nosocomial acquired [1]. Although this rate could be underestimated due to the fact that at least 4% of critically ill patients who die in an ICU present an unexpected fungal infection in post-mortem examination [12]. Furthermore, ICU admission itself has become an independent risk factor to develop candidiasis [48,53]. Although less frequently, aspergillosis, especially in patients with chronic obstructive pulmonary disease [15,21,30] and other emergent mycoses caused by moulds and yeasts such as *Trichosporon asahii* [55], *Saccharomyces boulardii* [27,34], *Hansenula anomala* [22], *Dipodascus capitatus* [14] or *Rhizopus microsporus* [28] have also been described in intensive care settings in the last few years with an elevated morbidity and poor outcome.

Candida infections have also been associated with significant mortality, especially among critically ill patients [26]. The crude mortality rate of these infections is high (40–75%), and the attributable mortality of candidemia has been estimated to be 25–38% by several authors [2,9,10,37,44,53,54]. In recent years, *Candida* species associated with candidemia have shifted from *Candida albicans* to non-*C. albicans* species (NCA). Approximately half of the reported cases of candidemia are now caused by NCA [2,9,10,23,45,53,54] and this change has been associated in several publications with a worse prognosis than those caused by *C. albicans* [6,24,33]. Other adverse outcome predictors described in candidemia episodes are ICU stay itself, renal failure, thrombocytopenia, hematological malignance and the need for mechanical ventilation or inotropic support [2,6]. In intensive care setting, an APACHE II score >20 at the time of candidemia was associated with a higher mortality in a Spanish multicenter study [37], whereas early treatment with antifungal medication and removal of central venous catheters were protective factors for death [2,37]. For this reason, the early identification of risk factors to develop a candidemia, such as peritonitis, abdominal surgery, previous administration of broad spectrum antibiotics, parenteral nutrition, multiple lumen catheters, prior *Candida* spp colonization, renal replacement therapy and mechanical ventilation [4,8,44,51] become in itself the main cornerstone of empirical treatment of fungal infections in the ICU setting in order to reduce the high mortality of these infections [16,19,35].

Furthermore, poor outcomes are, in part, associated with the difficulty in establishing the microbiological diagnosis in an early stage of the infection. Blood culture results are positive in only 50% of invasive *Candida* and *Fusarium* infections and are very rarely positive in cases of invasive aspergillosis. Cultures of bronchoalveolar lavage fluid or brushing specimens are only positive for <50% of patients with invasive pulmonary aspergillosis. Finally, positive results of cultures of specimens from nonsterile body sites may be related to either colonization or infection, and distinguishing between these can be difficult. Nonculture-based diagnostic tests may provide a useful adjunct to these more traditional approaches. Of these, detection of circulating (1→3)-ß-D-glucan, galactomannan, or antibodies to *C. albicans* germ tubes has appeared quite promising and could be very useful as preemptive therapy guide in this patients [18,32,38,41,49]; nevertheless, more studies are necessary to validate this approach in the critical care setting.

Recently Piarroux et al. [47] assess the efficacy of a preemptive antifungal therapy, in preventing proven candidiasis in critically ill surgical patients, using a corrected colonization index to measure the intensity of *Candida* mucosal colonization. Patients with corrected colonization index ≥0.4 received early preemptive antifungal therapy with fluconazole and the incidence o ICU-acquired proven candidiasis decreased significantly from 2.2% to 0%. However, the overload of samples sent to the microbiology laboratory could limit the widespread use of this approach.

Although previous published data did not show a reduction in mortality rates with fluconazole prophylaxis in surgical critical care patients [13,52], a recent meta-analysis of azole prophylaxis of *Candida* infections in trauma and surgical intensive care patients reported reduced rates of candidemia, attributable mortality and overall mortality rates in a heterogeneous population and should make us to be careful with the interpretation and the application of universal prophylaxis in this setting [11].

The past few years have brought exciting developments in antifungal pharmacotherapy. Evidence-based studies using these new agents are accumulating and are assuming important roles in the pharmacotherapy of invasive fungal infections in seriously ill and complex patients. However, data in these patients are more limited and usually recovered from general studies.

Voriconazole, the first available second-generation triazole, has been approved by the Food and Drug Administration and by the European Medicines Agency for the treatment of invasive aspergillosis, serious infections caused by *Fusarium* and *Scedosporium apiospermum*, fluconazole-resistant invasive *Candida* infections (like those caused by *Candida krusei* and *Candida glabrata*), and candidemia in non-neutropenic patients.

Voriconazole has proven efficacy in the treatment of invasive aspergillosis in a recent trial [17], the authors concluded that treatment with voriconazole resulted in a better clinical response, improved survival, and fewer serious adverse reactions than treatment with amphotericin B. Voriconazole also demonstrated that it was an effective and well-tolerated treatment for refractory or less-common invasive fungal infections [43]. These results imply that there is clear evidence to use voriconazole as first-line therapy, alone or combined, in suspected or proven invasive aspergillosis or other mould infections in the ICU setting.

However, the choice of the best first-line treatment for candidemia remains controversial, especially in critically ill patients. Clinical studies have shown that amphotericin B, fluconazole, caspofungin and voriconazole have similar efficacy in the treatment of *Candida* bloodstream infections [25,31,46,50]. In accordance with recent guidelines [40], many experts favor initial treatment with amphotericin B in severely ill or clinically unstable patients, but its renal toxicity could add a serious problem in this type of patients, which nowadays makes it difficult to choose this drug as first-line therapy [5,7]. While fluconazole may be selected on the basis of its efficacy and safety [46,50], the increasing frequency of patients infected with *Candida* strains resistant to this drug draw attention to the need for initial treatment with a broader-spectrum agent at least until the C*andida* species is identified, in order to avoid inadequate empirical antifungal treatment which entails a higher mortality rate [20]. Thus, de-escalation therapy in these cases may be mandatory. Itraconazole has recently developed its intravenous formulation which presents a wide spectrum of action, although the absence of clinical trials in *Candida* infections (especially in ICU

settings), together with drug interaction problems and the limited data regarding the use of its excipient cyclodextrin, makes it difficult to choose this agent as a first-line therapy in critically ill patients. Published data [31] suggest that caspofungin, a new class of antifungal compounds which has as a novel target the glucan synthesis enzyme complex, is at least equivalent to standard therapy for the treatment of *Candida* infections. However, the unknown proportion of patients admitted in ICU in this study, the impossibility to test its action in vitro, and the worrying number of breakthrough candidemias caused by *Candida parapsilosis* in the caspofungin group implies that the administration of this drug could have several limitations in ICU settings. On the other hand, due to its security profile, especially in renal dysfunction, caspofungin becomes a first-line agent in patients with renal insufficiency admitted in an ICU.

Successful therapy with compassionate use of voriconazole for the treatment of candidemia and invasive candidiasis in patients intolerant of other antifungal agents or with infection refractory to other antifungal agents has been reported [39]. This study showed that voriconazole may be a suitable agent for the salvage treatment of invasive candidiasis, even in the setting of previous azole exposure and *C. krusei* infection, findings that have also been confirmed by two Spanish studies [36,42].

Another observational Spanish multicenter study [3] has been performed to assess the clinical use and tolerability of voriconazole in daily practice in the ICU setting for the treatment of fungal infection in critically ill patients. The main contribution of this study is the description of the scenario in which voriconazole is used in daily practice in the ICU. Notably, voriconazole was frequently used for the salvage treatment of invasive fungal infections in the setting of previous azole exposure. The patient profile defines a middle aged man, with a medical underlying disease, in particular active malignancy or chronic bronchitis, treated with antibiotics, corticosteroids, or chemotherapeutic drugs before admission to the hospital, and with a high APACHE II score on ICU admission. Prescription of voriconazole is based on the presence of an episode of invasive fungal infection, with identification of the genus and species of the causative pathogen, which has been previously treated with other antifungal drugs. *C. albicans* and *Aspergillus fumigatus* were the most common pathogens and the use of voriconazole was effective in 50% of cases. The drug was well tolerated and discontinuation of treatment due to adverse events was not necessary.

Recently, results from the first randomized, prospective, multicenter study in non-neutropenic patients with candidemia treated with voriconazole versus amphotericin B deoxycholate have shown equivalent results regarding efficacy and mortality in both treatment arms [25]. There were many infections due to NCA species (55%) with a similar distribution of the species in the two treatment groups. Successful response rates were similar between the voriconazole and amphotericin B/fluconazole arms, but for *Candida tropicalis*, the proportion of patients responding successfully was substantially higher in the voriconazole group, although these strains were susceptible in vitro to amphotericin B. Renal dysfunction was significantly lower in the voriconazole group. Although the incidence of visual disturbances was slightly higher, these minor side effects are usually transient and resolve after the patient has become tolerant to the drug or treatment was discontinued. Moreover, in critically ill patients it is difficult to detect the presence of the latter complication because most patients are sedated and mechanically ventilated.

These results can be easily applied to critically ill patients because about a half of patients included were admitted in an ICU. The only limitation to use intravenous administration of voriconazole in these patients could be the accumulation and toxicity of its excipient (cyclodextrin) in severe renal dysfunction, although there is no data about this concern in patients under renal replacement therapy. There is no need for the adjustment of oral voriconazole in patients with renal dysfunction. The potential drug interactions may also be considered, although currently no dose–drug level-response relationship for voriconazole has been observed, a wide inter-patient variability exits with contrasting predictive intra-individual kinetics.

Encouraging clinical experience with this drug suggests that voriconazole may be a new therapeutic alternative in critically ill patients, not only as salvage treatment but also as a first-line option in suspected or proven *Candida* and *Aspergillus* infection.

The application of early de-escalation therapy in critically ill patients with fungal infection should be mandatory. For this reason, voriconazole, due to its broad spectrum and good profile in ICU settings, and caspofungin, especially in renal dysfunction, could be two attractive options to apply this strategy in critically ill patients.

The availability of new antifungal agents with single mechanisms of action and improved tolerability has widened the possibilities for the use of combination antifungal therapy for difficult-to-treat opportunistic mycoses. Furthermore, additive in vitro interactions of voriconazole and echinocandins suggest a great potential for combination therapy and confirm the need for further investigation [29]. Although there are no clinical trials about combination therapy in *Candida* infections in critically ill patients, the high mortality observed could justify its administration. Further clinical trials are required to resolve this problem in intensive care settings.

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