Epidemiology and etiology of invasive fungal infections

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. These often involve the “collateral damage” of circumventing the body’s normal defense mechanisms.

Approximately 10.4% of infections in an intensive care unit (ICU) are related to *Candida* species, with the majority being nosocomial [1]. However, 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 during postmortem examination [2]. Furthermore, ICU admission itself has become an independent risk factor for the development of a *Candida* species infection [3,4]. Although less frequent, aspergillosis (particularly in patients with chronic obstructive pulmonary disease [5–7]) and other emergent molds and yeasts such as *Trichosporon asahii*, *Saccharomyces cerevisiae*, *Hansenula anomala*, *Dipodascus capitatus*, and *Rhizopus microsporus* have been described in ICU settings during the last few years, with associated elevated morbidity and poor outcomes [8].

Mortality and associated risk factors

*Candida* infections are associated with a significant mortality rate, particularly among critically ill patients [9]. The crude mortality rate of these infections has been estimated at 40–75%, and the mortality rate attributable to candidemia at 25–38% [3,10–12]. A review of matched cohort and case–control studies has examined the mortality rate that could be linked to candidemia [13]. This analysis included studies that compared the mortality rate of patients with candidemia with that of matched patients without candidemia. The data suggested that candidemia is indeed associated with a considerable mortality rate that can be attributed, at least to some degree, to the infection itself and not only to the presence of comorbidities.

In recent years it has been found that the species of *Candida* resulting in candidemia have shifted from *Candida albicans* to non-*C albicans* (NCA). Approximately half of the reported cases of candidemia are now caused by NCA species [3,12,14], and several publications have indicated that these cases have a worse prognosis than those caused by *C albicans* [15–17]. This increase has been attributed to the use of fluconazole prophylaxis [18].

Other adverse outcome predictors described in candidemia episodes are the length of stay in the ICU, renal failure, thrombocytopenia, hematological malignancy, and...
the need for mechanical ventilation or inotropic support [12,16]. In a Spanish multicenter study involving ICU patients in 28 hospitals, an Acute Physiology and Chronic Health Evaluation II (APACHE II) score of >20 at the time of candidemia was associated with a higher mortality rate [11], whereas early treatment with antifungal medication and the removal of central venous catheters were protective against death [11,12]. Furthermore, inadequate empiric antibiotic treatment it is associated with invasive fungal infections (IFIs) and a worse prognosis [19]. Two reports have demonstrated a strong association between a delay in the start of antifungal therapy and an increase in hospital mortality rates [20,21]; thus, it is necessary to recognize that time is of the utmost importance when considering the therapy of patients who are at risk for IFIs.

Assessing risk
The early identification of risk factors for the development of candidemia – such as peritonitis, abdominal surgery, previous administration of broad-spectrum antibiotics, parenteral nutrition, multiple lumen catheters, prior Candida species colonization, renal replacement therapy, and mechanical ventilation [10,22,23] – has become the cornerstone of empiric treatment of fungal infections in the ICU setting in order to reduce the high mortality rate associated with these infections [24,25].

The “Ostrosky-Zeichner prediction rule”
In a multicenter, retrospective setting (12 units in the USA and Brazil), Ostrosky-Zeichner et al. created a prediction rule for invasive candidiasis [26]. The rule was obtained through the analysis of a group of 2890 patients, in which the incidence of invasive candidiasis was 3% (88 cases). Statistical modeling revealed a particularly high risk for patients under systemic antibiotic treatment (days 1 to 3) or with an indwelling central venous catheter (days 1 to 3) and at least two of the following factors: total parenteral nutrition (TPN; days 1 to 3), any dialysis (days 1–3), any major surgery (days –7 to 0), pancreatitis (days –7 to 0), any use of steroids (days –7 to 3), or use of other immunosuppressive agents (days –7 to 0). The rule was associated with a sensitivity of 34% and a specificity of 90%. Its positive predictive value (PPV) and negative predictive value (NPV) was 1% and 97%, respectively. This rule applies to approximately 10% of patients who stay in the unit for >4 days, and approximately 10% of patients to whom this rule is applied will develop proven or probable invasive candidiasis. In this study, patients with any combination of diabetes mellitus, new-onset hemodialysis, use of TPN, or receipt of broad-spectrum antibiotics had an invasive candidiasis rate of 16.6%. This compared with a rate of 5.1% in patients who lacked these characteristics (p=0.001). Fifty-two percent of patients who stayed in the ICU for ≥4 days met this rule, and the rule captured 78% of patients who eventually developed invasive candidiasis.

The Candida score
A Spanish group has developed a bedside scoring system that allows early antifungal treatment when candidemia is suspected in non-neutropenic ICU patients [27]. This “Candida score” is based on the predictive value of previously reported risk factors. Using a logistic regression analysis and adjusting for possible confounding variables, the authors found several factors to be independently associated with a greater risk for proven candidal infection. The scores for the individual factors were: parenteral nutrition (+0.908), prior surgery (+0.997), multifocal Candida colonization (+1.112), and severe sepsis (+2.038). In this large cohort of critically ill patients, the authors concluded that a “Candida score” of ≥2.5 could accurately select patients who would benefit from early antifungal treatment (sensitivity 81%, specificity 74%).

Assays
Poor outcomes are, in part, associated with difficulties in establishing the microbiological diagnosis at an early stage of infection. Blood culture results are positive in only 50% of invasive Candida and Fusarium infections, and are rarely positive in cases of invasive aspergillosis (IA). Furthermore, cultures of bronchoalveolar lavage (BAL) fluid or brushing specimens are positive in <50% of subjects with invasive pulmonary aspergillosis. Finally, positive cultures of specimens from non-sterile body sites may be related to either colonization or infection, and distinguishing between these can be difficult. Non-culture-based diagnostic tests may provide a useful adjunct to these more traditional approaches. Indeed, detection of circulating (1–3)-β-D-glucan (BG), galactomannan, or C albicans germ tube antibodies (CAGTA) have appeared promising, and could be useful as a pre-emptive therapy guide [28–31].

BG assay
The results of multicenter clinical trials have demonstrated that the assay for BG can be used to measure serum BG levels in clinical specimens with a high specificity and PPV for subjects with proven or probable IFI when compared with control subjects [30]. This test appears to be useful both as a single-point assay for hospitalized patients with a possible fungal infection and as part of a surveillance strategy in high-risk patients. A cut-off value of 60 or 80 pg/mL appears to be optimal for this test. In a detailed evaluation, the BG assay had a high PPV for patients.
infected with Candida (except C. parapsilosis), Aspergillus, or Fusarium species. The performance of the assay did not seem to be significantly affected by antifungal therapy. However, the assay did not detect elevated BG levels in patients infected with Mucor, Rhizopus, or Cryptococcus species. Furthermore, the results in patients undergoing hemodialysis must be considered with caution due to false-positive results.

**Galactomannan assay**

Galactomannan is a polysaccharide fungal cell wall component that is released during Aspergillus tissue invasion and can be detected in serum or BAL fluid using a double-sandwich enzyme-linked immuno-sorbent assay. This test has been approved by regulatory authorities in Europe and USA for surveillance for IA in immunocompromised patients. Recently, a meta-analysis including twenty-seven studies was performed to assess the accuracy of a galactomannan assay for diagnosing IA [32]. The meta-analysis shows a moderate accuracy of this assay for the diagnosis of IA in immunocompromised patients. The test is more useful in patients who have hematological malignancy or who have undergone hematopoietic cell transplantation than in solid-organ transplant recipients.

**Immunofluorescence assay**

In 2006, the present authors’ group evaluated an immunofluorescence assay for CAGTA detection (C. albicans immunofluorescence assay immunoglobulin G; Vircell, Granada, Spain) in a selected population of critically ill patients (Fig. 1) [33]. Although there were no differences between CAGTA-positive and -negative patients in terms of age, gender, sequential organ failure assessment score, and renal and hepatic failure, the intra-ICU mortality rate was significantly lower in patients who tested positive for CAGTA (25% vs. 65.2%; p=0.025). These results imply that a strategy based on the early determination of CAGTA expression might reduce the ICU mortality rate of patients with risk factors for the development of invasive candidiasis. However, more studies are needed to validate this approach in the critical care setting.

**Corrected colonization index**

Piarroux et al. assessed the efficacy of a pre-emptive antifungal therapy in preventing proven candidiasis in critically ill surgical patients, using a corrected colonization index (CCI; ratio of highly positive samples to the total numbers of samples cultured) to measure the intensity of Candida mucosal colonization [34]. Patients with a CCI value of ≥0.4 received early pre-emptive antifungal therapy with fluconazole, and the incidence of ICU-acquired proven candidiasis decreased significantly from 2.2% to 0%. However, it is possible that the overload of samples sent to the microbiology laboratory could limit the widespread use of this approach.

**Available antifungal agents and therapy options**

The past few years have brought exciting developments in antifungal pharmacotherapy. Evidence-based studies using new antifungal agents are accumulating, and these drugs are assuming important roles in the pharmacotherapy of IFIs in seriously ill and complex patients. However, data from these patients are more limited and must be recovered from general hospital population studies. The principal advantages and disadvantages of systemic antifungal agents in the ICU setting are summarized in Table 1.

**Azoles**

**Voriconazole**

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

Herbrecht et al. have shown that voriconazole is efficacious in the treatment of IA [35], with the authors concluding that treatment with this agent resulted in a better clinical response, improved survival rate, and fewer serious adverse reactions than treatment with amphotericin B. Moreover, voriconazole has been demonstrated to be an
effective and well-tolerated treatment for refractory or less common IFIs [36].

However, 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 [37–40]. In accordance with the last Infectious Diseases Society of America (IDSA) guidelines [41], many experts favor initial treatment with amphotericin B in severely ill or clinically unstable patients, although the recently published Swiss guidelines for fungal infections [42] do not support this statement. Its renal toxicity could present a serious problem in these individuals, which may preclude its use as first-line therapy [43,44].

Results from the first randomized, prospective, multicenter study in non-neutropenic patients with candidemia who were treated with either voriconazole alone or amphotericin B

<table>
<thead>
<tr>
<th>Antifungal class</th>
<th>Drug</th>
<th>Potential advantages</th>
<th>Potential disadvantages</th>
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<tr>
<td>Polyenes</td>
<td>Amphotericin B</td>
<td>Clinical efficacy, broad-spectrum activity.</td>
<td>Nephrotoxicity, other adverse events.</td>
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<td></td>
<td>deoxycholate</td>
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<td></td>
<td>Amphotericin B</td>
<td>Broad-spectrum activity, possibility of combination with other</td>
<td>Only assayed in one large retrospective study, nephrotoxicity, other</td>
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<td></td>
<td>lipid complex</td>
<td>antifungal drugs and Mycograb®, less nephrotoxicity than amphotericin B</td>
<td>adverse events.</td>
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<td>deoxycholate.</td>
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<td></td>
<td>Liposomal amphotericin B</td>
<td>Clinical efficacy, broad-spectrum activity, possibility of combination with other antifungal drugs and Mycograb®, less nephrotoxicity than amphotericin B deoxycholate.</td>
<td>Nephrotoxicity, other adverse events.</td>
</tr>
<tr>
<td>Azoles</td>
<td>Fluconazole</td>
<td>Clinical efficacy, good safety profile, low cost.</td>
<td>Poor activity against C. glabrata and no activity against C. krusei.</td>
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<td></td>
<td>Itraconazole</td>
<td>Clinical efficacy, good safety profile, low cost.</td>
<td>Absence of clinical trials in Candida infections, drug–drug interactions, limited data regarding the use of cyclodextrin in its formulation, poor activity against C. glabrata and C. krusei.</td>
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<td>Posaconazole</td>
<td>Clinical efficacy, broad-spectrum activity, good safety profile,</td>
<td>Oral formulation only, efficacy demonstrated in open trials.</td>
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<td>possibility of combination with other antifungal drugs, activity</td>
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<td></td>
<td>Voriconazole</td>
<td>Clinical efficacy, broad-spectrum activity, good safety profile,</td>
<td>Intravenous formulation should be restricted in severe renal failure, drug–drug interactions.</td>
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<td>possibility of combination with other antifungal drugs, first-line</td>
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<td>Echinocandins</td>
<td>Superiority to fluconazole in clinical trials, broad-spectrum activity, good safety profile, available for use in renal failure, possibility of combination with other antifungal drugs.</td>
<td>C. parapsilosis breakthrough candidemia, no intensive care unit data.</td>
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<td>Anidulafungin</td>
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<td></td>
<td>Caspofungin</td>
<td>Clinical efficacy, broad-spectrum activity, good safety profile, use</td>
<td>C. parapsilosis breakthrough candidemia, pending in vitro susceptibility study methodology.</td>
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<td>in renal failure, possibility of combination with other antifungal drugs.</td>
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<td>Micafungin</td>
<td>Broad-spectrum activity, good safety profile, use in renal failure,</td>
<td>C. parapsilosis breakthrough candidemia, not licensed in Europe.</td>
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<td>possibility of combination with other antifungal drugs.</td>
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deoxycholate followed by fluconazole have demonstrated equivalence of these two regimens with regard to efficacy and mortality rates [40]. There was a high proportion of infection due to NCA species (55%), with a similar distribution of species between the two treatment groups. Response rates were similar in the two arms; however, for C tropicalis infection, the response rate was significantly higher in the group treated with voriconazole despite in vitro susceptibility of these strains to amphotericin B. Although renal dysfunction was significantly lower in the voriconazole-treated group, the incidence of visual disturbances was slightly higher. These disturbances are usually transient and resolve after the patient has become tolerant to the drug or treatment is discontinued. However, this complication can be difficult to detect in critically ill patients, because most are sedated and mechanically ventilated.

These results can be easily applied to critically ill patients as approximately half of the patients included in the study were admitted to an ICU. The only limitation to the use of intravenous voriconazole in these patients could be the accumulation and toxicity of its excipient (cyclodextrin) in severe renal dysfunction, although there are no data regarding this concern in patients undergoing renal replacement therapy. There is no need for the adjustment of oral voriconazole dosage in patients with renal dysfunction, although severe hepatic dysfunction could limit its use. Potential drug interactions should also be kept in mind although, to date, no dose-dependent relationship for voriconazole has been observed. However, a wide inter-patient variability exists with contrasting predictive intra-individual kinetics, and voriconazole must be discontinued in the case of interactions with rifampicin or sirolimus [45].

Successful salvage therapy with voriconazole for the treatment of candidemia and invasive candidiasis in patients intolerant or refractory to other antifungal agents has been reported [46]. This study showed that voriconazole may be a suitable agent for salvage therapy of invasive candidiasis, even in the setting of previous azole exposure and C krusei infection. These findings have been confirmed by two Spanish groups [47,48].

Another observational Spanish multicenter study has been performed to assess the clinical use and tolerability of voriconazole in daily practice in the ICU setting for the treatment of fungal infections in critically ill patients [49]. Notably, voriconazole was frequently used for the salvage treatment of IFIs in subjects with previous azole exposure. The typical patient was a middle-aged man with an underlying medical disease – in particular, active malignancy or chronic bronchitis – who had received treatment with antibiotics, corticosteroids, or chemotherapy drugs before admission to the hospital, and who had a high APACHE II score on admission to the ICU. The prescription of voriconazole was based on the presence of documented IFI that had been previously treated with other antifungal drugs. C albicans and A fumigatus were the most common pathogens, and voriconazole was effective in 50% of cases. The drug was well tolerated and there were no treatment discontinuations due to adverse events.

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

**Fluconazole**

Fluconazole may be selected on the basis of its efficacy and safety [37,38]. However, the increasing frequency of patients infected with fluconazole-resistant Candida strains, and the knowledge that simple clinical factors do not allow the clinician to effectively identify patients who are infected with NCA pathogens or with possible fluconazole-resistant fungi [50], highlight the need for initial treatment with a broader-spectrum agent (at least until the Candida species is identified) in order to avoid inadequate empiric antifungal treatment and an associated increased mortality rate [51]. Thus, de-escalation therapy may be considered [52].

De-escalation of antifungal therapy, following Kollef’s definition, can be thought of as a strategy to balance the need to provide adequate initial antifungal treatment of high-risk patients with the avoidance of unnecessary antimicrobial utilization, which promotes resistance [50]. An early, broad-spectrum antifungal agent is initially prescribed, switching to a narrower-spectrum drug (fluconazole) when mycological identification and susceptibility studies are available. However, it is necessary to achieve a dose/minimum inhibitory concentration (MIC) ratio of ≥100 to ensure a high cure rate in candidemia patients who are treated with fluconazole [53]. For this reason, when the de-escalation is performed, the fluconazole dose must be correctly adjusted.

**Posaconazole**

Posaconazole, an extended-spectrum triazole, has in vitro activity against a variety of pathogenic fungi, including Aspergillus, Candida, Cryptococcus, and Histoplasma. It has been extensively studied in a variety of animal models of mycoses and has been shown to be a useful oral agent in open trials for mycoses, including refractory fungal infections [54]. In patients undergoing chemotherapy for acute myelogenous leukemia or myelodysplastic syndromes, posaconazole has been found to prevent IFIs more effectively than either fluconazole or itraconazole, and to improve the overall survival
rate [55]. However, posaconazole is administered as an oral suspension, and it is therefore very difficult to consider this drug as a therapeutic option for invasive candidiasis in critically ill patients at present.

Itraconazole
Another triazole, itraconazole, is available as an intravenous formulation and has a wide spectrum of activity. However, the absence of clinical trials in Candida infections (particularly in the ICU setting), issues of drug interactions, and limited data regarding the use of its excipient, cyclodextrin, may restrict its use as a first-line therapy in critically ill patients. In addition, 46–53% of C. glabrata and 31% of C. krusei isolates are resistant to itraconazole [52].

Echinocandins
The echinocandins represent a novel class of antifungal compounds that target the glucan synthesis enzyme complex. Currently, three echinocandins are available: caspofungin, micafungin, and anidulafungin.

Caspofungin
Published reports suggest that caspofungin is equivalent in efficacy to standard therapy with amphotericin B in the treatment of Candida infections [39]. Mora-Duarte et al. compared a caspofungin with amphotericin B deoxycholate (D-AmB) in the treatment of invasive candidiasis in non-neutropenic (n=200) and neutropenic (n=24) patients. Caspofungin was as efficacious as D-AmB, with favorable response rates of 73.4% and 61.7%, respectively. From a second analysis, including only those patients treated for ≥5 days, superiority of caspofungin to D-AmB was concluded, based on success rates of 80.7% and 64.9%, respectively. There was no difference in survival rates at a 6–8 week follow-up, but significantly more patients in the D-AmB group experienced nephrotoxic effects and hypokalemia.

Anidulafungin
Anidulafungin is the only antifungal compound that has been able to demonstrate superiority over fluconazole in invasive candidiasis, although these results must be considered with caution as the study involved was powered a priori for equivalency [56]. However, the efficacy and safety profile of anidulafungin indicate that it should be readily considered as a first-line option for the treatment of invasive candidiasis.

Micafungin
Micafungin has become the second agent in the echinocandin class approved for use in clinical practice, although this approval is currently limited to the USA and Japan for the treatment of esophageal candidiasis and prophylaxis in subjects with neutropenia [57]. Caspofungin and micafungin have an identical spectrum of in vitro activity against C. albicans, NCA, and Aspergillus. Recently, two different studies of micafungin in seriously ill patients with invasive candidiasis have been published [58,59]. In these, micafungin was as effective as liposomal amphotericin B [59] or caspofungin [58] as a first-line treatment of candidemia and invasive candidiasis, and caused fewer adverse events than liposomal amphotericin B.

Limitations of echinocandins in the ICU setting
Despite their efficacy in clinical trials, the administration of echinocandins in the ICU setting could be limited by: the lack of data about the number of patients admitted to the ICU in the study of Mora-Duarte et al. [39]; the hepatotoxicity of caspofungin when used in combination with cyclosporine [60]; the high cost of the echinocandins; difficulties in studying their action in vitro (particularly caspofungin) due to its exclusive mechanism of action; and the worrying number of breakthrough candidemias caused by C. parapsilosis in caspofungin-treated patients [39].

Furthermore, isolates from many of the echinocandin treatment failures published in the literature have had high MICs, particularly against C. parapsilosis, although it is well known that fungemia caused by C. parapsilosis is associated with a lower mortality rate [61]. However, due to their good safety profile and high activity on biofilms, particularly in renal dysfunction, the echinocandins have become first-line agents in patients with renal insufficiency who are admitted to an ICU, or when the infection is related to artificial devices (biofilms) [62].

A similar and uniform strategy
A publication in 2006 demonstrated a shift toward the use of antifungal drugs other than fluconazole, due to the increasing number of NCA isolates [18]. Consequently, the application of an early de-escalation therapy in critically ill patients with fungal infection is recommended [63]. Owing to the increasing prevalence of NCA isolates, voriconazole (due to its broad spectrum and good profile in the ICU setting), caspofungin, and anidulafungin (particularly in renal dysfunction) could be attractive options in critically ill patients. Finally, the choice of antifungal drug must be based on the individual characteristics of the patient, and particularly focus on the presence of renal or hepatic failure and possible interactions with other drugs. A strategy for the de-escalation of antifungal drugs, and the diagnosis status–treatment protocol, are proposed in Figs. 2 and 3.

Combination therapy
The availability of new antifungal agents with distinct mechanisms of action and improved tolerability has widened
the possibility for the use of combination antifungal therapy (i.e. a combination of two antifungal drugs) for difficult-to-treat, opportunistic mycoses. Few randomized clinical trials have examined the role of this type of therapy for invasive mycoses, and no prospective, randomized trial of antifungal combinations has been completed for invasive mold infections. The results of in vitro studies and animal models suggest that combination therapy with azoles and echinocandins may have additive activity against Aspergillus species and suggest a great potential for combination therapy, confirming the need for further investigation [64]. However, the possible benefit of combination therapy with voriconazole for disseminated cryptococcosis and invasive candidiasis (or other emerging yeasts) needs to be elucidated. At present, a combination of amphotericin B plus flucytosine or monotherapy with fluconazole, caspofungin, voriconazole, or amphotericin B may be more desirable in these settings.

The use of other classes of drugs along with antifungal agents – as a combination therapy – should also be considered. Mycograb (NeuTec Pharma, Manchester, UK), a human recombinant monoclonal antibody against heat shock protein 90, was shown to act synergistically with amphotericin B against a broad spectrum of Candida species in vitro [65]. Subsequently, a double-blind, randomized study was conducted to determine whether lipid-associated amphotericin B plus Mycograb was superior to amphotericin B plus placebo in patients with culture-confirmed invasive candidiasis [66]. Patients received lipid-associated amphotericin B plus a 5-day course of Mycograb or placebo, having been stratified on the basis of Candida species (C albicans vs. NCA). A favorable overall response was defined as a complete clinical and mycological response, with resolution of all signs and symptoms of candidiasis and culture-confirmed eradication of the pathogen. At day 10, a favorable response was obtained for 29 of 61 (48%) patients in the amphotericin B alone group, compared with 47 of 56 (84%) patients in the Mycograb combination therapy group (p<0.001). A greater percentage of patients in the combination therapy group, compared with the amphotericin B alone group, met individual efficacy criteria, including clinical response (86% vs. 52%; p<0.001), mycological response (89% vs. 54%; p<0.001), Candida-attributable mortality rate (4% vs. 18%; p=0.025), and rate of culture-confirmed clearance of the infection (hazard ratio 2.3; p=0.001). These results underscore the potential of combination therapy in critically ill patients. Nevertheless, further clinical trials are required to clarify this issue in the ICU setting.

The role of severe sepsis in the election of empirical antifungal treatment

The presence of hemodynamic instability is a major factor for choosing empirical therapy – as the present authors show in Fig. 2. This fact has been considered by the recently published
guidelines that recommend a tailored therapy (de-escalation), in particular in conditions of severe sepsis or septic shock [41,42]. These guidelines, including the most recent ongoing IDSA guidelines, strongly recommend the use of echinocandins in non-neutropenic patients with invasive candidiasis when hemodynamic instability is present. The high rate of clinical success of these agents in candidemia, their low toxicity, their excellent safety profile, and their broad spectrum against non- C. albicans species makes this recommendation feasible. A recent publication has corroborated the use of caspofungin in critically ill patients [67].

**Conclusion**

IFIs, especially in the critical care setting, have become an excellent target for prophylactic, empiric, and pre-emptive therapy interventions due to high morbidity and mortality rates, an increasing incidence, and their associated healthcare costs. Early diagnosis and treatment are associated with a better prognosis in invasive candidiasis, and such infection in critically ill patients can be treated with fluconazole, voriconazole, amphotericin B, or echinocandins. The choice of antifungal drug must be based on the individual characteristics of the patient and a tailored therapy (de-escalation) must also be considered in the ICU setting. Importantly, echinocandins have become the first-line option when hemodynamic instability is present, for example in patients with severe sepsis.

**Disclosures**

The authors have no relevant financial interests to disclose.

**References**


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