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How to select an antifungal agent in critically ill patients☆

George Dimopoulos MD, PhD[a], Anastasia Antonopoulou MD[a], Apostolos Armaganidis MD[a], Jean-Louis Vincent, MD, PhD[b,*]

[a]*2nd Department of Critical Care Medicine, Medical School, University of Athens, University Hospital ATTIKON, Athens, Greece*
[b]*Department of Intensive Care Medicine, Erasme Hospital, Université Libre de Bruxelles, Brussels, Belgium*

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Abstract Fungal infections are common in critically ill patients and are associated with increased morbidity and mortality. *Candida spp* are the most commonly isolated fungal pathogens. The last 2 decades have seen an increased incidence of fungal infections in critical illness and the emergence of new pathogenic fungal species and also the development of more effective (better bioavailability) and safer (less toxicity, fewer drug interactions) drugs. The distinction between colonization and infection can be difficult, and problems diagnosing infection may delay initiation of antifungal treatment. A number of factors have been identified that can help to distinguish patients at high risk for fungal infection. The antifungal agents that are most frequently used in the intensive care unit are the first- and second-generation azoles and the echinocandins; amphotericin B derivatives (mainly the liposomal agents) are less widely used because of adverse effects. The choice of antifungal agent in critically ill patients will depend on the aim of therapy (prophylaxis, pre-emptive, empiric, definitive), as well as on local epidemiology and specific properties of the drug (antifungal spectrum, efficacy, toxicity, pharmacokinetic/pharmacodynamic properties, cost). In this article we will review all these aspects and propose an algorithm to guide selection of antifungal agents in critically ill patients.

1. Introduction

Invasive fungal infections are increasingly common in intensive care unit (ICU) patients and are associated with prolonged duration of hospitalization and increased mortality [1-3]. Early diagnosis remains difficult because of the lack of specific symptoms, difficulty discriminating fungal from bacterial infections, and poor sensitivity of available diagnostic methods [4]. The worldwide EPIC II study conducted in 2007 revealed that almost 20% of all isolated pathogens in ICU patients were fungi, with *Candida spp* ranking fourth after *Staphylococcus spp*, *Pseudomonas* spp, and *Escherichia coli* [5]. *Candida* spp were the most commonly isolated fungal strain, responsible for almost 88% of fungal infections [5]. The cited attributable mortality for *Candida* infections varies from 5% to 71% [6]. *Aspergillus* species, most frequently *A fumigatus*, accounts for almost 7% of fungal infections in critically ill patients [5]. The incidence of fungal infections in ICU patients is increasing for various reasons, including the increasing number of patients with immune system alterations (eg, patients with human immunodeficiency virus; transplant patients receiving anti-rejection chemotherapy) requiring ICU admission, the ageing population of ICU

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* Corresponding author. Department of Intensive Care, Erasme Hospital, 1070 Brussels, Belgium. Tel./fax: +32 2 555 3380/4555.
E-mail address: jlvincen@ulb.ac.be (J.-L. Vincent,).

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patients, and the large number of invasive medical devices (catheters, mechanical ventilation, renal support…) used in our ICUs [7]. The aim of this review is to provide intensivists with a summary of the more recent data on fungal infections to help guide antifungal management in critically ill patients.

2. Epidemiology and risk factors

The SENTRY Antimicrobial Surveillance Program and the EPIC II study showed that *Candida albicans* is the most frequently isolated fungus worldwide with occurrence varying according to geographical region [5,8]. Many risk factors for *Candida* infections in critically ill patients have been reported, including abdominal surgery; peritonitis; burns; use of broad spectrum antimicrobial agents, central venous catheters and other invasive devices; parenteral nutrition; prolonged mechanical ventilation; renal replacement therapy; prolonged ICU stays; and high disease severity, as reflected by a high Acute Physiology and Chronic Health Evaluation (APACHE) II score [9-12]. *Candida* colonization is also an important risk factor for subsequent infection [12,13]. During the last 2 decades there has been an epidemiological shift towards *Candida* non-*albicans* species, with *C parapsilosis, C glabrata* and *C tropicalis* being the most commonly isolated non-*albicans* pathogens [9,14]. *C parapsilosis* is associated with increased tendency for skin colonization, biofilm formation in intravascular devices, and nosocomial spread because of poor hand hygiene measures [8,15,16]. Candidemia due to *C parapsilosis* is associated with lower mortality rates compared to that caused by other *Candida* species but *C parapsilosis* is the most frequent cause of breakthrough candidemia and may be less sensitive to echinocandins [16]. *C tropicalis* is more virulent than *C albicans* and affects mainly cancer patients. *C krusei,* is less commonly observed, but is associated with higher mortality rates than other *Candida* spp [1,17]. Some authors [18,19] have suggested that non-*albicans Candida* infections are associated with specific risk factors including corticosteroid use, central venous catheters and prior candiduria, and especially previous exposure to fluconazole, although this is still debated [20]. Key characteristics of non-*albicans* species are summarized in Table 1.

Table 1 Characteristics of non-*albicans Candida* species

Candida strain	Characteristics
C parapsilosis	Skin colonization Poor hand hygiene associated spread Forms biofilm Higher MICs to echinocandins Lower mortality compared to *C albicans*
C glabrata	More common in patients with HIV and the elderly Innate resistance to azoles
C tropicalis	Favors oncology patients
C krusei	Less common Higher mortality compared to *C albicans*

Table 2 Risk factors for fungal infections in the ICU setting [9-12,27]

Risk factors	
- Chemotherapy (agent, dose, duration)	- Renal replacement therapy
- Radiotherapy	- Mucositis
- Corticosteroids	- Total parenteral nutrition
- Immunosuppression	- Malnutrition
- Recent or current use of antibiotics	- Prolonged ICU stay
- Central venous catheters	- Hospital environment
- Comorbid diabetes	- Sepsis
- Fungal colonization	- Surgery
- Mechanical ventilation	- High disease severity (APACHE score)

Invasive aspergillosis affects mainly patients with immunosuppression as a result of hematological malignancies, neutropenia, stem-cell or solid organ transplantation, and chronic granulomatous disease. Other risk factors include chronic obstructive pulmonary disease treated with corticosteroids [21-23] and the presence of cirrhosis [24]. Critically ill patients are also at risk for *Aspergillus* infections [24,25], and mortality rates in infected patients are high [24].

An increasing incidence of mucormycosis, another opportunistic fungal infection, characterized by vascular invasion and necrosis, has also been described in recent years [26]. Although poorly controlled diabetes mellitus, use of corticosteroids, dialysis, and immunosuppressive therapies are common risk factors for all fungal infections, patients with neutropenia or hematological malignancies are particularly at risk of developing mucormycosis. Treatment consists of a combination of antifungal agents and surgical debridement, which may still not control the rapid progression of this disease [26].

A summary of risk factors for fungal infections is provided in Table 2. Significant correlation with invasive fungal infections has been demonstrated for surgery, fungal colonization, renal replacement therapy, diabetes, sepsis and high APACHE II score, and intensivists should be particularly alert to these factors [27].

3. Diagnosis

Invasive fungal infections present as a clinical syndrome with different degrees of severity. The clinical presentation is not very different from that caused by bacteria; moreover, risk factors for fungemia do not differ from those predisposing to bloodstream infections by multi-drug resistant bacteria. Prompt diagnosis of fungal infections remains a

challenge because there are no specific signs and symptoms, yet early diagnosis is essential to allow timely treatment, as delay in starting appropriate therapy has been associated with greater hospital mortality in critically ill patients [28]. Despite advances in culture methods, which have increased the sensitivity of *Candida* detection to almost 70%, these cultures may become positive only late in the course of the infection [29,30]. Real-time polymerase chain reaction (RT-PCR) has been applied in order to detect fungal gene targets and RT-PCR kits have been developed for the simultaneous detection of bacterial and fungal species but their value in the clinical setting requires further evaluation [31].

Newer methods of detecting fungal infections include non-culture techniques relying on detecting components of the fungal cells. The measurement of serum concentration of glucans (components of the cell wall of most fungi except *Zygomycetes* and *Cryptococcus*) can be used to rule out invasive fungal infections because of the high negative predictive value of this test [32,33]. The detection of glucans has also been evaluated as a surveillance method in high-risk patients and as a single-point assay with high specificity and positive predictive value in patients with probable or proven fungal infection [4]. A recent study by Posteraro et al [34] suggests that a single β-D-glucan assay at the onset of sepsis may help discriminate patients at high risk of invasive fungal infection, with a negative predictive value of nearly 99%.

Serological methods have also been developed to detect circulating fungal antigens, as well as antibodies against these, but present a number of limitations of which the most important is the lack of ability to discriminate between infection and colonization [35]. This may be explained by the particular conditions of the infectious site that may interfere with the release of antigens and free DNA of the invading fungi, which may alter the amount of antigen detected [36]. The detection of fungal antigens and antibodies is considered an extremely supportive diagnostic tool for the diagnosis of fungal infections in high-risk patients. Serological tests for *Candida* infections include measurement of serum mannan and anti-mannan antibodies, enolase and arabinitol levels. Circulation of mannans in the bloodstream is intermittent, so that serial measurements are recommended and anti-mannan antibodies can usually be detected when mannan antigens disappear [37]. Sensitivity and specificity of serum mannan and anti-mannan levels have been evaluated in studies involving mainly patients with hematological malignancies. The sensitivity of the separate techniques has been estimated at around 50% and specificity around 95%, whereas their combination leads to a sensitivity of around 80% and a specificity of around 90% [38].

Serum galactomannan (a cell wall component released during the growth phase of the fungus) measurements have been used in neutropenic patients as a tool to diagnose invasive aspergillosis, an infection often only confirmed by autopsy. The usefulness of this measure has also been evaluated in critically ill patients without malignancies and is associated with the advantage of earlier diagnosis (8 days before diagnosis established by radiological and culture methods) [4,24]. The cutoff values for this method have not been fully defined, but a recent meta-analysis suggested that a cut-off value of 1.5 Optical Density Index increased specificity to 95% for proven or probable invasive aspergillosis as defined by the EORTC/MSG consensus [39]. The possibility of false-positive and false-negative results due to antimicrobial treatment with piperacillin-tazobactam or to prior antifungal therapy is a major limitation of the method, but serial measurements can yield higher positive and negative predictive values [40,41].

4. Antifungal agents

4.1. Amphotericin

Amphotericin B was, for a long-time, considered as the "gold standard" in the treatment of invasive fungal infections. This polyene binds with ergosterol, present in fungal cell membranes, creating pores that allow leakage of cell constituents leading to fungal cell death. All *Candida* species (except *C lusitaniae* and *C guilliermondii)*, *Zygomecetes*, *Aspergillus* spp and *Cryptococcus* spp are susceptible to amphotericin B [4]. The development of resistance is rare, although *C glabrata* and *C krusei* filamentous fungi may exhibit higher minimum inhibitory concentrations (MICs) than other species [42]. Derivatives of amphotericin B were developed to limit the toxicity, including renal failure. Evidence from a single center study in neutropenic patients suggests that toxicity of deoxycholate amphotericin B may be limited by prolonged infusion over 24 hours [40]. Use of lipid formulations is associated with good fungicidal activity, low emergence of resistance and fewer adverse effects, in particular nephrotoxicity, with no difference in efficacy [43,44]. The pharmacokinetic/pharmacodynamic variable that best determines amphotericin B efficacy is the area under the curve/MIC ratio, with a target of 10.0 for *Candida* infections and 2.4 for pulmonary aspergillosis [44]. Different studies have suggested that accumulation of the lipid formulations in tissues may even allow for intermittent dosing regimens, and there is no requirement for dose adjustment in renal or moderate liver failure [44,45]. Dose adjustment is also not required for patients receiving continuous renal replacement therapy (CRRT) [46].

4.2. Azoles

Azole compounds include itraconazole, fluconazole, voriconazole, and posaconazole. These substances inhibit the synthesis of ergosterol by the fungal cell membrane. Fluconazole, in contrast to itraconazole and voriconazole, is not active against *Aspergillus* spp. *Zygomecetes* spp are also not susceptible to the azoles, with the exception of the only

orally available compound, posaconazole [4]. Fluconazole remains the most frequently used antifungal agent because of its safety, tolerability and low cost. According to current guidelines, it is recommended as the primary treatment for candidemia in most adult non-neutropenic patients, notably those with less severe disease and no previous azole exposure [47]. Fluconazole is an inhibitor of cytochrome CYP3A4 and thus can interact with other drugs, in particular immunosuppressants, such as cyclosporine and tacrolimus, so that monitoring of drug levels is required during co-administration. Other noteworthy interactions with drugs commonly used in critical illness include elevated levels of warfarin, benzodiazepines and phenytoin; rifampin can decrease serum concentrations of fluconazole [45]. Drug doses may need adjustment in patients with renal failure receiving CRRT with the type of renal replacement therapy influencing the dose [48]. CRRT modalities have been shown to increase fluconazole elimination and it is, therefore, suggested that higher doses are required for patients receiving continuous venovenous hemofiltration and hemodiafiltration [49].

Voriconazole is a second generation azole with a broader spectrum than fluconazole. However, it cannot be empirically used against *Candida* strains resistant to fluconazole, particularly *C glabrata,* because of the development of cross-resistance [45]. Administration requires an initial loading dose. Because of possible accumulation of the carrier, cyclodextrin, parenteral use should be discontinued if the creatinine clearance is less than 50 ml/min [46,47]. For patients receiving CRRT, no dosage adjustment is required unless there is also hepatic failure. The oral form of voriconazole has a high bioavailability (>90%) and can be used even in patients with renal failure, although it is not recommended in cases of invasive candidiasis [45]. Voriconazole is both a substrate as well as an inhibitor of the cytochrome enzymes, CYP2C19 and CYP2C9, and co-administration with warfarin, benzodiazepines, cyclosporin, or tacrolimus may increase their serum concentrations [45].

Itraconazole is an older agent, but a parenteral form has become available recently. Its spectrum also includes *Aspergillus* spp but there is not enough evidence to support its use in the ICU setting. Parenteral administration of itraconazole is best avoided in patients receiving CRRT.

Resistance to azoles has been attributed to mechanisms such as efflux pumps, alterations of the target enzyme, up-regulation of the target enzyme concentration and replacement of ergosterol on the fungal cell membrane. Resistance of *Candida* spp and *C albicans* in particular remains low [50,51], although widespread use as prophylaxis may encourage development of resistance. The types of cross-resistance of *Candida* spp. to azoles vary: Complete cross-resistance has been described for *C glabrata* strains, and intrinsic resistance to fluconazole has been described for *C krusei* strains that are, however, susceptible to voriconazole [4,43].

4.3. Echinocandins

Echinocandins are a more recent class of antifungal agent that inhibit synthesis of the β-(1−3)-D-glucan compound of the fungal cell wall. The three members of this group are caspofungin, micafungin and anidulafungin; all are available only for parenteral use. The antifungal spectrum of echinocandins includes all *Candida* and *Aspergillus* spp but not *Zygomycetes*, *Cryptococcus* or moulds other than *Aspergillus* [47]. Echinocandins are considered fungicidal against *Candida* spp but not against *Aspergillus* spp. Their activity, based mainly on animal models, appears to be concentration-dependent with the area under the curve/MIC value being the best PK/PD parameter to describe their action [52]. Another property that is unique to these agents is the *Eagle effect*, a term used to describe the paradoxical in vitro growth of *Candida* and *Aspergillus* strains when the dose of echinocandins is increased above the MIC [53]. This effect, however, is not exhibited to the same extent by all echinocandins or with all fungal strains, occurring less with anidulafungin and *C glabrata* [53,54]. Although the clinical implication of this effect has not been completely clarified, it may have an impact in infections associated with biofilm formation [52,55]. Furthermore, echinocandins possess a post-antifungal effect against *Candida* spp, the value of which has not been fully elucidated with the current dosing regimens [52]. Echinocandins are safe drugs with few adverse events reported. There is no need for dose adjustment in patients with renal function impairment or receiving CRRT; however, caspofungin requires dose adjustment in moderate liver dysfunction. Caspofungin and micafungin undergo hepatic metabolism, although not cytochrome-mediated, in contrast to anidulafungin, which undergoes spontaneous degradation [45]. Concerns about possible hepatotoxicity of micafungin have been raised because of the formation of liver tumors in rodents. These studies however used high dosages for prolonged periods; no similar effects have been reported in other animals or in humans [52]. Interactions with other medications may occur (Table 3), although are not common, and these agents are recommended as a primary treatment option for candidemia in moderately or severely ill non-neutropenic and neutropenic patients [45,47]. Although there have been reports of

Table 3 Echinocandins and drug interactions

Caspofungin	Micafungin	Anidulafungin
Interactions with ○ Cyclosporine ○ Tacrolimus ○ Rifampicin ○ Efavirenz ○ Nevirapine ○ Dexamethasone ○ Phenytoin ○ Carbamazepine	Low potential for interactions with medications metabolized via CYP3A-mediated pathways	No known clinically relevant interactions Not an inhibitor, inducer or substrate of CYP450

resistant strains in patients previously treated with echinocandins resistance remains low [56]. The clinical meaning of MICs has been debated, however, strains of *C parapsilosis* appear to have higher MICs [43,51].

5. When to start an antifungal agent in critically ill patients

Treatment strategies can be separated into prophylactic, pre-emptive, empirical and definitive (or targeted). Prophylactic antifungal treatment is used when a patient presents a high risk of fungal infection because of underlying conditions (eg, bone marrow or solid organ transplantation or gastrointestinal tract perforation). Pre-emptive treatment is initiated based on positive results from the various available biomarkers or suggested scores. Empiric antifungal treatment starts when compatible signs and symptoms are present but the incriminated organism is unknown. Definitive treatment relies on overt invasive fungal infection with microbiological evidence that allows for specific, targeted therapy [4].

5.1. Prophylaxis

A recent Cochrane database review concluded that antifungal prophylaxis in non-neutropenic critically ill patients can reduce mortality by 25% [57]. However, there are no consistent data to support giving prophylactic antifungal treatment to all critically ill patients, in contrast to hematology and cancer patients for whom the value of prophylaxis is well established [57-60]. Eggimann et al [61] demonstrated, in a placebo-controlled double-blind clinical study, that prophylaxis with fluconazole in critically ill patients with abdominal surgery (recurrent gastrointestinal perforation or anastomotic leakage in particular) who are at high-risk of *Candida* infections may reduce colonization and infection with *Candida*. However, these authors recognized the risks of resistance development [61]. In a randomized study in ICU patients with fever and risk factors for invasive candidiasis, Schuster et al [62] reported no benefit of fluconazole over placebo in terms of a composite endpoint comprising resolution of fever, absence of invasive fungal infection, toxicity, and need for a non-study, systemic antifungal medication. A study by Senn et al, albeit limited by its single-center non-comparative design, suggested that echinocandins may also have a role in the prophylaxis of *Candida* infections in high-risk surgical patients [63]. Further study is needed to accurately define groups of patients who may benefit from prophylactic therapy.

5.2. Pre-emptive therapy

Several groups have proposed scoring systems to predict the likelihood of fungal infection and thus the need for pre-emptive treatment. In a semantic study, Pittet and colleagues proposed the use of a so called "colonization index", defined as the ratio of the number of body sites colonized with the same strain to the total number of sites cultured, to predict subsequent *Candida* infection [64]. A colonization index of >0.5 had a specificity of 69% for *Candida* infection and a positive and negative predictive value of 66% and 100% respectively. When the colonization index was corrected for heavy colonization (ratio of heavily colonized sites to all colonized sites), values ≥ 0.4 gave positive and negative predictive values of 100%. Another strategy is the *Candida* score, which evaluates the presence of severe sepsis, multifocal colonization, total parenteral nutrition, and surgery; a score greater than 2.5 is predictive of invasive candidiasis with 81% sensitivity and 74% specificity [65,66]. Posteraro et al [34] suggested that a combination of the colonization index and a β-D-glucan assay may be of greater value in risk discrimination, a suggestion that needs to be further elucidated in critically ill patients; supporting this notion is evidence from a study by Hanson et al that evaluated usefulness of serial β-D-glucan measurements in critically ill surgical patients [67]. A comparison of pre-emptive and empiric therapy against invasive mould infections revealed no difference on survival benefit [68].

5.3. Empiric and targeted therapy

Empiric therapy must be initiated promptly in patients with severe sepsis and risk factors for invasive fungal

Table 4 Treatment options for systemic *Candida* infections in non-neutropenic patients according to the 2009 IDSA guidelines [47]

Type of infection	Initial treatment options
Candidemia	Fluconazole (loading dose 800 mg, followed by 400 mg daily), echinocandins or alternatively liposomal amphotericin B or voriconazole). Echinocandins are preferred for patients with moderately severe to severe illness or with recent azole exposure; fluconazole is recommended for patients who are less critically ill and with no recent azole exposure.
Pyelonephritis	Fluconazole, alternatively liposomal amphotericin B
Endophthalmitis	Amphotericin B plus 5-flucytosine or fluconazole (for less severe infections). Surgical intervention is an important adjunct
Endocarditis	Liposomal amphotericin B or echinocandin
Suppurative thrombophlebitis	Liposomal amphotericin B or fluconazole or echinocandin
CNS infection	Liposomal amphotericin B with or without 5-flucytosine

infection in order to optimize chances of survival; it has been shown that delay in administration of antifungals equal to or greater than 12 hours after blood culture collection doubles mortality [69].

6. Which agent to use?

Data suggest that empiric treatment for suspected candidemia is equally successful with fluconazole, amphotericin B or caspofungin, but fluconazole and caspofungin are associated with less toxicity compared to amphotericin. Caspofungin was also found to be superior to liposomal amphotericin B as empiric therapy in invasive mold disease [68]. However, local fungal epidemiology is an important consideration when selecting empirically. For example, echinocandins should be preferred when infection by *C glabrata* is suspected, whereas fluconazole should be preferred for *C parapsilosis* [70].

Targeted therapy relies on culture results. Positive cultures in the critical care setting, however, require distinction between colonization and true infection, a differentiation that is not always easy to make. Candidemia, endophthalmitis, endocarditis, and peritonitis are *Candida* infections that must be treated. Candiduria frequently does not reflect true infection and clinical signs and symptoms must be taken into consideration when deciding whether or not to treat.

Clinical trials have shown that echinocandins and voriconazole have similar efficacy to fluconazole or amphotericin B in the treatment of systemic fungal infections [71,72]. In a double-blind, randomized, multicenter, non-inferiority trial comparing anidulafungin versus fluconazole in the treatment of candidemia or invasive candidiasis, Reboli et al [73] showed that anidulafungin-treated patients had a higher successful global response rate

Table 5 European expert opinion on the management of invasive candidiasis in adults [78]

Which antifungal agent?	Answer
Uncomplicated fluconazole-susceptible *C albicans* candidemia	Fluconazole (400 mg daily) or Echinocandin Patient stable, isolate sensitive - Step down to fluconazole (lower cost, oral availability)
Azole-naïve, non-neutropenic, adult ICU patient with candidemia	Fluconazole, in uncomplicated sepsis, with normal renal and hepatic function (consider that anidulafungin showed superiority to fluconazole even in less severely ill patients) Echinocandin in patients with severe sepsis - Anidulafungin, caspofungin and micafungin have very little difference in overall efficacy. EMA but not the FDA has issued a caution that micafungin should only be used if other antifungals are not appropriate (rat experiments, but no data from humans, suggested a potential risk for the development of liver tumors)
Uncomplicated *C glabrata* candidemia	Echinocandin or Fluconazole in high doses (800 mg daily)
Uncomplicated *C krusei* candidemia	Echinocandin
Responding patient infected with *C parapsilosis* in whom an echinocandin has been started	Another class of antifungal drug even if the susceptibility of the strain was within the range usually considered to be susceptible in vitro (eg, MIC of 1 mg/L)
Azole naïve patient with candidemia during a prolonged hospital stay	Fluconazole
Candidemia previously treated with fluconazole during this admission	Echinocandin or lipid-based formulation of amphotericin B
Neutropenic hematology patient with candidemia who had not received azole prophylaxis	Echinocandin in uncomplicated sepsis with normal renal and hepatic function (anidulafungin is not currently licensed for this indication in Europe)
Primary combined therapy with two antifungal agents in invasive candidiasis	No proven indications
Candida endocarditis	Lipid-associated amphotericin B plus flucytosine or echinocandin plus flucytosine
Cerebral *Candida* infection	Fluconazole or voriconazole or combined therapy mostly lipid-associated amphotericin B + flucytosine
The role for d-amphotericin B [a] in the treatment of adult patients with invasive candidiasis	No role A lipid-based formulation of amphotericin B as second-line treatment of candidemia

EMA, European Medicines Agency; FDA, Food and Drug Administration.
[a] d-amphotericin B, deoxycholate amphotericin B.

Table 6 ESCMID Guidelines for initial treatment of candidemia and invasive candidemia [79]

Compound	SoR	QoE	Comments
Echinocandins Anidulafungin 200*/100 mg daily Caspofungin 70*/ 50 mg daily Micafungin 100 mg daily	A	I	Broad spectrum, safety, few drug-drug interactions, activity against *C glabrata* and *C krusei*, rare resistance
Voriconazole	B	I	Narrower spectrum than echinocandins, drug interactions, i.v. administration associated with renal failure
Fluconazole	C	I	Limited spectrum, inferiority to anidulafungin in patients with high APACHE II score
Polyenes			Similar efficacy to
Amphotericin B liposomal	B	I	echinocandins, more adverse events, higher toxicity
Amphotericin B lipid complex	C	IIa	
Amphotericin B colloidal dispersion	D	IIa	
Amphotericin B deoxycholate	D	I	

SoR, strength of recommendation; QoE, quality of evidence.

than did fluconazole-treated patients for every pathogen except *C parapsilosis*. In this study, a successful response to intravenous treatment was obtained in 76% of patients with candidemia treated with anidulafungin compared to 61% of those treated with fluconazole (P=.02). In a post hoc analysis, global response to anidulafungin was superior to that of fluconazole in patients with severe illness, as defined by APACHE II score of 15 or more, requirement for intensive care, or evidence of severe sepsis [74]. These post-hoc results [74] are, therefore, consistent with the 2009 IDSA guidelines [47], which recommend use of an echinocandin as first-line treatment in patients with systemic candidiasis and moderate to severe illness. A quantitative review of 7 randomized trials on 1951 patients revealed that echinocandins were superior to triazoles and polyenes in the treatment of invasive candidiasis over a wide range of illness severity [75]. In contrast, post hoc analysis of a randomized trial comparing micafungin and liposomal amphotericin B showed no differences in treatment success rates in ICU patients [76]. Similarly, in another post hoc analysis of a randomized controlled trial, DiNubile et al reported no differences in response or relapse rates between caspofungin and amphotericin B treatment [77]. The conflicting results of these analyses support the need for further prospective investigation.

Therapeutic recommendations for the treatment of *Candida* infections adapted from the 2009 IDSA guidelines [47] are shown in Table 4. A more concise approach for invasive candidiasis showing the European perspective is summarized in Tables 5 and 6 [78,79]. Echinocandins are considered as first choice agents for initial treatment in patients who have previously been exposed to azoles, and removal of all implanted devices is strongly recommended when possible [47]. On the other hand, an official statement by the American Thoracic Society differentiates treatment options for candidemia according to patients' clinical stability and proposes either amphotericin B or and echinocandin as the initial choice in an unstable patient with candidemia by an unknown strain, although state there is insufficient evidence to provide a definite recommendation [80]. Fig. 1 shows a suggested algorithm for the management of fungal infections in critical illness.

Regarding mold infections, data have mostly been derived from evaluation of hematology patients and liposomal amphotericin B or voriconazole is preferred as targeted therapy [68]. *Zygomycetes* are emerging pathogens in immunocompromised hosts (recipients of hematopoetic stem cells or solid organ transplants and patients with diabetes or renal failure) and their treatment is difficult, often requiring combinations of antifungal agents (liposomal amphotericin B, predominantly) and surgical treatment [81].

6.1. Cost-effectiveness

The selection of antifungal agents must take into account not only their availability, efficacy and different toxicities but also the cost-effectiveness of the various agents, particularly because invasive fungal infections in the ICU setting are associated with prolonged hospital stays and thus increased hospitalization costs [82]. The available data are limited but it appears that the empiric treatment of suspected fungal infections is cost-effective [72]. A model simulation showed that fluconazole was a cost-effective empirical approach with micafungin representing an adequate alternative [83]. In a recent review, Wilke [60] suggested that caspofungin is a cost-effective approach in invasive candidiasis and as empiric therapy in suspected infections whereas micafungin is an alternative to liposomal amphotericin B in hematopoetic stem-cell transplant recipients and in settings with high fluconazole resistance. Most authors propose a step-down therapy as a reasonable approach from a pharmacoeconomic point of view. Table 7 provides a summary of the common characteristics and adverse effects of the commonly used antifungal agents.

7. Conclusion

Invasive fungal infections represent an emerging problem in the management of critically ill patients despite

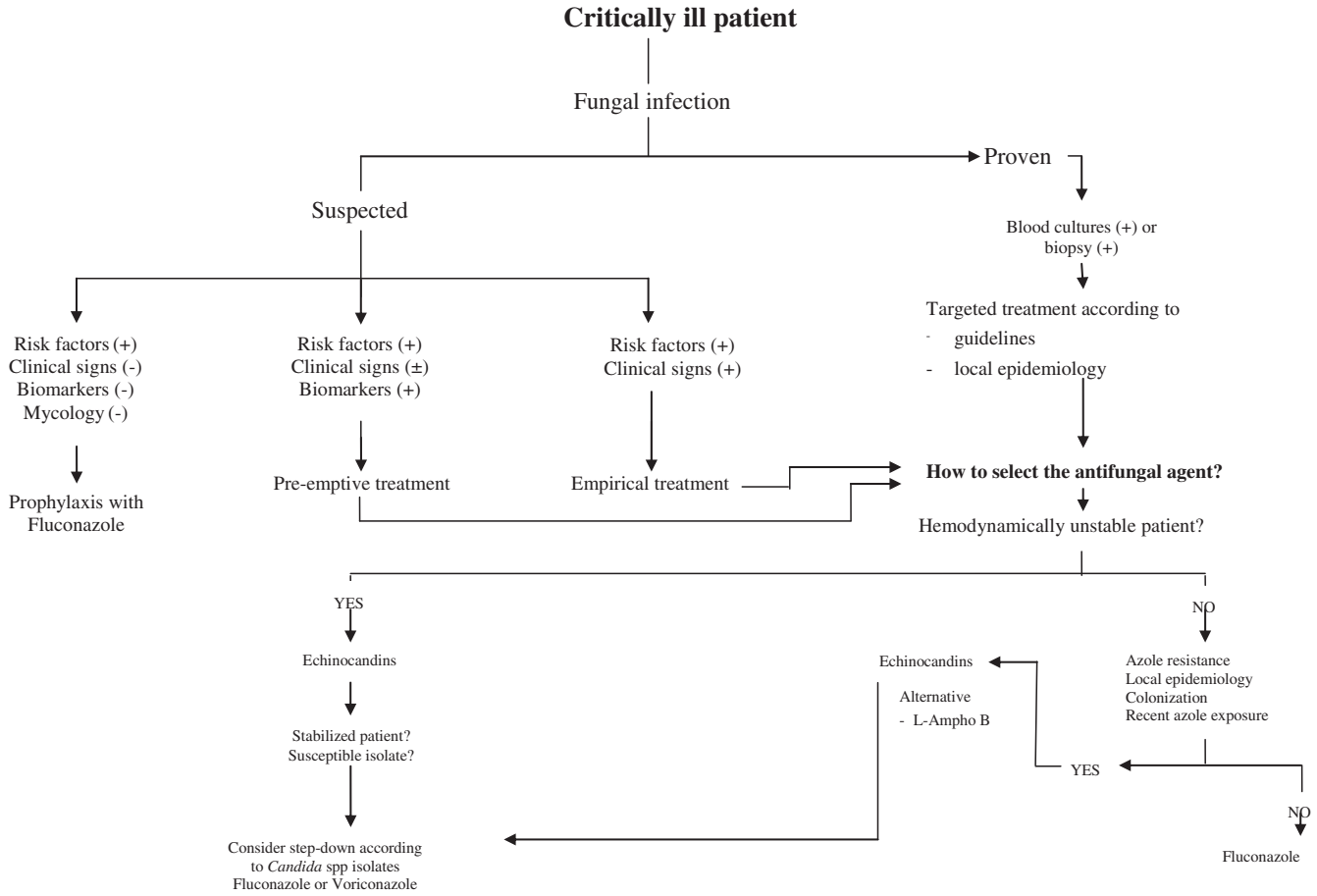

Fig. 1 Suggested algorithm for the management of candidiasis in the ICU patient.

advances in diagnostic techniques and availability of antifungal drugs. Early diagnosis and prompt initiation of therapy are crucial in decreasing mortality. To this extent, clinical criteria and novel diagnostic techniques are being employed in an approach termed pre-emptive therapy aiming at identifying patients at high risk of infections who may benefit from early treatment. There is little place for prophylaxis in the ICU setting. Definitive treatment relies on culture techniques and is usually accompanied by a certain time delay. Novel techniques will hopefully provide clinicians with better decision making tools. Selecting an antifungal in the critically ill setting, either as pre-emptive or empirical treatment, must be guided by epidemiological data, pharmacokinetic/pharmacodynamic

Table 7 Characteristics of the most commonly used antifungal agents

Characteristic	AmB	Imidazoles	1st generation triazoles	2nd generation triazoles	Echinocandins
Resistance					
Intrinsic	Rare	Rare	Rare	Rare	Yes (*Cryptococcus)*
Acquired	Rare	Yes	Yes	Yes	Yes
Adverse events	Hepatotoxicity	Many	Hepatotoxicity Itraconazole	Hepatotoxicity Voriconazole	Hepatotoxicity
	Renal failure Erythropoietin suppression		- GIT intolerance - arrhythmias - renal failure	- renal failure (iv) - CNS - photopsia Posaconazole - GIT intolerance	
Drug interactions	Few	Many	Some	Many	Some

AmB, amphotericin B; CNS, central nervous system; GIT: gastrointestinal tract.

drug properties, degree of organ dysfunction and risks of toxicity, as well as efficacy and cost-effectiveness.

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