

REVIEW

Bench-to-bedside review: Therapeutic management of invasive candidiasis in the intensive care unit

Matteo Bassetti*, Małgorzata Mikulska and Claudio Viscoli

Abstract

Candida is one of the most frequent pathogens in bloodstream infections, and is associated with significant morbidity and mortality. The epidemiology of species responsible for invasive candidiasis, both at local and worldwide levels, has been changing – shifting from *Candida albicans* to non-*albicans* species, which can be resistant to fluconazole (*Candida krusei* and *Candida glabrata*) or difficult to eradicate because of biofilm production (*Candida parapsilosis*). Numerous intensive care unit patients have multiple risk factors for developing this infection, which include prolonged hospitalisation, use of broad-spectrum antibiotics, presence of intravascular catheters, parenteral nutrition, high Acute Physiology and Chronic Health Evaluation score, and so forth. Moreover, delaying the specific therapy was shown to further increase morbidity and mortality. To minimise the impact of this infection, several management strategies have been developed – prophylaxis, empirical therapy, pre-emptive therapy and culture-based treatment. Compared with prophylaxis, empirical and pre-emptive approaches allow one to reduce the exposure to antifungals by targeting only the patients at high risk of candidemia, without delaying therapy until the moment blood *Candida* is identified in blood cultures. The agents recommended for initial treatment of candidemia in critically ill patients include echinocandins and lipid formulation of amphotericin B.

Introduction

Fungal infections are being increasingly diagnosed in patients admitted to the intensive care unit (ICU). Advances in medical science allow patients with severe

and complicated diseases to survive, and thus a population of subjects vulnerable to a range of infections is created. *Candida* is the most common fungal pathogen in ICU patients, and the main clinical forms are bloodstream infection, followed by peritonitis and other abdominal infection, endocarditis, and so forth. Most of the patients included in studies on epidemiology or treatment of invasive candidiasis had candidemia (approximately 68 to 90%), with or without other sites affected, while peritonitis was the second most common disease (approximately 7 to 30% of subjects) [1-3].

Candidemia is a life-threatening infection with high morbidity and mortality, especially in immunocompromised and critically ill patients [4-7]. In the ICU, this infection may represent up to 15% of nosocomial infections and the crude mortality rate has been found as high as 25 to 60%, varying according to the study design and the population – with the estimated attributable mortality as high as 47% [8-11]. Additionally, the estimated costs of each episode of invasive candidiasis in hospitalised adults are tremendous [11,12]. Finally, nosocomial fungal infections have one of the highest rates of inappropriate therapy – consisting mostly of omission of initial empirical therapy and an inadequate dose of fluconazole – which has been associated with increased mortality [13-16].

Moreover, during the past decade, several new anti-fungal drugs have been developed and obtained approval for treatment of *Candida* infections. Among them, echinocandins are the most important from the point of view of treating candidemia in critically ill patients. Epidemiology, risk factors, diagnosis and, in particular, treatment strategies and guidelines will therefore be discussed further.

Epidemiology of invasive candidiasis

Candidemia is one of the most frequent and most serious infections in patients admitted to the ICU, being the fourth most frequent pathogen of bloodstream infections in North America [17]. Moreover, candidemia in the ICU is by far more common than in most other wards and can

*Correspondence: matteo.bassetti@hsanmartino.it
Clinica Malattie Infettive, A.O.U. San Martino, L.go R.Benzi 10, 16132 Genova, Italy

affect up to about 10% of all admitted patients [18,19]. Additionally, *Candida* species account for approximately 3% of all surgery-related peritoneal infections, both community-acquired infections and nosocomial infections [20]. A recent French study on invasive candidiasis in the ICU revealed that approximately one-third of patients presented each of the clinical forms: isolated candidemia, invasive candidiasis with candidemia and invasive candidiasis only [1].

The epidemiology of *Candida* infections – both on a worldwide scale and, more importantly, on a local level – has significant implications for management of this infection. In particular, given the well-known, albeit not universal, differences in antifungal susceptibility among different *Candida* species, the choice of the most appropriate empirical treatment can be successfully based on epidemiological data regarding the frequency of *Candida parapsilosis* and fluconazole-resistant species in a given centre.

During the past two decades, most hospitals have reported a progressive shift in the species of *Candida*. In the past, almost all isolates responsible for bloodstream infections were *Candida albicans*, whereas in recent years a growing proportion of episodes of candidemia have been caused by *Candida* species other than *C. albicans* [21-25]. Even though, *C. albicans* remains the predominant strain in most countries [26,27], even among critically ill patients [1,7,21,28,29], non-*albicans* species are increasingly common – some ICUs have reported recently that non-*albicans* species are responsible for over 50% of candidemia episodes in adult critically ill patients [24,30]. The most common non-*albicans* species are *C. parapsilosis* or *Candida glabrata*, followed by *Candida tropicalis* and *Candida krusei* [1,24,31-33]. Rare *Candida* species reported to cause candidemia include *Candida lusitanae*, *Candida guilliermondii* and *Candida rugosa* [15,31].

Numerous studies have tried to find reasons for this shift, and several risk factors have been associated with candidemia due to different species [25,34]. It is understandable that the widespread use of fluconazole can predispose patients to the development of infections due to species that are resistant to azoles, either intrinsically fully resistant such as *C. krusei* or in dose-dependent fashion such as *C. glabrata*. Indeed, previous use of fluconazole has been found to be a risk factor for the presence of non-*albicans* fungaemia [24,25,35] even though some studies did not find this association [23]. Specific risk factors for candidemia due to other non-*albicans* strains have also been reported, such as for example the presence of in-dwelling devices, hyperalimentation and being a neonate for *C. parapsilosis* [31]. The specific risk factors associated with different *Candida* species are outlined in Table 1.

Table 1. Particular risk factors associated with candidemia due to different *Candida* species

<i>Candida</i> species	Risk factor
<i>Candida tropicalis</i>	Neutropenia and bone marrow transplantation
<i>Candida krusei</i>	Fluconazole use Neutropenia and bone marrow transplantation
<i>Candida glabrata</i>	Fluconazole use Surgery Vascular catheters Cancer Older age
<i>Candida parapsilosis</i>	Parenteral nutrition and hyperalimentation Vascular catheters Being neonate ^a
<i>Candida lusitanae</i> and <i>Candida guilliermondii</i>	Previous polyene use
<i>Candida rugosa</i>	Burns

Adapted from [6,31,70,71]. ^aEpidemics due to nosocomial horizontal transmission via hands of health personnel have been reported [72,73].

Even though the overall rise in incidence of non-*albicans* strains is alarming, from the clinical point of view there are important differences among the different species. Specifically, the main difference between *C. albicans* and *C. krusei* or *C. glabrata* is the resistance to the most frequently used antifungal (that is, fluconazole). The differences in susceptibility to various antifungals are partially predictable and are reported in Table 2. Species identification and knowledge of the local epidemiology of *Candida* strains causing candidemia are therefore of the utmost importance for guiding appropriate empirical therapy. On the contrary, *in vitro* susceptibility testing of clinical isolates of *Candida* proves extremely valuable for guiding therapy in patients who have received prior antifungal treatment or who are not responding to empirical therapy.

Risk factors for invasive candidiasis in the ICU and predictive scores

Although invasive *Candida* infections can affect any hospitalised patient, they are more common and have unique attributes in certain populations, including patients with cancer, haematological malignancy or other immunosuppression. The predominant source of invasive *Candida* infection is endogenous, from superficial mucosal and cutaneous proliferation to haematogenous dissemination [36]. Rare cases of exogenous transmission have been described due to contaminated solutions and materials or transmission from healthcare workers to patients and from patients to patients [37,38].

The suppression of the normal bacterial flora in the gastrointestinal tract by broad-spectrum antibiotic

Table 2. Common susceptibility of various *Candida* species

Species	Amphotericin B	Echinocandins ^a	Fluconazole	Itraconazole	Voriconazole ^b
<i>Candida albicans</i>	S	S	S to R ^c	S	S
<i>Candida glabrata</i>	S	S	S-DD to R	S-DD to R	S to R ^d
<i>Candida krusei</i>	S	S	R	S-DD to R	S
<i>Candida lusitanae</i>	S to R ^e	S	S	S	S
<i>Candida parapsilosis</i>	S	S to R ^f	S	S	S
<i>Candida tropicalis</i>	S	S	S	S	S

Adapted from [1,44,67,74,75]. S, susceptible; S-DD, susceptible dose-dependent; R, resistant. ^aSusceptibility pattern is similar for all the echinocandins available (anidulafungin, caspofungin and micafungin). ^bPosaconazole has the same susceptibility pattern as voriconazole but, lacking intravenous formulation, has little place in the treatment of candidemia in the intensive care unit. ^cResistant in approximately 5%. ^dCross-resistance to azoles in more than 5%. ^eResistance uncommon but can develop in initially susceptible species. ^fHigher minimum inhibitory concentration values and poor activity against *C. parapsilosis* biofilm.

therapy also allows the yeast to proliferate, both in neutropenic patients with haematological malignancies [39] and in non-neutropenic patients [40], and long-term and high-density colonisation has been shown to lead to candidemia. Numerous conditions frequent in ICU patients – such as parenteral nutrition, intravascular catheters, trauma, hypotension, therapy with steroids or cyclosporine, and ischaemia and reperfusion – may damage the integrity of skin or the gastrointestinal mucosa with penetration by the yeast, potentially leading to systemic infection. The factors predisposing critically ill patients to candidemia are presented in Table 3, with the presence of vascular catheters or disruption of the gut or skin barrier among the most important.

Important efforts are focused on identifying critically ill patients at high risk of developing candidemia in order to apply the most efficacious management strategy and avoid high mortality. Risk prediction scores have thus been developed and different parameters combined to predict which patients would develop candidiasis. In particular, the score by Leon and colleagues included parenteral nutrition (1 point), surgery (1 point), multi-focal colonisation (1 point), and severe sepsis (2 points); subjects with score >2.5 were almost eight times more likely to develop candidiasis than those with score <2.5 [41]. The other score by Ostrosky-Zeichner and colleagues found that the combination of the systemic antibiotic treatment or central venous catheter and two or more of five other variables (parenteral nutrition, dialysis, major surgery, pancreatitis, treatment with steroids or other immunosuppressive agents) had, in their population, positive and negative predictive values of 10% and 97%, respectively [42]. Additionally, Dupont and colleagues published in 2003 a predictive score for peritoneum *Candida* infection in the ICU: the presence of three out of four factors (female gender, upper gastrointestinal tract origin of peritonitis, intraoperative cardiovascular failure and previous antibiotic therapy) had positive and negative predictive values of 67% and 72%, respectively [43].

Table 3. Factors predisposing intensive care unit patients to candidemia

Population	Risk factors
All patients	Prior abdominal surgery
	Intravascular catheters
	Parenteral nutrition
	Use of broad-spectrum antibiotics
	Immunosuppression, including corticosteroid therapy
	Acute renal failure
	Diabetes
	Transplantation
	Haemodialysis
	Pancreatitis
Specific for ICU patients	Prolonged stay in the ICU
	<i>Candida</i> colonisation, particularly if multifocal
	High Acute Physiology and Chronic Health Evaluation II score
	Low birth weight for neonatal ICU

Adapted from [4,6,76]. ICU, intensive care unit.

Thanks to such scores specifically developed and then validated in ICU patients, the risk of invasive candidiasis can be estimated because the presence of the above-mentioned risk factors is directly related to the percentage probability of developing invasive candidiasis, allowing one to judge whether risk of candidemia warrants any therapeutic measures.

Diagnosis of candidemia

Blood cultures remain the mainstay for diagnosing candidemia, but the sensitivity reported frequently is not optimal. Moreover, the time from blood sample collection and the microbiological response of growing yeast is often lengthy. Furthermore, several more days are required for species identification and susceptibility testing. New methods for diagnosis of invasive *Candida* infection have therefore been investigated, including

serological markers (mannan and β -D-glucan) and real-time PCR; however, only the use of β -D-glucan has been included in the 2008 Infectious Diseases Society of America guidelines for diagnosing invasive fungal disease [44].

The use of β -D-glucan is currently being investigated in ICU populations. Even though the results seem promising, no large prospective studies have been performed and the main problems for the use of β -D-glucan remain its high cost and high rate of false positive results (mostly due to concomitant bacterial bloodstream infections and intensive care measures such as haemofiltration, albumin or immunoglobulin use) [45]. Traditional culture from sterile sites other than the bloodstream (for example, the peritoneum) are useful for diagnosis of invasive candidiasis. For specific details on the diagnosis of invasive candidiasis in the ICU, a recent review is available [46].

Management of candidemia in the ICU

As far as management of candidemia in the ICU is concerned, there is no single strategy that can be considered the most appropriate. In fact, different approaches can be chosen and can be judged as the best for a given clinical situation. In particular, four management options are available: prophylaxis, empirical therapy, pre-emptive therapy and treatment of a culture-proven infection. So how is the best strategy chosen?

The knowledge of epidemiological data, the above-mentioned risk factors and, first of all, the analysis of local epidemiology of candidemia in a singular ICU allow one to determine whether a patient is at low, modest or high risk of developing this infection. Consequently, a choice between the most appropriate management strategies can be made – the patients with low or modest risk of infection can be monitored less frequently for *Candida* colonisation, while high-risk subjects may benefit from immediate diagnostic procedures (cultures of both sterile and nonsterile sites, testing for serological markers) and empirical antifungal therapy. In the case of negative results of testing for yeasts, antifungal prophylaxis might be considered. Naturally, knowing the most frequent species and susceptibility patterns of *Candida* isolated in a single ICU is the basis for choosing an adequate antifungal agent (Table 4).

Prophylaxis in the ICU

Prophylaxis – defined as administration of an antifungal agent to a patient with no evidence of infection – has been evaluated in several studies and meta-analyses [27,47-50], and its main advantage is a possible reduction in the rate of candidemia.

Since morbidity and mortality rates in patients with systemic fungal infections are exceedingly high, the use

of an effective antifungal prophylaxis in selected high-risk patients is very attractive and might be an option in this select population. The strategy of antifungal prophylaxis is now well established in patients with persistent neutropenia after treatment for haematological malignancies or after bone marrow transplantation, but routine use of antifungal prophylaxis in the general ICU setting is discouraged [51-53]. Nonetheless, the implementation of targeted antifungal prophylaxis has been shown to be effective in certain ICU settings [27,47], and three randomised placebo-controlled trials reported a clear >50% decrease in the incidence of *Candida* infections with fluconazole prophylaxis [54-56]. Moreover, two meta-analyses confirmed that prophylactic fluconazole administration in ICU patients reduced the rate of *Candida* infection, but no clear survival advantage was observed [49,50]. In the meta-analysis by Playford and colleagues, however, only when the studies on prophylaxis with both fluconazole and ketonazole were considered was the total mortality found reduced by approximately 25% and the incidence of fungal infection by 50% [50]. The meta-analysis by Cruciani and colleagues also reported, along with a relative risk reduction in candidemia, a decrease in overall mortality with antifungal prophylaxis with various agents [48].

On the other hand, the disadvantages of fluconazole prophylaxis include possible toxicity and profound influence on local epidemiology with the emergence of fluconazole-resistant isolates [57]. From expert opinion expressed in reviews and guidelines [44,58], therefore, antifungal prophylaxis might be warranted only for ICUs with a high rate of invasive candidiasis, as compared with the normal rates of 1 to 2%, particularly for selected patients who are at highest risk (>10%) [42]. The approach of limiting prophylaxis to a subgroup of patients with the highest risk of candidemia may help to limit the quantity of antifungals used and delay the emergence of infections due to fluconazole-resistant *Candida* strains seen in immunocompromised patients. In fact, this approach is supported by the recent Infectious Diseases Society of America guidelines that recommend fluconazole prophylaxis at a dose of 400 mg (6 mg/kg) daily for high-risk adult patients hospitalised in ICUs that have a high incidence of invasive candidiasis [44].

Empirical therapy

Empirical treatment is defined as administration of antifungals in the presence of persistent and refractory fever in patients who are at high risk for fungal infection. This strategy was developed almost three decades ago for neutropenic patients, when it became evident that the lack of sensitivity of microbiological and clinical findings resulted in delayed diagnosis and increased morbidity and mortality.

Table 4. Choice of antifungals for treatment of candidemia in critically ill patients

Treatment	First choice	Alternative
Pre-emptive or empirical	Echinocandin	Lipid formulation of amphotericin B
Culture-proven candidemia		
<i>Candida albicans</i>	Echinocandin	Fluconazole or lipid formulation of amphotericin B
<i>Candida glabrata</i>	Echinocandin	Lipid formulation of amphotericin B
<i>Candida krusei</i>	Echinocandin	Lipid formulation of amphotericin B
<i>Candida parapsilosis</i>	Lipid formulation of amphotericin B	Echinocandin or fluconazole

Even though the first studies on empirical therapy were underpowered, the treatment being used in different clinical settings and numerous antifungals are being registered and recommended for empirical treatment of invasive candidiasis, both in neutropenic patients and in non-neutropenic patients [44]. All these efforts are aimed at reducing morbidity and mortality by starting treatment as early as possible, given the evidence that a delay in antifungal prescription increases mortality rates significantly in candidemia [13,14]. In the ICU, however, where numerous patients have different risk factors for fungal infections, the routine use of empirical therapy in cases of persistent fever may result in significant overtreatment. The strategy of a pre-emptive approach therefore appears promising. In fact, US guidelines recommend that such an approach (although they continue to call it empirical treatment) should be considered for critically ill patients with risk factors for invasive candidiasis and no other known cause of fever, based on clinical assessment of risk factors, serologic markers for invasive candidiasis and/or culture data from nonsterile sites [44] (Table 4).

Pre-emptive therapy

The main concept of a pre-emptive strategy is to better identify patients at high risk for developing candidemia. The overall use of antifungals in the ICU can therefore be reduced, without delaying therapy in patients who need it. The recent availability of more sensitive and specific clinical and laboratory tools allows for better identification of high-risk patients, and this approach has been used successfully [59]. The question arises, however, of how to define a patient at high risk for developing candidemia. No clear predictive rule exists, but the two score systems described above for ICU patients can be of some help. In brief, multifocal colonisation by *Candida* and/or the presence of well-described factors outlined in Table 3 make the patient a suitable candidate for empirical therapy if any signs or symptoms of infection compare.

In particular, the efficacy of a pre-emptive strategy in ICU patients has been recently established in a single-institution study in which the use of fluconazole in patients with corrected colonisation index ≥ 0.5 ,

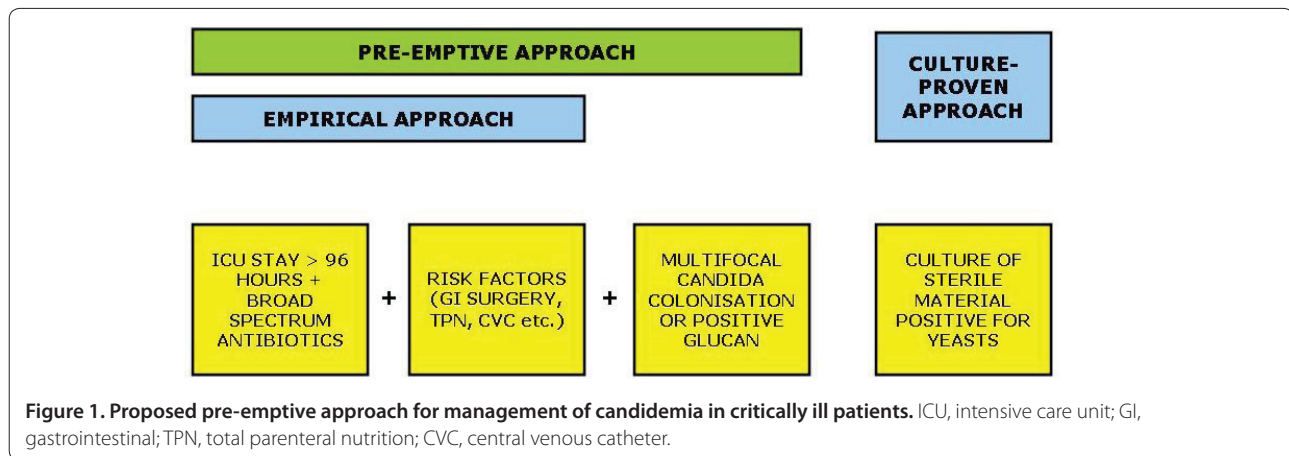
described previously by Pittet and colleagues [40], has significantly decreased the incidence of invasive candidiasis [60]. Moreover, surrogate markers of invasive fungal infections have been studied extensively. In particular, β -D-glucan is a component of the cell wall of *Candida* and other fungi and has been investigated as a serological marker for fungal infections, including candidemia [61]. Even though false positive results have been reported and its routine use in the ICU requires further validation, persistently high serum levels of β -D-glucan in ICU patients were found indicative of fungal disease [45].

A pre-emptive approach in critically ill patients might therefore be defined as starting antifungals when the following conditions are satisfied: the presence of long ICU stay (>96 hours), and broad-spectrum antibiotic therapy; the presence of any other risk factors, such as severe sepsis, gastrointestinal surgery or parenteral nutrition; plus microbiological evidence of *Candida* infection, including multifocal colonisation or a positive result for serum β -D-glucan. The proposed approach is shown in Figure 1 and, as with any new strategy, will warrant validation in prospective trials. One of the main advantages of such an approach is limiting the use of antifungals in low-risk patients, while starting treatment for candidemia without delay when symptoms appear in patients at high risk for this infection. The benefit of early therapy, in terms of morbidity and mortality, can thus be obtained, while overtreatment can be avoided (Figure 2).

Treatment of a culture-documented candidemia

For ICU patients with low/medium risk of developing candidemia, blood cultures should be performed if a clinical suspicion of systemic infection is present, even in the absence of fever. Numerous blood cultures, both from a central venous catheter and a peripheral line, remain the cornerstone for diagnosis of candidemia. As any delay before administering primary therapy can lead to a noticeable increase in mortality, antifungals should be prescribed as soon as there is growth of yeasts in blood samples.

The choice of antifungal for an unknown *Candida* species should be based on the knowledge of local



epidemiology. In an ICU where most infections are due to *C. albicans* and where fluconazole resistance is low, fluconazole is the drug of choice. On the other hand, in an ICU where fluconazole-resistant species are common (for example, *C. glabrata*) or in patients colonised with fluconazole-resistant strains, echinocandins are the drugs of choice. Moreover, for patients in severe or moderately severe clinical conditions (for example, haemodynamically unstable patients, with suspected concomitant endocardial involvement), echinocandins are recommended because of their bactericidal activity against *Candida*; the side effects are less common than those reported for the other fungicidal agent – liposomal amphotericin B [44]. The antifungal treatment might be modified according to the results of susceptibility testing, and de-escalation to fluconazole has been successful for stable patients with susceptible isolates [44].

Other aspects of treating candidemia in the ICU

Once the initial therapy for candidemia is started, several clinical issues remain open. Firstly, the efficacy of the treatment should be assessed by the documentation of blood cultures returning sterile. Moreover, the date of the first negative blood culture is important, because the recommended length of treatment is 14 days after the documented clearance of *Candida* from the bloodstream and resolution of symptoms attributable to candidemia.

Secondly, the antifungal chosen empirically can be changed based on the results of species determination or susceptibility testing. For stable patients with *C. albicans* or other fluconazole-susceptible strains, fluconazole is therefore the drug of choice. Importantly, fluconazole is the preferred treatment for *C. parapsilosis*, since resistance to echinocandins has been reported [62].

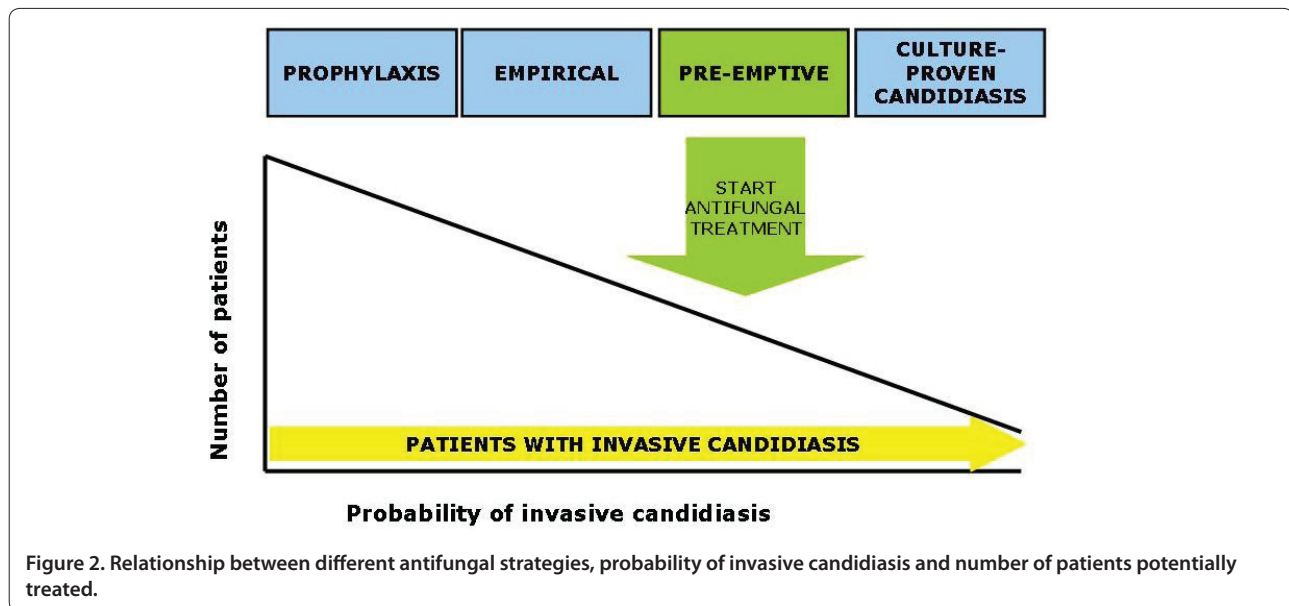
Thirdly, patients who improved clinically and who cleared *Candida* from the bloodstream might be suitable for step-down oral therapy to complete the course of 14 days. The available oral antifungals are fluconazole,

itraconazole, voriconazole and posaconazole. Fluconazole is an obvious choice for susceptible species, while voriconazole can be indicated as step-down therapy for *C. krusei* or voriconazole-susceptible *C. glabrata*.

Additionally, ophthalmologic fundus examination is warranted in all the patients to exclude disseminated endocular infection, and endocarditis should be excluded in case of persistently positive blood cultures, known valve pathology or any other sign or symptom suggestive of endocardial involvement. In both cases, the duration of treatment is much longer (>4 weeks and up to lifelong suppressive therapy) and is described in detail elsewhere [44].

Last but not least, intravenous catheter removal is strongly recommended for patients with candidemia. Guidelines both on management of candidiasis and on management of catheter-related bloodstream infection state clearly that catheters should be removed, even though grade II and grade III of such statements indicate that there are no data from properly randomised, controlled trials [44,63,64]. Interestingly, a recent study of 842 adults included in candidemia trials did not find on multivariate analysis any benefit from early catheter removal; the expert guidelines remain the best synthesis of all available data, however, and removing the catheter should thus be attempted in all ICU patients with candidemia [64].

Biofilm production is a well-documented phenomenon for *Candida* species that significantly contributes to *Candida* pathogenicity in catheter-related bloodstream infections, resulting in recurrent or persistent infections and biofilm-mediated antifungal resistance leading to treatment failure [65]. Moreover, the mortality in patients with invasive infections due to biofilm-producing *Candida* species has been reported significantly higher [66]. The activity of antifungals against biofilm therefore has important clinical implications and is known to vary among different agents. In particular, fluconazole and



azoles – which are static against *Candida* – are also not active against sessile forms, while echinocandins and amphotericin B offer both bactericidal activity and good penetration into a biofilm formed on vascular devices. However, a study performed on 43 *Candida* species – including 12 *C. albicans*, 12 *C. parapsilosis*, 10 *C. tropicalis* and nine *C. glabrata* isolates – found that the activity of caspofungin and micafungin against a biofilm of *C. parapsilosis* and *C. tropicalis* was significantly lower than that of amphotericin B [67]. Table 5 outlines the susceptibility of different *Candida* species to two antifungals that are active against biofilm-producing strains.

Antifungal agents

In recent years, numerous new antifungal drugs have been developed, studied and approved for various indications, and almost all of these new drugs are licensed to treat candidemia in different patient populations. The most appropriate antifungal drug can be chosen from the three main groups: the polyenes (amphotericin B deoxycholate, lipid complex, liposomal); the azoles (fluconazole, voriconazole, posaconazole, itraconazole, ravuconazole); and the echinocandins (caspofungin, micafungin, anidulafungin).

Most of the studies on efficacy in candidemia have not shown significant differences between various agents. The differences in drug-related toxicity are significant, however, and the possibility of drug–drug interactions – so important in critically ill patients that receive numerous medications – varies significantly among the single agents. The choice of the best antifungal therefore still poses a challenge for a clinician. The detailed

Table 5. Activity against different *Candida* species of two antifungals active against *Candida* biofilm-producing strains

Species	Amphotericin B	Echinocandins
<i>Candida albicans</i>	S	S
<i>Candida glabrata</i>	S	S
<i>Candida krusei</i>	S	S
<i>Candida lusitanae</i>	S to R ^a	S
<i>Candida parapsilosis</i>	S	S to R ^b
<i>Candida tropicalis</i>	S	S to R ^b

S, susceptible; R, resistant. ^aResistance uncommon but can develop in initially susceptible species. ^bHigher minimum inhibitory concentration values and poor activity against biofilm for caspofungin and micafungin [67].

description of various agents used for treating candidemia is beyond the scope of the present review, but the dosing of the main antifungals is reported in Table 6. Moreover, given that echinocandins are the most recently introduced class of antifungals and general recommendations do not usually specify which of them should be used, Table 7 outlines the differences in indication, dosing, and so forth, for three echinocandin compounds. Considering that many ICU patients have other significant comorbidities, data on the treatment with various antifungals in the case of renal or hepatic insufficiency are reported in Table 8.

Management of candidemia in the neonatal ICU

The incidence of candidemia in the neonatal ICU has been increasing, mostly due to the fact that more low-birth-weight and very-low-birth-weight newborns survive longer thanks to advances in medical technology. These

Table 6. Dosing of currently available antifungals for treating candidemia

Drug	Loading dose (first 24 hours)	Daily dose
Fluconazole	800 mg (12 mg/kg)	400 mg (6 mg/kg)
Itraconazole	–	200 mg/day*
Voriconazole	6 mg/kg every 12 hours for first two doses	3 mg/kg every 12 hours
Posaconazole	–	200 mg x 3*
Amphotericin B deoxycholate	–	0.5 to 1 mg/kg
Liposomal amphotericin B	–	3 mg/kg
Lipid complex amphotericin B	–	5 mg/kg
Anidulafungin	200 mg	100 mg
Caspofungin	70 mg	50 mg
Micafungin	–	100 mg

*After a full meal.

Table 7. Main differences between the three echinocandins available

Variable	Anidulafungin	Caspofungin	Micafungin
Loading dose	200 mg	70 mg	None
	100 mg for EC	No loading dose for EC	
Daily dose for different indications	100 mg/day	50 mg/day	100 mg/day for candidemia
	50 mg/day for EC		150 mg/day for EC
			50 mg/day in prophylaxis
Age of patients according to FDA indication	Adults	>3 months	Neonates
			Children
			Adults
Metabolism	Slow chemical degradation at physiologic temperature and pH	Hepatic metabolism + spontaneous chemical degradation	Hepatic metabolism + enzymatic biotransformation
Indication for <i>Aspergillus</i> infection	None	Yes, in patients who are refractory to or intolerant of other therapies	None
Indications in neutropenic patients	None	Empirical therapy for presumed fungal infections in febrile, neutropenic patients	Prophylaxis of <i>Candida</i> infections in HSCT recipients
Dose adjustment in moderate hepatic impairment	None	Dose reduced (see Table 9)	None
Dose adjustment in severe hepatic impairment	None	Unknown	Unknown

Data deriving from Food and Drug Administration (FDA) labels. EC, oesophageal candidiasis; HSCT, haematopoietic stem cell transplant.

newborns are more likely to develop infectious complications, and candidemia is one of the most frequent nosocomial bloodstream infections in this population. The reported risk factors for candidemia in neonates and adults are similar, and include central venous catheters and arterial lines, parenteral nutrition, mechanical ventilation, and the extended use of antibiotics. Unlike in the adult ICU, *C. albicans* remains the most common isolate in the neonatal ICU – although non-*albicans* species such as *C. parapsilosis* and *C. tropicalis* are

increasingly common [68,69]. Fortunately, these species are susceptible to fluconazole.

The recent Infectious Diseases Society of America guidelines on management of *Candida* infections offer recommendations for paediatric patients. In particular, the following treatments are regarded as first-line therapy for neonatal candidiasis: amphotericin B deoxycholate, or liposomal amphotericin B if urinary tract involvement is excluded, and fluconazole. The guidelines also state that echinocandins should be used with caution and are

Table 8. Dose adjustment required in case of renal and hepatic impairment

Drug	Dose adjustment	Comments
Renal impairment		
All echinocandins	None	–
Fluconazole	Yes	50% of the dose if CrCl <50
Itraconazole oral solution	None	Do not use intravenous formulation due to carrier accumulation (cyclodextrin) if CrCl <30
Posaconazole	None	If CrCl <20, monitor closely for breakthrough infections due to the variability in exposure
Voriconazole, oral formulation only	None	Do not use intravenous formulation due to carrier accumulation (cyclodextrin) if CrCl <50
Amphotericin B deoxycholate	Do not use	Switch to less nephrotoxic formulation
Amphotericin B lipid formulations	Unknown	–
Hepatic impairment		
Anidulafungin	None	
Caspofungin	Yes	Moderate hepatic impairment (Child–Pugh score 7 to 9) 35 mg daily, with 70 mg loading dose
Micafungin	None	No data in severe hepatic impairment
Fluconazole	None	
Itraconazole oral solution	Unknown	Patients with impaired hepatic function should be carefully monitored when taking itraconazole
Posaconazole	None	
Voriconazole	Yes	50% of maintenance dose in mild to moderate hepatic impairment (Child–Pugh class A and B); no data in Child–Pugh class C; patients with hepatic insufficiency must be carefully monitored for drug toxicity
Amphotericin B	Unknown	

CrCl, creatinine clearance (ml/minute).

generally limited to situations in which resistance or toxicity precludes the use of fluconazole or amphotericin B. Dosing of antifungals in paediatric patients is outlined in Table 9.

Additionally for neonates, a lumbar puncture and a dilated retinal examination – preferably by an ophthalmologist – are recommended in those with sterile body fluid and/or urine cultures positive for *Candida*, and removal of the intravascular catheter is strongly recommended. Finally, in nurseries with high rates of invasive candidiasis, fluconazole prophylaxis may be considered in neonates with birth weight <1,000 g.

Conclusions

Candida is one of the most common causes of nosocomial bloodstream infection. Morbidity and mortality associated with candidemia are significant and the epidemiology of species has been changing, at both local and worldwide levels. Even though numerous risk factors for invasive *Candida* infection have been reported and several antifungals are widely available, the optimal management of candidemia remains a challenge. The agents recommended for initial treatment of candidemia in critically ill patients include echinocandins and lipid formulation of amphotericin B, but the choice between prophylactic, empirical and pre-emptive therapy is

Table 9. Dosing of antifungals in paediatric patients

Drug	Dose
Amphotericin B deoxycholate	1 mg/kg daily
Liposomal amphotericin B	3 mg/kg daily
Lipid complex amphotericin B	3 to 5 mg/kg daily (>1 month old)
Fluconazole	12 mg/kg daily
Caspofungin	50 mg/m ² , with a loading dose of 70 mg/m ² (>1 year old)
Micafungin	2 mg/kg daily in children if <40 kg
Anidulafungin	1.5 mg/kg/day, with a loading dose of 3 mg/kg/day (in children 2 to 17 years old)
Voriconazole	7 mg/kg every 12 hours, up to age 12 years

Data presented in order of strength in recommendation for invasive candidiasis.

crucial. Compared with prophylaxis, empirical and pre-emptive approaches allow the clinician to reduce exposure to antifungals by targeting only patients at high risk of candidemia, without delaying therapy until yeast is identified in blood cultures. A pre-emptive strategy is based on the presence of numerous risk factors, together with microbiological documentation for the presence of *Candida*, such as multifocal colonisation or positive serum β-D-glucan. Further prospective studies are

warranted to confirm the benefits from routine use of pre-emptive treatment of candidemia.

Abbreviations

ICU, intensive care unit; PCR, polymerase chain reaction.

Competing interests

In the past 5 years, MB has been an advisor/consultant for Gilead Sciences, Merck Sharp and Dohme, Novartis, Pfizer and Schering Plough. He has been paid for talks on behalf of Angelini, Astellas, Astra Zeneca, Aventis, Bayer, Cephalon, Glaxo SmithKline, Gilead Sciences, Jansen Cilag, Merck Sharp and Dohme, Novartis, and Pfizer. The other authors declare that they have no competing interests.

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