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EXPERT REVIEWS

# Occurrence, presentation and treatment of candidemia

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*Candida* is one of the most common causes of nosocomial bloodstream infections. Candidemia is not confined to hematological patients, intensive care units or abdominal surgery wards, but it is remarkably frequent in the internal medicine setting. High mortality associated with candidemia can be reduced by prompt, appropriate antifungal therapy. The epidemiology of species has been shifting toward non-*albicans* strains. Significant improvements in nonculture-based diagnostic methods, such as serological markers, have been made in recent years, and novel diagnostic techniques should be further studied to enable early pre-emptive therapy. Treatment guidelines indicate that echinocandins are at present the best choice for patients who are severely ill or possibly infected with fluconazole-resistant strains.

**KEYWORDS:** (1,3)-β-D-glucan • *Candida* • echinocandin • mannan • mortality • non-*albicans* • pre-emptive therapy

*Candida* is a yeast responsible for most of the systemic invasive fungal infections in humans. The incidence of systemic *Candida* infections, particularly nosocomial bloodstream infections (candidemia), has increased significantly in recent years [1], being the fourth most common pathogen isolated in blood cultures in the USA [2]. In Europe, it ranks among the ten most frequently isolated pathogens [3,4] and in a recent survey of intensive care units (ICUs) worldwide, the prevalence of candidemia was found to be 6.9 per 1000 patients [5]. While general incidence of candidemia has increased, possibly due to a rising number of patients with comorbidities and risk factors for invasive candidiasis (IC), settings such as ICU or stem cell transplant units have experienced a decrease in candidemia after introducing fluconazole prophylaxis [6–8].

Candidemia is a life-threatening infection with high morbidity and mortality [9,10]. Although most commonly reported around 30–40%, crude mortality rates might be as high as 50–60% [5,11–14]. However, attributable mortality may be substantially lower, ranging from 10 to 49%, depending on the definition used [15–17].

Until not long ago, *Candida albicans* accounted for the majority of infections. Nowadays, non-*albicans* species, which can be resistant to fluconazole (*Candida krusei* and *Candida glabrata*), are being more and more frequently isolated [14]. Immunocompromised patients, such as those affected by solid tumors or hematological malignancies, are at the highest risk for developing candidemia, whereas other well-known risk groups include ICU patients, low birthweight neonates or patients undergoing repeated intestinal surgery. More recently, a patients population characterized by multiple comorbidities, such as older age, need for parental nutrition or bacterial infections, is increasingly being described as being at risk of systemic candidiasis. Indeed, recent reports show that more than 50% of all candidemia episodes occur in this patient population, usually hospitalized in internal medicine wards [14,18].

The diagnosis of candidemia is not straightforward, as clinical signs and symptoms are aspecific, and, due to a low diagnostic yield of traditional blood cultures (still the gold standard for diagnosis), a significant percentage of candidemias go undetected. The use of antifungal prophylaxis further hampers diagnostic sensitivity, while predisposing patients to infections due to fungi with intrinsic or acquired resistance to some antifungals. Moreover, antifungals are not free of interactions and toxicities. Mortality rate in cases of IC, particularly candidemia, remains high but can be decreased by appropriate and timely antifungal therapy [19–22]. Thus, a prompt identification of patients with possible candidemia, for example, by clinical prediction rules, positive serological markers or suggestive clinical presentation, is mandatory. Fortunately, the clinical conditions that predispose patients to fungal infections


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are being better understood and new noninvasive diagnostic methods, such as high-quality radiological imaging and serologic markers (e.g., 1,3 β-D-glucan testing) are increasingly available. Last but not the least, new effective and less toxic antifungal drugs, in particular echinocandins, are being increasingly used and numerous international guidelines have been developed in order to help clinicians in the correct management of this infection. Epidemiology, risk factors, diagnosis and management of candidemia will be discussed further.

## Epidemiology & risk factors

### *Shift in Candida species*

The epidemiology of invasive *Candida* infections, either on a worldwide scale or, more importantly, on the local level, has significant implications for the choice of the appropriate management strategy. During the past two decades, most healthcare institutions have reported a progressive shift in the species of *Candida*. In the past, almost all the isolates responsible for bloodstream infections were *C. albicans*, whereas in recent years a growing proportion of episodes of candidemia have been caused by *Candida* species other than *albicans* [23–28]. Albeit *C. albicans* remains the predominant strain in many countries [5,12,29,30], non-*albicans* species are increasingly common and may be responsible for over 50% of candidemias [14,26,31–33]. The most common non-*albicans* species are *Candida parapsilosis* and *C. glabrata*, followed by *Candida tropicalis* and *C. krusei* [12,14,26,32,34,35], and their incidence varies among institution and different geographical regions, with *C. glabrata* being more frequent in the USA, *C. parapsilosis* or *C. tropicalis* in South America and South Europe [36]. Other species causing candidemia include *Candida lusitaniae*, *Candida guilliermondii* and *Candida rugosa* [18,32,34].

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

| *Candida* species | Risk factor |
|---|---|
| All species of *Candida* | Prior abdominal surgery |
| | Intravascular catheters |
| | Parenteral nutrition |
| | Use of broad-spectrum antibiotics |
| | Immunosuppression, including corticosteroid therapy |
| | Acute renal failure |
| | Diabetes |
| | Transplantation |
| | Hemodialysis |
| | Pancreatitis |
| *Candida tropicalis* | Neutropenia and bone marrow transplantation |
| *Candida krusei* | Fluconazole use |
| | Neutropenia and bone marrow transplantation |
| *Candida glabrata* | Fluconazole use |
| | Surgery |
| | Vascular catheters |
| | Cancer |
| | Older age |
| *Candida parapsilosis* | Parenteral nutrition and hyperalimentation |
| | Vascular catheters |
| | Being neonate† |
| *Candida lusitaniae* and *Candida guilliermondii* | Previous polyene use |
| *Candida rugosa* | Burns |

†Epidemics due to nosocomial horizontal transmission via hands of health personnel have been reported [39,40].
Adapted with permission from [42].

### *Risk factors for emergence of non-albicans species*

The reasons for this shift in *Candida* species have been investigated and several risk factors have been associated with the emergence of non-*albicans* species [27,37–42]. A widespread use of fluconazole has been associated with the development of infections due to non-*albicans* species that are intrinsically resistant to fluconazole or have developed resistance during treatment [26,27,43]. The fluconazole exposure can be considered either on a patient level, for example, in case of long-term fluconazole prophylaxis that predisposes patients to *C. krusei* infection, or on the level of a ward or hospital, when bulk consumption can change ecology of *Candida* species [44]. Whereas the patient-level association has been confirmed in numerous studies [27,43], the hospital-level influence is more controversial and has been observed in some centers [26,45], but not in others [44]. Additionally, the relationship with a heavy consumption of an antifungal and an increase in minimum inhibitory concentration to this drug has been established in ICU not only for azoles, but also for echinocandin or polyenes [45].

Other risk factors have been reported for candidemia due to *C. parapsilosis* and they include the presence of in-dwelling devices, hyperalimentation and neonatal age [34]. The specific risk factors associated with IC caused by different *Candida* species are reported in Table 1 [23,28,33,34,39–41,46–49].

### *Species identification & susceptibility testing*

The overall rise in the incidence of non-*albicans* strains is alarming, since there are important differences among species. The most important one probably regards susceptibility to antifungal agents, especially fluconazole [50]. In fact, *C. krusei* is intrinsically resistant to fluconazole, while *C. glabrata* has reduced and still dose-dependent susceptibility, which means that treatment with high doses of fluconazole (800 mg daily) might still be successful. In addition, some non-*albicans* species

(e.g., *C. glabrata*) have been associated with an increased risk of death, even after having adjusted for all statistically significant risk factors [43].

The species identification should be thoroughly pursued, as it can predict susceptibility and guide clinicians in choosing the active agent before susceptibility testing are available. Increasing resistance has been reported, not only to older azoles, such as fluconazole, but also to new drugs such as echinocandins [51]. Of note, similar to what has been observed for azoles, previous therapy with echinocandins seems to predispose to infection with echinocandin-resistant strains, due to the development of mutations in *FKS* genes coding for β-1,3-glucan-synthase [52–54]. Interestingly, none of the caspofungin-resistant strains belonged to the intrinsically less-susceptible species *C. parapsilosis* or *C. guilliermondii* [54]. In fact, higher minimum inhibitory concentration (MIC) values for echinocandins in *C. parapsilosis* seem not to influence the outcome of treatment with these agents [55].

Fortunately, the resistance to azoles and echinocandins remains uncommon – less than 5% in worldwide SENTRY Antimicrobial Surveillance Program 2008–2009 and 7% in a multicenter Spanish surveillance study [56,57]. Nonsusceptibility mainly regards *C. glabrata*. Indeed, in the SENTRY surveillance study, resistance in 156 strains of *C. glabrata* was 3.8% to anidulafungin, 5.1% to caspofungin, 3.2% to micafungin, 7.7% to fluconazole, 5.1% to posaconazole and 6.4% to voriconazole [56]. Among 134 strains from the Spanish surveillance study, resistance was 0% for anidulafungin and caspofungin, 18.7% for fluconazole and 2.2% for voriconazole [57].

The standardization of antifungal susceptibility tests represents a great advance in the detection of antifungal drug resistance, although this phenomenon is not as important as resistance to antibiotics in bacteria. Both the Clinical and Laboratory Standards Institute (CLSI) and European Committee on Antimicrobial Susceptibility Testing (EUCAST) reference methods are time consuming, but recently commercially available, standardized colorimetric panels based on CLSI method parameters made antifungal susceptibility testing more feasible. Moreover, CLSI MIC clinical break point for *Candida* species have been lowered and are now consistent with EUCAST [58], which makes reporting worldwide *Candida* nonsusceptibility rates much easier. Routine susceptibility testing is essential for species causing invasive infections, in case of antifungal prophylaxis or previous exposure and in patients who do not respond to treatment.

### *Identifying risk factors for IC*

In order to reduce *Candida*-related mortality, efforts have been made to identify patients who are at high risk of developing IC. Thus, the identified risk factors were combined to create reliable risk prediction scores. They include *Candida* colonization index in surgical patients [59], a score for peritoneal *Candida* infection in an ICU population [60], a five-parameter clinical score reported by Ostrosky-Zeichner *et al.* [61], and the most widely studied Candida Score [62], which was subsequently validated and found useful, especially for its high negative predictive value [63,64].

## Clinical presentation & diagnosis

Clinical presentation of candidemia, depending on patients and risk factors, may span from the absence of specific symptoms to severe sepsis or septic shock. The latter presentation is particularly important, as it is associated with high mortality and a prompt treatment with fungicidal agents is recommended.

### *Conventional diagnosis*

Blood cultures remain the mainstay for the diagnosis of candidemia, but their sensitivity is limited as they are positive in approximately 50% of cases of candidemia [65,66]. Furthermore, at least 48 h are required for species identification and susceptibility testing, and a recent study found that there are differences in time to positivity among different *Candida* species: significantly longer for *C. glabrata* and shorter for *C. tropicalis*, when compared with other species [67].

### *Nonculture-based diagnostic methods*

Noninvasive biomarkers have been extensively investigated and they include serological markers (mannan, antimannan and (1,3)-β-d-glucan) and molecular methods identifying fungal DNA. Mannan antigen and antimannan commercially available immunoenzymatic tests have been marketed for almost 10 years but their performance differ significantly among the studies in terms of sensitivity and specificity [68]. In order to achieve satisfactory sensitivity and specificity values, detection of both the mannan antigen and antimannan antibodies is recommended, as outlined in a recent review by the European Conference on Infections in Leukaemia group [68]. The (1,3)-β-d-glucan assay is recommended as a complementary tool for the diagnosis of invasive mycoses in high-risk hematological patients [69,70], but its role in other more heterogeneous populations remains unknown. The main problems of the routine use of (1,3)-β-d-glucan are its high cost and high rate of false positive results due to bacterial bloodstream infections, presence of surgical gauzes, use of glucan-containing membranes for hemofiltration and use of albumin or immunoglobulins [71]. The (1,3)-β-d-glucan test seems useful in hematology–oncology patients, particularly for excluding the presence of invasive fungal infections [72], while its routine utility in other populations needs to be further studied. Recently, the clinical performance of (1,3)-β-d-glucan assay in early diagnosis of nosocomial candidemia has been evaluated in a prospective study [73]: the test turned out to be fairly reliable, with a sensitivity and specificity of 77 and 83%, respectively. Data emerging from this study are very similar to those published in a meta-analysis regarding (1,3)-β-d-glucan assay in fungal invasive infections [74–76]. Finally, the performance of full blood PCR in diagnosing candidemia has been promising, though standardization and cost–effectiveness remain to be established [77]. Recently, performance of commercially available assay was tested in nonhematology patients with IC, reporting 80% sensitivity and 70% specificity [78]. Of note, sensitivity was higher in deep-seated candidiasis than in candidemia (89 vs 59%) [78]. The main features of these nonculture-based diagnostic methods are summarized in Table 2. Great expectations come

Table 2. The main features of nonculture based diagnostic methods for invasive candidiasis.

| Test | Sensitivity and specificity (%) | Comments | Ref. |
|---|---|---|---|
| (1,3)-β-D-glucan | 77 and 85<br>76 and 86<br>80 and 82<br>50 and 99 | Studies used different assays, although only one is available in Europe and the USA. Significant heterogeneity of studies in the first three meta-analyses. The fourth included only cohort studies on hematology patients and the performance of two positive samples was calculated. Main limitations of the test include high cost and high possibility of false positive results, although all the meta-analyses consistently reported high specificity | [74]<br>[76]<br>[75]<br>[72] |
| Mn and A-Mn | Mn: 58 and 93<br>A-Mn: 59 and 83<br>Mn/A-Mn: 83 and 86 | Better performance of combined testing. Different antigen sensitivity with different species (the lowest for *Candida krusei*). Reported clinical usefulness in diagnosis hepatosplenic candidiasis. The assays have been recently modified and their performance remains to be confirmed | [68] |
| PCR | 95 and 92 | Promising performance of some assays in candidemia. Standardization and large-scale validation are needed to recommend one assay over another | [77] |

A-Mn: Antimannam; Mn: Mannan.

from studies that have used MALDI-TOF MS and fluorescence in situ hybridization.

## Prevention & treatment

### *Timing of therapy*

On the of main points regarding invasive *Candida* infections is the fact that delaying antifungal treatment significantly increases mortality [19–22]. Even 12–24 h delay can result in twofold increase in crude mortality rate in candidemia. In a study by Blot *et al.* from 2002, the mortality was 78% when therapy was delayed more than 48 h from onset of candidemia, compared with 44% in patients who had more timely therapy. Similarly, Morrell *et al.* reported that in multivariate analysis, the odds of death was twofold higher if adequate therapy was delayed more than 12 h [22,79]. Additionally, in 230 patients with candidemia treated with fluconazole, mortality rate was 15% if fluconazole was started on the same day the culture was performed, but increased to 24, 36 and 41% if started on days 1, 2 and 3, respectively [80]. In fact, nosocomial invasive fungal disease has one of the highest rates of inappropriate therapy, that consists mostly of omission of including an antifungal in the initial empirical therapy or the use of inadequate doses, both of which have been associated with increased mortality [18,79–81]. Thus, early diagnosis followed by rapid appropriate treatment remains the cornerstone of successful management that aims at reducing mortality associated with candidemia.

Different strategies can be used for managing suspected or documented candidemia, including prophylaxis, empirical or pre-emptive therapy and treatment of a culture-proven infection.

### *Prophylaxis*

Based on the incidence of IC, prophylaxis may be judged appropriate in patients with high risk of this infection, while in settings with lower incidence rate, patients might benefit from pre-emptive therapy based on clinical presentation and risk factors, formal predictive scores or serological assays.

Prophylaxis, defined as administration of an antifungal to a patient with no clinical evidence of infection, has been evaluated in surgical and critically ill patients in several studies and meta-analyses [30,82–91]. Fluconazole prophylaxis reduced by approximately 50% the incidence of IC, and seemed associated with improved outcome [88–90]. Conceivably, the higher the prevalence of candidemia, the more cost-effective is the prophylaxis, since the number of patients needed to treat is inversely proportional to the prevalence of *Candida* infections. On the other hand, the disadvantages of fluconazole prophylaxis include overtreatment, possible toxicity and profound influence on the local epidemiology with the emergence of azole-resistant isolates [92]. The prophylaxis of *Candida* with fluconazole is frequent in hematopoietic stem cell transplant recipients and low birthweight neonates. In general, antifungal prophylaxis might be indicated only for patients or procedures in which the rate of IC is higher than 10%, as compared with lower rates [50,93]. In such populations in ICU, the number needed to treat is fewer than 20, as compared with over 100 in an average population of ICU patients with the incidence of IC of 1–2% [50,93].

### *Empirical treatment*

Empirical treatment is defined as administering antifungals in the presence of persistent or refractory fever in subjects who are at high risk of developing an invasive fungal infection. This strategy was developed almost 30 years ago for neutropenic cancer patients, when it was noted that poor sensitivity of clinical and microbiological findings was resulting in delayed diagnosis and increased morbidity and mortality [94]. Despite the fact that the first studies on empirical therapy included small numbers of patients and had numerous methodological flaws [94], this fever-driven strategy continues to be used in different clinical settings and various antifungals are recommended for empirical treatment

of IC, both in neutropenic and non-neutropenic patients [50]. Empirical antifungal treatment might be useful in neutropenic hematology and oncology patients who do not receive antifungal prophylaxis, but widespread fluconazole use in these populations significantly reduced the incidence of candidemia, and thus the need for empirical treatment of *Candida* infections. In fact, empirical therapy in high risk patients with hematological malignancies or stem cell transplant is now directed mostly against invasive aspergillosis, which is not prevented by fluconazole administration. Similarly to what was noted for immunocompromised subjects with cancer, numerous causes of protracted fever can be identified in ICU or surgery patients. This might be the reason why in a randomized multicenter study in critically ill patients, the empirical therapy with fluconazole was not more beneficial than placebo [95].

### Pre-emptive treatment

Following the availability of improved diagnostic tools, such as radiological imaging or serological markers, it became evident that a diagnosis-driven approach was feasible and should be pursued. Pre-emptive treatment is based on starting antifungal therapy when one or more microbiological or clinical markers results positive. However, there is still a certain degree of confusion between empirical and pre-emptive approach in patients with high risk of invasive fungal infections. In fact, the Infectious Diseases Society of America guidelines recommend a pre-emptive therapy (although it is called empirical treatment) based on clinical assessment of risk factors, serologic markers and/or culture data from nonsterile sites, rather than fever [50]. Different management strategies of IC have been recently reviewed elsewhere [96].

### Treatment of a documented infection

Despite the advances in diagnostic tools, repeated blood cultures, both from central venous catheter and peripheral line, remain the cornerstone of diagnosis of candidemia, and any positive blood culture for *Candida* must be considered as an infection and treated appropriately. The initial choice of antifungals depends on patient's clinical condition and the risk of infection caused by an azole-resistant strain, due to previous azole exposure or local epidemiology [50]. The available treatment options for patients with candidemia are reviewed in Table 3. For patients in severe or moderately severe clinical conditions (e.g., hemodynamically unstable or with suspected concomitant organ involvement), echinocandins are the first choice because of their cidal activity against *Candida* and excellent toxicity profile [50,97]. Moreover, two recent retrospective analyses of data from large prospective trials favored echinocandins over other antifungals [98,99]. In the first, the global response rate was higher for anidulafungin than for fluconazole (71 vs 54%, respectively), although the original study was designed to establish noninferiority; there was also a trend for lower 14-day all-cause mortality, but this advantage was not present at 28 days [98]. In the second, treatment with an echinocandin was associated with significantly reduced mortality (27% for echinocandins vs 36% for other regimens), compared with the use of a drug from either the triazole or polyene classes, and this superiority was evident for both *C. albicans* and non-*albicans* groups and in patients with a wide range of severity of illness, with exception of those with the highest (>24) Acute Physiology and Chronic Health Evaluation II score [99].

An alternative to echinocandins is represented by liposomal amphotericin B, which is also fungicidal and active against biofilm, although with a higher rate of renal toxicity. Due to an increasing incidence of non-*albicans* species and the possibility of acquired resistance during pre-exposure to fluconazole, broad spectrum antifungals are usually recommended for the first line treatment, while species identification is pending. Once the species is known and it is susceptible to fluconazole, a de-escalation can be attempted [50]. On the contrary, if fluconazole-resistant species is recovered but oral therapy is needed, for example, to terminate the cycle of treatment for candidemia or if long-term suppressive therapy is necessary, other azoles, such as voriconazole or posaconazole can be successfully used once cross resistance is excluded.

Which echinocandin should be preferable is an unsolved issue. First, there is no evidence for superiority of one echinocandin over another and even the guidelines do not indicate which one is to be chosen [50,97]. Small differences in fungal MIC values, liver toxicity and volume of liquids infused do not represent valuable reasons for choosing one echinocandin over another. Metabolism is different, but this can be an issue only in severe hepatic failure. All the three agents are approved for the treatment of candidemia in non-neutropenic adults, although other licensed indications differ among the molecules. For example, caspofungin is recommended for neutropenic patients with candidemia, as the other two echinocandins have limited or no data in this setting.

Once the initial therapy for candidemia is started, several clinical issues remain to be resolved. First, the efficacy of the treatment should be confirmed by blood cultures turning negative. Additionally, the day when blood cultures become negative is important for determining the length of treatment. Antifungal therapy should be continued for 14 days after the first negative blood culture and resolution of symptoms attributable to candidemia. Second, the initially chosen antifungal can be changed on the basis of species identification or susceptibility testing. Thus, in stable patients with *C. albicans* or other azole-susceptible strains, fluconazole can be administered. Furthermore, triazoles should be preferred over echinocandins for treating *C. parapsilosis*, as caspofungin MICs for *C. parapsilosis* are higher than those for other *Candida* species [50,100], although in a recent analysis of data from five clinical trials, which included 71 cases of infection due to *C. parapsilosis*, the success rate was comparable with that observed for other non-*albicans* species [101]. Third, patients who improved clinically and cleared *Candida* from the bloodstream might be suitable for a step-down oral therapy to complete the course of treatment. Triazoles are the only available oral drugs: fluconazole, itraconazole, voriconazole and posaconazole. Fluconazole is an obvious choice for susceptible species, while voriconazole can be indicated as a step-down therapy for *C. krusei* or voriconazole-susceptible *C. glabrata* and in ocular or cerebral infections, because of its excellent tissue concentration. With this respect, ophthalmologic fundus examination is

Table 3. Treatment options available for patients with candidemia.

| Drug class | Antifungal | Advantages | Limitations |
|---|---|---|---|
| Azoles | Fluconazole | Extensive experience in its use<br>Low toxicity<br>Oral formulation available for switch from intravenous therapy<br>Inexpensive<br>Good eye and meningeal penetration<br>High concentration in urine | Possible resistance, both intrinsic and induced<br>Fungistatic not fungicidal |
| | Itraconazole | Oral formulation available<br>Usually used for treating mucosal candidiasis, especially after fluconazole failure | Intravenous formulation unavailable in some countries<br>Low bioavailability of capsules<br>Better serum concentrations with oral solution that should be administered on empty stomach<br>Poor tolerability |
| | Posaconazole | Active against strains with intrinsic fluconazole-resistance<br>Oral formulation available | No indication for primary candidiasis therapy<br>No intravenous formulation<br>Suboptimal absorption<br>Low serum levels with concomitant use of proton pomp inhibitors |
| | Voriconazole | Active against strains with intrinsic fluconazole-resistance<br>Oral formulation available for switch from intravenous therapy<br>Excellent eye and brain penetration<br>Therapeutic monitoring is available | Important pharmacological interactions<br>Fungistatic not fungicidal<br>Intravenous formulation should be used with caution in case of renal insufficiency |
| Echinocandins | Anidulafungin<br>Caspofungin | Fungicidal<br>Low toxicity<br>Active against biofilm | Very limited eye and brain penetration |
| | Micafungin | Better survival reported in some recent studies | No oral formulations |
| Polyenes | Conventional amphotericin B | Fungicidal<br>Active against biofilm<br>Active against all species<br>Inexpensive | Frequent nephrotoxicity<br>Infusion reactions |
| | Lipid formulations of amphotericin B | Fungicidal<br>Active against biofilm<br>Active against all species (except for *Candida lusitaniae*)<br>Good brain penetration of liposomal amphotericin B | Nephrotoxicity, though significantly lower than in case of conventional amphotericin B<br>High cost of lipid formulations |

indicated in all patients to exclude endocular infection, such as chorioretinitis and endophalmitis, which in a large prospective study were found to affect 14.4% and 1.6% of all patients, respectively [102]. In case of an ocular infection, it should be kept in mind that echinocandins are large molecules that do not cross the blood–eye barrier. Other possible localizations include endocarditis, which should be excluded in case of persistently positive blood cultures, known valve pathology or any other sign or symptom suggestive of cardiac involvement. Obviously, in disseminated infection, a prolonged treatment is necessary (more than 4 weeks and up to a lifelong suppressive therapy) [50]. Finally, intravenous catheter removal is strongly recommended for patients with candidemia. Indeed all guidelines, both on the management of candidiasis and on the management of catheter-related bloodstream infections, state clearly that catheters should be removed, even though one should admit that all statements indicate grade II or III of scientific validity of recommendation, in the absence of data from properly randomized, controlled trials [50,103]. However, the issue might still be controversial since a recent study, based on a multivariate analysis of 842 adults included in candidemia trials, did not find any survival benefit of an early central venous catheter removal (i.e., within 24 or 48 h after initiation of antifungal therapy) [104]. On the contrary, another study that was also based on the analysis of 1915 patients included in candidemia trials, found that the removal of a central venous catheter was significantly associated with decreased mortality [99]. However, as elegantly pointed out in the accompanying editorial, all the *post hoc* analyses may suffer from important bias; thus their results should be interpreted with caution because in all the analyzed trials there were no standard criteria on catheter

removal, and certainly patients had to be alive in order to have a catheter removed [105].

If the removal of a central venous catheter is absolutely contraindicated or not feasible, agents active against biofilm, such as echinocandins or liposomal amphotericin B should be used. Additionally, local catheter-lock therapy may be considered, although its role is not well defined because most data come from *in vitro* studies [106–109].

Despite recent advances in diagnosis and treatment, the prognosis in case of candidemia remains far from desirable, with overall mortality affecting up to one patient in three. Recently, genetic factors, such as polymorphisms in cytokine genes have been reported to influence the outcome of candidemia, with a production of proinflammatory cytokines being associated with persistent fungemia [110].

## Conclusion

*Candida* is one of the most common causes of nosocomial bloodstream infections. Morbidity and mortality associated with candidemia are significant and the epidemiology of species has been shifting toward non-*albicans* strains. There is an increasing knowledge of predisposing risk factors and significant improvements in nonculture-based diagnostic methods, such as serological markers, have been made. Several antifungals are widely available and treatment guidelines indicate that echinocandins are the best choice for severely ill patients. While prophylaxis might be beneficial in some highly selected populations with high incidence of candidemia, novel diagnostic techniques should be further studied to enable pre-emptive treatment in populations with lower incidence rates. Despite all recent advances, successful management of candidemia remains a challenge.

## Expert commentary

Candidemia is a well-known cause of in-hospital morbidity and mortality. Healthcare workers should increase their knowledge of this potentially lethal infection. Candidemia is not confined to ICUs or abdominal surgery wards, but, on the contrary, is found with remarkable frequency in the internal medicine setting. Frequently, physicians do not take into consideration blood cultures positive for *Candida spp.*, considering it a simple contaminant. Therefore, all clinicians should include candidemia as a possible cause of persistent fever and clinical worsening in hospitalized patients with risk factors such as previous antibiotic treatment, major surgery, total parenteral nutrition or central venous line. Concomitant conditions, such as diabetes, cancer and immunosuppression can further increase the risk of getting candidemia. Only the increased awareness of possible candidemia will prompt an immediate diagnostic effort and antifungal treatment and reduce the risk of dying of candidemia.

## Five-year view

In the next few years the diagnostic methods for *Candida* detection should be improved. Therefore, culture techniques should be more efficient and sensitive, allowing the clinician to start antifungal treatment as early as possible. In addition, indirect methods such as DNA or antigens detection should be validated or improved, respectively, making them more easily available even in small facilities. The increase of resistance is to be expected if an extensive use of antifungals continues. In particular, if echinocandins are widely used, more resistance to this class of agents will be observed. Thus, new issues such as cross resistance among echinocandins, resistance to both azoles and echinocandins and clinical outcome of patients infected with less susceptible strains will need to be addressed. As regards antifungal drugs, the current armamentarium is quite satisfactory, considering that other molecules will soon become available. However, an effort should be made to improve the management of candidemia, particularly in timely diagnosing ocular involvement or switching from intravenous to oral medications.

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## Key issues

- Candidemia is a frequent nosocomial infection.
- Main risk factors include: immunocompromised status, stay in intensive care unit, wide-spectrum antibiotic therapy, low birthweight, abdominal surgery, parenteral nutrition and intravascular catheters.
- Mortality associated with candidemia remains significant, particularly in the presence of other comorbidities (from 10 to 49%).
- Non-*albicans* strains are becoming more frequent than *Candida albicans*, with an increase in fluconazole-resistant strains such as *Candida glabrata*.
- Previous exposure, both to azoles and also to caspofungin, has been associated with the emergence of resistant strains.
- Susceptibility testing is standardized and reproducible and should be performed in all cases of candidemia.
- Novel diagnostic tools include: serum (1,3)-D-glucan, mannan antigen and antimannan antibodies and PCR.
- Echinocandins are considered first-line therapy in severely ill patients or if resistance to fluconazole can be expected.

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