Virulence 5:1, 161–169; January 1, 2014; © 2014 Landes Bioscience

Invasive candidiasis as a cause of sepsis in the critically ill patient

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Keywords: *Candida albicans*, sepsis, candidiasis, echinocandin, risk factors

Invasive fungal infections are an increasingly frequent etiology of sepsis in critically ill patients causing substantial morbidity and mortality. *Candida* species are by far the predominant agent of fungal sepsis accounting for 10% to 15% of health-care associated infections, about 5% of all cases of severe sepsis and septic shock and are the fourth most common bloodstream isolates in the United States. One-third of all episodes of candidemia occur in the intensive care setting. Early diagnosis of invasive candidiasis is critical in order to initiate antifungal agents promptly. Delay in the administration of appropriate therapy increases mortality. Unfortunately, risk factors, clinical and radiological manifestations are quite unspecific and conventional culture methods are suboptimal. Non-culture based methods (such as mannan, anti-mannan, β-d-glucan, and polymerase chain reaction) have emerged but remain investigational or require additional testing in the ICU setting. Few prophylactic or pre-emptive studies have been performed in critically ill patients. They tended to be underpowered and their clinical usefulness remains to be established under most circumstances. The antifungal armamentarium has expanded considerably with the advent of lipid formulations of amphotericin B, the newest triazoles and the echinocandins. Clinical trials have shown that the triazoles and echinocandins are efficacious and well tolerated antifungal therapies. Clinical practice guidelines for the management of invasive candidiasis have been published by the European Society for Clinical Microbiology and Infectious Diseases and the Infectious Diseases Society of North America.

Introduction

Fungi can induce a broad spectrum of host responses that result in colonization, infection, sepsis, hypersensitivity disorders, or toxic reactions. Fungal infections can be classified into superficial or deep-seated infections and grouped as opportunistic mycoses (such as candidiasis, cryptococcosis, and aspergillosis) occurring in immunocompromised hosts or as endemic mycoses (such as histoplasmosis, blastomycosis, coccidioidomycosis, and penicilliosis) caused by geographically restricted fungi infecting otherwise immunocompetent hosts. The gamut of immunocompromised host is rapidly expanding and also includes debilitated and critically ill medical, surgical and intensive care unit (ICU) patients with prolonged hospital stays.

As a consequence of the rapidly growing population of immunocompromised patients, the spectrum of opportunistic invasive fungal infections has increased considerably. Among yeasts and molds, *Candida* and *Aspergillus* species are the most frequent nosocomial fungal pathogens including in the critical care setting.[1-3] Fungi such as *Cryptococcoccus*, *Pneumocystis jirovecii, Penicillium marneffei, Zygomycetes*, *Fusarium*, and *Scedosporium* may also cause severe infections in HIV-infected patients, onco-hematological and transplants patients, and in patients treated with corticosteroids, disease-modifying drugs, or monoclonal antibodies directed against immune mediators. Given the scope of this special issue of *Virulence*, this review will focus on invasive candidiasis as a cause of sepsis in critically ill and ICU patients.

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Submitted: 07/28/2013; Revised: 08/11/2013; Accepted: 08/16/2013
http://dx.doi.org/10.4161/viru.26187

Epidemiology

Approximately 15% of health-care associated infections are caused by fungi. *Candida* accounts for 70–90% of all invasive fungal infections and *Aspergillus* for 10–20%. Recent epidemiological studies have shown that invasive mycoses increased as a cause of life-threatening infections in critically ill and ICU patients. In a one-day, prospective, point prevalence study (EPIC II) performed in 2007 which included 7087 infected ICU patients from 75 countries, *Candida* was the third most common pathogen with an infection rate of 17%.[4] According to a survey of the Fungal Infection Network of Switzerland, a third of all episodes of *Candida* bloodstream infections (BSI) occur in patients admitted to the ICU.[1] The incidence of candidemia (ranging between 2 and 6.7 per 1000 admissions) is 5- to 10-fold higher in the ICU than in medical or surgical wards. In the United States, *Candida* is at present the third or fourth most commonly isolated microorganism in blood cultures accounting for 8–10% of BSI. The situation is quite different in Europe since *Candida* is usually between the 6th and 10th positions of blood isolates accounting for only 2–3% of BSI.[5]

Microbiological data collected in recent randomized clinical trials of adjunctive therapies for severe sepsis or septic shock indicated that fungi are responsible for no more than 5% of all cases.[6-8] Candida is the most frequent cause of fungal severe sepsis or septic shock in ICU patients.[9] In a cohort of 386 patients with positive blood cultures and septic shock, candidemia

was documented in 16 patients (4.1%) of whom 10 (2.6%) had pure candidemia and 6 (1.5%) mixed candidemia and bacteremia.[10] Likewise, in the EPISS study, a large prospective multicenter study in French ICUs, fungi were identified as causative microorganisms in 33 (3.2%) among 1035 patients with microbiologically documented infections.[11] Conversely, the proportion of patients with candidemia who develop severe sepsis or septic shock is in the range of 8% to 30% and 23% to 38%, respectively.[12-14]

Invasive *Candida* infections are associated with high morbidity and mortality, especially in the ICU. Overall crude mortality among patients with invasive candidiasis or candidemia is in the range of 40% to 60%, which reflects in part the contribution of the underlying condition.[14-16] In the AmarCand study, the case fatality ratio was 45.9% and no significant differences in mortality were observed between patients with isolated candidemia (47.7%) or with invasive candidiasis with (48.7%) or without (41.2%) candidemia.[15] Of note, in a recent prospective study of 271 ICU patients with *Candida* peritonitis, mortality was 38%,[17] but death rates in excess of 60% have been reported previously.[18] The attributable mortality of invasive candidiasis was reported to be somewhere between 5% and 71%.[16,19,20] This wide range probably reflects the inherent difficulty of assessing whether these critically ill patients died either with or from fungal infections. When complicated by septic shock, candidemia is a highly lethal condition with mortality rates beyond 60%.[9,10,15,21-24] Fungal sepsis increased the length of ICUs or hospital stays and impacted negatively on treatment costs.[25,26]

Geography, patient's age and the use of antifungal agents are the main factors impacting on the distribution of *Candida* species. *Candida parapsilosis* is more frequent in the southern hemisphere (Latin America and Australia) or Southern Europe than in North America or Northern Europe.[27] *Candida glabrata* becomes more frequent with increasing patient's age. Worldwide, *Candida albicans* was historically the predominant species accounting for about two-thirds of *Candida* infections. However, the epidemiology of candidiasis is changing. Over the two last decades, species other than *C. albicans* (primarily *C. glabrata*, *C. krusei*, *C. tropicalis*, and *C. parapsilosis*) have emerged. These non-*albicans Candida* species are now responsible for up to 50% of all cases in some centers and are associated with intrinsic resistance (*C. krusei*) or reduced susceptibilities to azoles (*C. glabrata*) or to echinocandins (*C. parapsilosis*).[27] In a prospective, multicenter study of 136 patients with candidemia, 42.6% of infections were caused by non-*albicans Candida*. *C. glabrata* was the second most frequent pathogens isolated.[15] Susceptibility to fluconazole was 95.6% for *C. albicans* strains, but only 68% for non-*albicans Candida*.[28] In a retrospective study including 189 patients with candidemia in four general ICUs in Greece, Australia, Belgium, and Brazil, non-*albicans Candida* were recovered in 44% of the cases.[29] Finally, in the prospective AmarCand study, non-*albicans Candida* accounted for 42% of the species. Dose-dependent susceptibility or resistance to fluconazole was documented in 17.1% of *Candida* isolates.[30] Although changes in fungal ecology is a complex issue, there is mounting evidence supporting the idea that the global shift in the epidemiology of candidemia and invasive candidiasis is most likely driven first and foremost by a widespread use of antifungal agents, especially azoles. These recent trends highlight the importance of and need for longitudinal epidemiological studies to monitor changes in the distribution of fungal species over time, especially in hospital hot spots like the ICU. This information is essential for driving the choice of empirical antifungal therapy.

Risk Factors

Candida is part of the normal skin, vaginal, and gastrointestinal flora. The vast majority of candidal infections are endogeneous. Given its opportunistic nature, *Candida* will not cause infection unless the ecology of the normal flora or the host antifungal defense response has been perturbed. Modification of the endogenous microbial flora by antibacterial agents is a major risk factor allowing for fungal overgrowth on mucosal and skin surfaces. Alteration of the physical integrity of the skin and mucous membranes barriers by intravascular access devices, wounds, surgery, chemotherapy, or of host defenses are other key pathogenic elements facilitating dissemination of infection into the systemic circulation.

Colonization of mucous membranes and skin is a critical step in the pathogenesis of invasive candidiasis. It has been used for predicting the development of infections in critically ill patients. However, differentiation between colonization and infection is not easy. Pioneering work by Pittet et al. in 29 high-risk surgical and neonatal ICU patients identified the extent of *Candida* colonization and the severity of illness assessed by APACHE II score as independent risk factors for development of infection.[31] A colonization index of 0.5, defined as the ratio of non-bloodstream body site(s) positive for *Candida* species over the total number of body sites tested, successfully identified patients at risk of developing invasive infections with a positive predictive value of 66%. A corrected colonization index (CCI) of 0.4, defined as the product of CI times the ratio of the number of heavily colonized body sites divided by the total number of body sites colonized, had a positive predictive value of 100%. The CCI index was validated in an intervention study in ICU patients with historical controls confirming the utility of antifungal therapy based on colonization.[32] In a prospective study involving 92 medical ICU patients with prolonged ICU stay, 39.1% of patients with invasive *Candida* infections had a CI of 0.5.[33] A CI greater than 0.8 and extensive gastro-abdominal surgery was associated with invasive *Candida* in a group of 59 ICU patients.[34]

Risk factors of the development of invasive fungal infections in ICUs patients have been analyzed in numerous retrospective studies with a heterogeneous patient population. Various conditions including patient's age, prolonged length of stay, administration of broad-spectrum antibiotics, central vascular catheters, diabetes mellitus, parenteral nutrition, mechanical ventilation, renal insufficiency, hemodialysis, colonization, antifungal prophylaxis, surgery, pancreatitis, and treatment with corticosteroids and chemotherapy were the most frequently identified risk factors. Prior to surgery, *Candida* colonization, acute renal failure, hemofiltration, use of parenteral nutrition,

presence of triple lumen catheter, and ICU length of stay were factors also identified in prospective studies (**Table 1**).[35-37] Few studies have analyzed factors predisposing to the occurrence of septic shock.[31] In a retrospective cohort of 15 patients, the only risk factor was time spent in ICU until the development of candidemia.[21] APACHE score, delayed administration of antifungal therapy, neutropenia, immunosuppression, and retention of central venous catheters have been proposed as factors of poor prognosis.[9,21,22] Studies have yielded conflicting results regarding the impact of *Candida* species isolated from blood cultures and patient's survival.[15,38-40] BSI due to *C. glabrata*, *C. krusei*, and *C. tropicalis* were reported to be associated with the highest mortality in some but not all studies. There was no significant relationship between *Candida* species and death in the large AmarCand study.[15] The lack of reproducibility of these findings is likely to reflect the large heterogeneity of the patient's population and an insufficient power to control for confounding factors (i.e., underlying comorbidities, presence of neutropenia or the timing to onset of appropriate therapy).

Candida species are commensals of the digestive tract and may therefore invade the peritoneal cavity upon perforation of the gastrointestinal tract or after surgical section of the intestinal wall. Depending upon the underlying condition and circumstances, *Candida* will either be cleared promptly or else cause infection which may then disseminate to the bloodstream and other organs.[41-45] It is not always easy to determine when *Candida* is an "innocent bystander" or when it is playing a pathogenic role. In a study of 49 surgery patients with *Candida* isolated from the peritoneal fluid, we reported that recurrent gastrointestinal perforation and acute necrotizing pancreatitis were risk factors for the development of intra-abdominal candidiasis with a risk of systemic dissemination of about 20%.[18] Serial semi-quantitative cultures indicated that a high initial growth of *Candida* or an increasing amount in follow-up cultures were early indicators of infection. Thus, recurrent gastrointestinal leakage with sustained seeding of *Candida* into the peritoneal cavity is a major risk factor for infection after surgery.

Predictions Rules and Scoring Systems

Clinical and microbiological prediction rules and scores have been developed to identify patients at high risk of fungal infections.[46-51] Various combinations of clinical, laboratory, and management parameters have been utilized to build predictive models. Using a stepwise logistic regression model, Michalopoulos et al. proposed a model based on four independent risk factors (invasive mechanical ventilation ≥10 d, nosocomial bacterial infections, cardiopulmonary bypass, and diabetes mellitus) that predicted candidemia in cardiothoracic ICU patients.[46] The model was validated in two centers and found to have a sensitivity of 57.9%, specificity and positive predictive value (PPV) of 100% and a negative predictive value (NPV) of 99.6%. In a retrospective study of patients who stayed in a surgical ICU for more than 3 d, Phaphitou et al. showed that patients with any combination of diabetes mellitus, hemodialysis, total parenteral nutrition and broad spectrum antibiotic had an increased rate of invasive candidiasis (16.6% vs. 5.1% in patients without these characteristics).[51] In a follow-up study, Ostrosky-Zeichner et al. identified a predictive rule with a negative predictive value of 97% based on the following parameters: ICU stay of at least 4 d, systemic antibiotic therapy, presence of central venous catheter, total parenteral nutrition, dialysis, major surgery, pancreatitis, use of steroids, or immunosuppressive agents.[52] More recently, in a very large cohort, Shorr et al. developed a score based on age (i.e., less than 65), temperature, altered mental status, cachexia, previous hospitalization within 30 d, and mechanical ventilation.[53] The rates of candidemia increased from 0.4% (when no risk factor was present) to 0.8%, 1.6%, 3.2%, 4.2%, 9.6%, and 27.3% when the number of risk factors increased from 1 to 6. Using a retrospective multicenter cohort study of 1699 ICU non-neutropenic patients, Leon and colleagues constructed a *Candida* score for patients who stayed in the ICU for at least 7 d.[54] This easy-to-use scoring system relies on four risk factors: total parenteral nutrition, surgery, multifocal *Candida* colonization and severe sepsis. A score greater than 2.5 identifed patients at risk of developing invasive *Candida* infections with a sensitivity of 81% and a specificity of 74%. The clinical utility of the score was then tested in a prospective study that included 1107 ICU non-neutropenic patients from Spain, Argentina, and France. The incidence rates of invasive candidiasis were 2.3%, 8.5%, 16.8%, and 23.6% with a *Candida* score of less than 3, 3, 4, and 5, respectively. This trend was confirmed in a small prospective cohort study in which the rates of invasive candidiasis was 0% in patients with a score of 2, 17.6% in patients with a score of 3, and 50% in patients with a score of 4.[55] In the Leon study, a *Candida* score equal to or greater than 3 had a negative predictive value of 97.7%, a sensitivity of 77.6%, and a specificity of 66.2%.[48] These data suggest that the main value of the *Candida* score is to rule out invasive candidiasis. The clinical utility of these prediction rules and scoring systems on the management of patients should be assessed prospectively in larger studies.

Table 1. Risk factors for invasive *Candida* infections in the critically ill patient

Age
Colonization of body sites with *Candida*
Length of ICU stay
Administration of broad-spectrum antibiotics
Intravascular access devices
Diabetes mellitus
Parenteral nutrition
Mechanical ventilation
Renal insufficiency
Hemodialysis, hemofiltration
Antifungal prophylaxis
Surgery
Acute necrotizing pancreatitis
Treatment with corticosteroids

ICU, Intensive Care Unit.

As mentioned above, *Candida* peritonitis is a difficult diagnosis to ascertain. Notwithstanding the issue of infection vs. colonization, the presence of *Candida* in an intraabdominal sample should be considered as a marker of disease severity. The isolation of yeasts in the peritoneal fluid of patients with community-acquired peritonitis was associated with the development of sepsis.[56] In a retrospective study of 221 ICU patients with peritonitis, Dupont et al. developed a score to predict yeast isolation from peritoneal samples based on 4 independent risk factors (female gender, a proximal gastrointestinal source of peritonitis, intraoperative cardiovascular failure, and antimicrobial treatment within 48 h of the development of peritonitis).[50] When at least 3 risk factors were present, the sensitivity and specificity were 84% and 50%, respectively.

Clinical Manifestations

The spectrum of *Candida* infections in critically ill patients is rather broad. Clinical manifestations include infections of the skin (intertrigo, wound infections), of mucous membranes (oropharyngitis, esophagitis, and vulvovaginitis) and of the lower urinary tract representing colonization of a urinary catheter in most instances. These are usually very mild infections. In contrast, infections of deep-seated organs (such as the peritoneum, liver, spleen, or the upper urinary tract), of intravascular access devices, of the cardiovascular system (i.e., bloodstream infections, endocarditis, and septic thrombophlebitis) and disseminated infections are normally quite severe and are often associated with sepsis, severe sepsis, or septic shock. Occasionally, other rare infections like those of the central nervous system or mediastinum may be encountered. Candidemia is the most common clinical presentation of all forms of invasive candidiasis. In a large prospective, multicenter study conducted in 180 ICUs in France candidemia was present in more than two-thirds of the 300 adult patients, of whom 39.5% had primary bloodstream infections and 28.4% had invasive candidiasis with secondary candidemia. In surgical ICUs, *Candida* peritonitis is one of the most frequent forms of invasive candidiasis.

The clinical presentation of fungal sepsis is not different from that of bacterial sepsis. In a prospective, randomized, double-blind, multiple center study comparing the clinical manifestations of septic shock caused by bacteria or *Candida* spp., higher levels of lactate deshydrogenase in patients with bacterial septic shock and a higher incidence of renal and hepatic failure in patients with candidal septic shock were the only striking differences.[10] Interestingly, the time to onset of sepsis is not a factor that helps distinguishing bacterial from fungal etiologies. In a prospective study of 136 patients with candidemia, one-third of candidemia occurred within the first 5 d of ICU admission.[15] The clinical manifestations of *Candida* sepsis are not strain-dependent. In the study by Wisplinghoff et al., the inflammatory responses, clinical course (development of sepsis, severe sepsis, septic shock) or outcome were comparable in patients with bloodstream infections caused by *C. albicans* and non-*albicans Candida* species.[13] Thus, with rare exceptions fungal sepsis does not present with specific clinical manifestations or laboratory abnormalities and thus remains a real challenge for physicians.

Diagnosis

Invasive candidiasis is often fatal unless treated promptly with antifungal agents active against the infecting *Candida* species.[23,57,58] Hence, the absolute need to initiate prompt diagnostic measures. Notwithstanding the problems associated with the lack of specificity of risk factors, clinical and radiological manifestations, early diagnosis of fungal infection is difficult for three main reasons: (1) the yield of blood cultures is typically in the range of 50% to 70%,[59] (2) identification of the *Candida* species and antifungal susceptibility testing take several days, (3) deep tissue sampling is challenging especially in unstable patients and may not be possible in thrombocytopenic or coagulopathic patients. In patients with hepatic candidiasis, biopsy had a sensitivity of 61% in treatment naïve patients which dropped to 30% in patients treated with antifungal agents.[60] There is therefore an urgent need to improve our diagnostic armamentarium. Non-culture-based diagnostic methods rely on the detection of circulating fungal metabolites, antigenic components of the fungal cell wall, antibodies, and fungal DNA.

β-D-glucan (BDG)

BDG, a cell wall component of *Candida* and other fungi with the exception of cryptococci and zygomycetes, has been proposed as a biomarker of invasive fungal infections. Two recent systematic reviews have assessed the performance of various commercially available BDG tests for the diagnosis of invasive fungal infections.[61,62] Most of these studies were conducted in hemato-oncological patients with just a few focusing on ICU patients. Sensitivities and specificities of BDG vary widely, ranging from 57% to 97%, and from 56% to 93%.[62] In patients with proven infections, the pooled sensitivity of BDG was 79.1% (95% CI, 68.9–86.7%) and the specificity was 87.7% (95% CI, 82.4–91.6%). Based on an analysis of 11 selected studies, the sensitivity of BDG for the diagnosis of probable or proven *Candida* infections was 75%. A very high specificity, positive and negative predictive values were noted when two consecutive positive assays were taken into account.[61] Hemodialysis, severe mucositis, systemic bacterial infections, antibiotic therapy or human blood products have been linked to false positives especially in high-risk patients.[63] In a recent study in high-risk surgical ICU patients, BDG (Fungitell) was found to be superior to colonization indexes and to the *Candida* score for the diagnosis of intra-abdominal candidiasis.[64] Sensitivity of two consecutive positive tests was 65% and the specificity 78%. Interestingly, a positive BDG test anticipated the diagnosis of intraabdominal candidiasis by a median of 5 d. Of note, galactomannan assays are often performed together with BDG. A positive BDG and a negative galactomannan suggests candidiasis, whereas the reverse suggests of aspergillosis. In the recently published Surviving Sepsis Campaign Guidelines, BDG was given a 2B grade of recommendation for the diagnosis of invasive candidiasis.[65]

Mannan and anti-mannan antibodies assays

In a metaanalysis of 14 primarily retrospective studies of which seven were conducted in ICU and surgical patients, the detection of circulating mannan had a sensitivity of 58% (95% CI, 53–62) and a specificity of 93% (95% CI, 91–94) for the diagnosis of invasive candidiasis.[66] The sensitivity of the anti-mannan antibody assay was 59% (95% CI, 54–65) and the specificity 83% (95% CI, 79–97). Combining the two tests increased the sensitivity to 83% (95% CI, 79–87), but it did not improve the specificity (86%, 95% CI, 82–90). The sensitivity was higher for *C. albicans* than for *C. glabrata* or for *C. tropicalis*. In about three quarters of the candidemic patients one of the two tests was positive by a mean of 6 to 7 d prior to the results of blood cultures. In the Surviving Sepsis Campaign Guidelines, mannan and anti-mannan antibody assays were given a 2C grade of recommendation for the diagnosis of invasive candidiasis.

Polymerase chain reaction (PCR)

Detection of fungi by PCR is a real challenge. One of main reason is that the fungal cell wall interferes with cell lysis and the release of DNA resulting in false-negative signals. Fungal PCR technology is also prone to false-positive results because of exogenous contamination by fungal saprophytes or pathogens. It is obviously beyond the scope of this article to discuss the difficulties encountered in the development of panfungal and species-specific PCR technology and the various steps undertaken for improvement.[67] Suffice it to say that a great diversity of PCR assays (standard, nested, and real-time PCRs) and fungal targets (rRNA, cytochrome P450, L1A1, and several other genes) have been elaborated and chosen for the detection of fungal nucleic acids in the systemic circulation and tissues of patients with suspected infections. More than 50 PCR studies focusing on the diagnosis of invasive candidiasis were reviewed recently.[68] PCR turned out to be positive significantly earlier than standard culture methods. Overall, the pooled sensitivity and specificity for candidemia was 95% and 92%, respectively. In 142 surgical patients with bacterial and fungal sepsis, the recovery rates of pathogens with the SeptiFast multiplex technology were 78.6% for gram-negatives, 50% for fungi, and 47.6% for gram-positives. Moreover, detection of pathogen by PCR correlated with disease severity even if the blood cultures remained negative. Using the same multiplex PCR technology for the diagnosis of infection in febrile neutropenic cancer patients, Lamoth et al. identified 5 *Candida* infections that were not detected by blood cultures.[69] More recently, *Candida* real-time PCR performed in whole blood, plasma or serum was compared with the BDG assay in 55 patients with invasive candidiasis of whom 17 had candidemia, 33 deep-seated candidiasis, and 5 a combination of the two.[70] Plasma or serum PCRs were found to be more sensitive than BDG (80% vs 56%; $P = 0.03$), especially for deep-seated candidiasis (88% and 62%), but had similar specificity (70% vs 73%; P = NS). The same species of *Candida* were identified by PCR and culture in 82% of the patients. When combining blood culture with PCR or BDG the sensitivity reached 98% and 79%, respectively. In another study, PCR-based pathogen detection led to more rapid use of antifungal therapy when compared with conventional microbiological methods.[25] Most recently, the first results of a novel whole blood T2 magnetic resonance-based (T2MR) biosensing technology platform were published.[71] Combining PCR technology and nanoparticle-based hybridization, the technology allowed a rapid (less than 3 h), accurate and reproducible detection of 1 CFU per milliliter of 5 *Candida* species. Spiked blood samples analyzed by T2MR and conventional blood cultures revealed excellent positive (98%) and negative (100%) agreements. Unfortunately, given the lack of commercially available tests, fungal PCR assays remain at this stage available only in a limited number of skilled laboratories and mostly for research purposes only.

Prophylactic, Preemptive, and Targeted Antifungal Therapies

Appropriateness and timing of initiation of antifungal therapy have a crucial impact on the outcome of invasive candidiasis. Several studies have shown that inappropriate empirical therapy or delays in the introduction of appropriate antifungals are associated with an increased mortality in patients with candidemia or septic shock due to *Candida*.[9,57,58,72] Retrospective cohort studies demonstrated stepwise increases of mortality as a function of the time that elapsed between the first positive blood culture and initiation of fluconazole therapy.[9,57,58,72] At face value these data suggest a role for empirical or preemptive therapy in the management of invasive candidiasis. Yet, criteria for initiating empirical antifungal therapy in fungal sepsis remain ill defined and should be balanced against the potential risks of toxicity, selection of resistance, and treatment costs.[1,73] In the 2009 clinical practice guidelines of the Infectious Diseases Society of America (IDSA), it was suggested to consider empirical antifungal therapy in critically ill patients with risk factors for invasive candidiasis and no other known cause of fever.[74] Unfortunately, an early and accurate diagnosis of *Candida* infections is a difficult task and the place of *Candida* scores, colonization indexes, and other non-conventional diagnostic tools in facilitating the identification of patients who may benefit from early interventions remain to be established. Antifungal prophylaxis may be reasonable in ICU patients with a risk of infection greater than 10%. However, one has to acknowledge that this cut-off risk value is quite arbitrary and not supported by strong data. Reduction in the rate of *Candida* infections with the use of fluconazole prophylaxis has been demonstrated in some clinical trials and metaanalyses.[75-79] However, whether this prophylaxis strategy can provide a survival benefit is still controversial.

With the advent of the lipid formulations of amphotericin B, the newest triazoles (voriconazole and posaconazole) and the echinocandins (caspofungin, anidulafungin, and micafungin) the antifungal armamentarium has expanded quite substantially. Over the last 2 decades, numerous clinical studies have compared the efficacy and safety of the 3 major classes of systemic antifungal agents (i.e., polyenes, triazoles, and echinocandins) for the management of invasive candidiasis. Most of the large phase III clinical trials have enrolled non-neutropenic patients with candidemia with a limited number

Table 2. Summary of the IDSA clinical practice guidelines for the management of candidemia in non-neutropenic patients[74]

Management according to clinical condition and microbiological documentation	Recommendations
Initial therapy	Fluconazole A-I Echinocandin A-I
Moderately severe to severely ill	Echinocandin A-III
Recent azole exposure	Echinocandin A-III
Less critically ill and no recent azole exposure	Fluconazole A-III
C. glabrata	Echinocandin B-III
C. parapsilosis	Fluconazole B-III
Step-down therapy for clinically stable and isolate susceptible to fluconazole	Echinocandin to fluconazole A-II AmB-d or L-AmB to fluconazole
Duration of therapy	Two weeks after clearance of *Candida* bloodstream infection and resolution of symptoms: A-III
i.v. catheter removal	A-II

AmB-d, Amphotericin B deoxycholate; L-AmB, Lipid formulation of AmB

Table 3. Summary of the ESCMID guidelines for initial targeted treatment of candidemia and invasive candidiasis[93]

Antifungal therapy	Recommendations
Echinocandins:	
Anidulafungin	A-I
Caspofungin	A-I
Micafungin	A-I
Azoles:	
Fluconazole	C-I
Itraconazole	D-II
Posaconazole	D-III
Voriconazole	B-I
Polyenes:	
AmB deoxycholate	D-I
AmB colloidal dispersion	D-II
AmB lipid complex	C-II
AmB liposomal	B-I

AmB, Amphotericin B.

of deep-seated *Candida* infections.[39,80-83] These clinical studies have shown that triazoles and echinocandins are at least as efficacious as and under most instances better tolerated than deoxycholate or liposomal amphotericin B with overall response rates in the range of 60% to 75%.[5] A recent randomized trial suggested that anidulafungin might be superior to fluconazole as global treatment responses, clinical and microbiological successes evaluated at the end of intravenous or of all therapy were higher in patients treated with anidulafungin than in those treated with fluconazole.[84] In the recent review article of seven clinical trials by Andes et al., the use of an echinocandin therapy also reduced mortality (OR, 0.65; 95% CI 0.45–0.94; $P = 0.02$). Step-down therapy to fluconazole is recommended for patients who have improved clinically and who are infected with isolates susceptible to fluconazole.[81,83,85] Echinocandins should also be preferred in case of recent azole exposure or infections due to azole-resistant strains (such as *C. glabrata*). In contrast, it might be preferable to use fluconazole for infections due to *C. parapsilosis* because of lower MIC values. However, it remains to be demonstrated whether fluconazole therapy translates into better clinical and microbiological responses. For non-critically ill patients, fluconazole can be used as an empirical therapy for suspected invasive *Candida* infections. Given the increasing occurrence of infections by non-*albicans Candida* species in the ICUs, the selection of empirical antifungal therapy should always be tailored to local resistance patterns. Finally, until now there are no data supporting the superiority of combination antifungal therapy over monotherapy.[86] A summary of the main recommendations of the 2009 guidelines of the Infectious Diseases Society of America (IDSA) and of the 2012 guidelines of the Fungal Infection Study Group of the European Society for Clinical Microbiology and Infectious Diseases (ESCMID) for the treatment of candidiasis are shown in **Table 2** and in **Table 3**.

Adequate source control improves the outcome of patients with severe *Candida* infections.[87] In particular, central venous catheter removal has been associated with shorter duration of candidemia and reduced mortality.[88-90] But this issue remains controversial. Indeed, catheter removal was associated with better outcome ($P = 0.0001$) in a study of 1915 patients derived from seven recent clinical trials of invasive candidiasis with a patient-level quantitative assessment.[91] In contrast, early (i.e., within 24 or 48 h after treatment initiation) central venous catheter removal did not translate into clinical benefit in a study of 842 patients with candidemia who were followed prospectively.[92]

Conclusions

Fungal infections are associated with high mortality in critically ill patients and delayed antifungal treatment contributes to poor outcome. As the clinical manifestations of fungal infections are non-specific, diagnosis and management of fungal infections

remains a challenge. The increase in invasive fungal infections and the emergence of other than *C. albicans* species with reduced susceptibilities or intrinsic resistances to azoles highlight the absolute need of developing new diagnostic tools that could help identify among critically ill patients with invasive candidiasis those who may benefit from either prophylactic, preemptive, or empirical treatment strategies.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Acknowledgment

The research leading to these results has received funding from the European Community's Seventh Framework Programme (FP7-2007-2013) under HEALTH-F2-2010-260338-ALLFUN.

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