Diagnosis and Treatment of Candidemia in the Intensive Care Unit

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Abstract

Candidemia is the fourth most frequent health care-associated bloodstream infection, and the most frequent severe fungal infection developing in critically ill patients in intensive care units (ICUs). Diagnosis of candidemia in ICU patients is a complex task made of both early and late assessments involving both conventional diagnostic methods and novel rapid tests. Management strategies to optimize treatment of candidemia can be challenging and include starting early adequate therapy, use of an adequate dose and duration of therapy, de-escalating treatment whenever possible, and early discontinuation of useless antifungals in those with no definitive diagnosis of fungal infection. Herein, we will discuss recent epidemiological data on candidemia in ICUs and current diagnostic techniques before concentrating on antifungal treatments.

Keywords
- *Candida*
- ICU
- diagnosis
- biomarker
- pre-emptive
- echinocandins
- source control
- antifungals

Candidemia is the fourth most frequent health care-associated bloodstream infection, and the most frequent severe fungal infection developing in critically ill patients in intensive care units (ICUs).[1–4] Up to 33 to 55% episodes of candidemia have been estimated to occur in ICU wards, with a cumulative incidence of 3.5 to 10 episodes per 1,000 ICU admissions, with an increasing trend over time.[4–11] The most frequent *Candida* species causing candidemia in ICU are *Candida albicans* (54–70%), followed by *Candida glabrata* (13–15%) and *Candida parapsilosis* (8–19%).[7,8,10–12]

In the EPIC II point-prevalence study conducted in 1,265 ICUs in 76 countries, mortality of candidemia was higher than those of bloodstream infections caused by Gram-positive and Gram-negative bacteria (43 vs. 25 and 29%, respectively).[9,11] Similar results were found in the observational, prospective, multicenter EUROBACT study, conducted in 162 ICUs in 24 countries; 28-day mortality of candidemia was 41 versus 34 and 35% in bloodstream infections caused by Gram-positive and Gram-negative bacteria, respectively.[12,13] Candidemia tends to occur relatively late during ICU stay. The median times from ICU admission to invasive candidiasis (IC) or candidemia were 10 and 19 days in the two studies, respectively.[14,15] This late onset suggests that the sepsis-induced immunosuppression response[16] may contribute to this infection.

In light of the above epidemiological and mortality data, recognizing and appropriately treating patients with candidemia is considered an essential component of an optimized approach to ICU septic patients.[17–19] In this narrative review, we discuss the current state of the art regarding the diagnosis and therapy of candidemia in the ICU.

Diagnosis

There are no specific symptoms of candidemia, with fever unresponsive to antibacterial therapy being the most common clinical presentation.[20] The use of laboratory tests for the diagnosis of candidemia is therefore fundamental and characteristically influenced by two therapeutic considerations. First,

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candidemia is a severe infection needing antifungal treatment. Although this may seem obvious nowadays, the need for antifungal therapy in candidemic patients had been debated long in the past, and eventually accepted only in the mid-1970s and early-1990s for neutropenic and nonneutropenic patients, respectively.[21–25] The reason for this behavioral change was that candidemic patients with mild symptoms and no evidence of hematogenous dissemination, previously considered at low risk and left untreated to avoid amphotericin B toxicity, were convincingly shown to have, conversely, an unacceptably high mortality without treatment.[21,22] Second, candidemia should be treated promptly. Indeed, a delayed diagnosis—with consequent delayed therapy—has been associated with increased mortality in different studies.[26–28]

The major diagnostic considerations stemming from these two therapeutic considerations are: (1) treat all patients with candidemia and (2) make an early diagnosis. However, no currently available diagnostic test for candidemia has concomitantly 100% sensitivity and 100% specificity, and the turnaround time of the different tests varies markedly. Consequently, different complementary pieces of information may become available at different times. Therefore, diagnosis of candidemia is a complex task made of both early and late assessments (e.g., at the onset of symptoms and after blood culture results), to maximize the overall diagnostic performance and guarantee as much as possible both an early adequate therapy in patients with candidemia and the safe discontinuation of useless antifungals in those with no fungal infection.

A possible diagnostic work-flow to be adopted in ICU patients with suspected candidemia, based on the recent suggestions of a combined task force involving the systemic inflammation and sepsis and infection sections of the European Society of Intensive Care Medicine (ESICM) and the critically ill patients study group of European Society of Clinical Microbiology and Infectious Diseases (ESCMID),[17] is shown in ►**Fig. 1**, while a brief summary of the characteristics of laboratory tests for the diagnosis of candidemia is provided in ►**Table 1**.

Blood Cultures

Although remaining the diagnostic reference standard for candidemia, blood cultures are hampered by their suboptimal sensitivity, usually not higher than 63 to 83%.[20,29–36] This suboptimal sensitivity does not reflect the inability of blood cultures to detect viable *Candida* species, but more likely other factors, such as an intermittent/transient release of viable yeasts in the bloodstream, or their absence in the captured volume of blood.[29–31] Another critical limitation of blood cultures is their slow turnaround time (up to 48–72 hours).[20,30,32] Because of these limitations, blood cultures are not useful for early therapeutic decisions at the onset of symptoms (i.e., antifungal therapy yes versus no), which are usually based on risk prediction models and/or rapid nonculture diagnostics.

Still, blood cultures remain essential within a comprehensive diagnostic approach, as they allow both identification of *Candida* at the species level and susceptibility testing.[20,37,38]

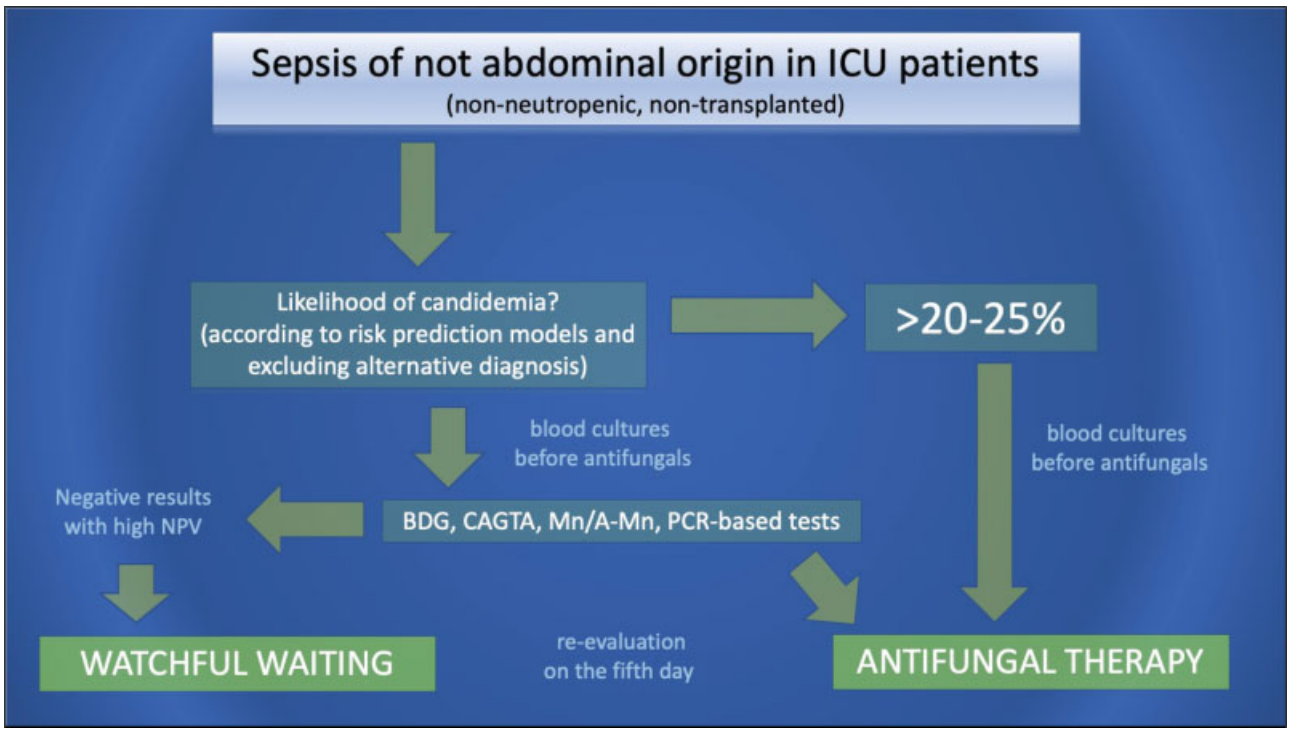

Fig. 1 Possible diagnostic algorithm in ICU patients with suspected candidemia according to the combined task force of the systemic inflammation and sepsis and infection sections of ESICM and the critically ill patients study group of ESCMID.[17] (Modified from Martin-Loeches et al 2019[17].) A-Mn, antimannan antibodies; BDG, (1,3)-β-D-glucan; CAGTA, *C. albicans* germ tube antigen; ESCMID, European Society of Clinical Microbiology and Infectious Diseases; ESICM, European Society of Intensive Care Medicine; ICU, intensive care unit; Mn, mannan antigen; PCR, polymerase chain reaction.

Table 1 Main characteristics of different laboratory tests for the diagnosis of candidemia

Test	Characteristics
Blood cultures	Allow identification at species level and susceptibility testing Suboptimal sensitivity Long turnaround time (reduced with MALDI-TOF technology)
BDG	Rapid turnaround time High NPV Suboptimal specificity
Mn/A-Mn	Rapid turnaround time Variable performance across studies Reported low PPV
CAGTA	Rapid turnaround time Heterogeneous specificity Reported possible better performance in candidemia with deep-seated infection than without deep-seated infection
PCR-based methods	Rapid turnaround time Promising results of some newer methods Heterogeneity in the performance of first developed in-house and commercial methods Inability to detect all *Candida* species Usually expensive

Abbreviations: A-Mn, antimannan antibodies; BDG, (1,3)-β-D-glucan; CAGTA, *C. albicans* germ tube antigen; MALDI-TOF, matrix-assisted laser desorption/ionization time-of-flight; Mn, mannan antigen; NPV, negative predictive value; PCR, polymerase chain reaction; PPV, positive predictive value.

Therefore, they should always be performed in the suspicion of candidemia, independent of the availability and results of noncultural diagnostics, possibly before treatment initiation to increase sensitivity.[17,32] Of note, after a blood culture turns positive, time to identification (but currently still not to susceptibility testing, at least outside research laboratories[39–46]) may be shortened by the use of matrix-assisted laser desorption/ionization time-of-flight (MALDI-TOF) technology (with >90% accuracy).[47,48] Huang and colleagues reported that the use of MALDI-TOF was able to reduce time to identification from 84 to 56 hours compared with conventional methods in a study involving 501 patients with bacteremia or candidemia.[49] Fluorescence in situ hybridization (PNA-FISH Yeast Traffic Light assay) differentiates between *C. albicans*, *C. parapsilosis* and *C. tropicalis*, and *C. glabrata*/*C. krusei* (less or not azole susceptible) within 1 hour of blood culture positivity.[50]

Risk Prediction Models

In general, risk prediction models, which attempt to quantify the risk of a certain disease, can be used in two different ways: (1) before the development of the disease, mainly with prevention purposes; (2) at the onset of the disease, for triggering dedicated diagnostic algorithms and/or guiding early therapeutic choices. In this latter situation, which is usually the case for candidemia, risk predictions models can be thought as an early component of the diagnostic process.

As such, being based on readily available clinical and possibly microbiological (colonization) information, their usually high negative predictive value (NPV) for candidemia allows to avoid, since the onset of the disease, useless fungal diagnostics and antifungal treatments in patients unlikely to have candidemia (i.e., those with low scores according to risk prediction models).[17] Conversely, since their positive predictive value (PPV) is very often modest, further diagnostics are indicated in patients deemed at risk of candidemia by prediction models. However, whether or not empirical antifungals should be administered in all patients at risk of candidemia according to prediction models (while waiting for the results of further diagnostics) is still a matter of debate.[3,51,52] A panel of experts has recently recommended to consider empirical antifungal therapy in ICU patients at risk of candidemia with septic shock and multiorgan failure (MOF; strong recommendation, low quality of evidence).[17] In addition, the panel has proposed an algorithm in which empirical antifungals are to be considered in septic ICU patients with high probability of candidemia (>20–25% according to risk prediction models), independent of the presence of septic shock and MOF.[17]

Most of the first proposed models were based on the presence of *Candida* colonization of nonsterile sites and/or on the intensity of *Candida* colonization (dependent of the number of colonized sites).[53–55] Some subsequent prediction models are conversely based exclusively on clinical variables and patients' medical history, and not on colonization. For example, predictive rules for the development of IC (including not only candidemia but also deep-seated candidiasis) in surgical ICU patients have been developed by Paphitou and colleagues.[56] The highest risk of developing proven or probable IC (20%) was observed in patients with at least one among three possible predisposing factors (diabetes, total parenteral nutrition prior to ICU admission, or new-onset hemodialysis) plus ICU stay longer than 4 days, use of broad-spectrum antibiotics, and no use of antifungals from day −7 to +3 with respect to ICU admission.[56] In another study conducted in cardiothoracic ICU patients, clinical variables that increased the risk of candidemia were ongoing mechanical ventilation ≥10 days, hospital-acquired bacterial infection, cardiopulmonary bypass time >120 minutes, and diabetes mellitus.[57] The model showed a NPV of 90 to 100%.[57] According to the score proposed by Ostrosky-Zeichner and colleagues, and based on a large cohort of 2,890 ICU patients, the combination of antibiotic therapy and presence of a central venous catheter (CVC) in the first 3 days of ICU stay plus at least two among surgery, immunosuppression, pancreatitis, total parenteral nutrition, and steroid use was associated with a 10% risk of developing IC, with 97% NPV.[58] Guillamet and colleagues developed a score based on clinical variables for predicting the risk of candidemia in 2,597 patients with severe sepsis or septic shock.[59] The independent predictors of candidemia included in the model were prior antibiotics within 30 days (+2 points), CVC (+2 points), admission from a nursing home (+2 points), total parenteral nutrition (+2 points), admission from another hospital (+1 point), mechanical ventilation (+1 point), and lung as the presumed source of sepsis (−6 points). The risk of candidemia was 1.2% for a cumulative score of –6 points and

43% for a cumulative score of +8 points.[59] According to the Nebraska Medical Center rule, developed in a cohort of 352 ICU patients, a NPV of 99% for IC may be obtained by employing a model based on antibiotic therapy, CVC, total parenteral nutrition, steroid therapy, abdominal surgery, and previous length of ICU stay.[60]

The "*Candida* score," developed by León and colleagues in a cohort of 1,699 ICU patients, is based on both clinical and microbiological information.[61] The independent predictors of IC included in the model were multifocal *Candida* colonization (+1 point), surgery on ICU admission (+1 point), severe sepsis (+2 points), and total parenteral nutrition (+1 point). A score of >2.5 points was proposed as a cut-off for prompting empirical antifungal therapy based on a risk ratio of 7.35.[61] Finally, Playford and colleagues by using two threshold scores identified three patient cohorts: those at high risk (score ≥ 6, 4.8% of total cohort, PPV: 11.7%), those at low risk (score ≤2, 43.1% of total cohort, PPV: 0.24%), and those at intermediate risk (score 3–5, 52.1% of total cohort, PPV: 1.46%).[14] Most prediction models have been internally or externally validated.[57,59–63]

Rapid Tests Based on Antigen/Antibody Detection

The detection of fungal antigens or antifungal antibodies in blood may accelerate the diagnosis of candidemia, in turn anticipating administration of antifungals in those true cases who are not treated empirically. The therapy based on the results of antigen/antibody tests or other rapid methods is commonly defined as pre-emptive therapy.[64]

(1,3)-β-D-Glucan

The (1,3)-β-D-glucan (BDG) test is based on the detection of the polysaccharide BDG in serum.[65,66] BDG is a cell-wall component of many pathogenic fungi, including *Candida*.[65–67] The nearly pan-fungal nature of BDG might appear as an important limitation for using it as a diagnostic tool for candidemia in the ICU. However, it should be noted that the other two most prevalent invasive fungal diseases (IFDs) in ICU patients (and less frequent than candidemia) are invasive pulmonary aspergillosis and *Pneumocystis jirovecii* pneumonia, in which serum BDG may well be positive, but often accompanied by pulmonary radiological signs. Conversely, in septic ICU patients without lung involvement a positive serum BDG is usually indicative of candidemia rather than other IFD.

In observational, prospective studies conducted in ICU patients at risk of candidemia, BDG showed high NPV (>95% in most studies), which thus makes candidemia unlikely when the test is negative.[68–77] It should nonetheless be noted that a few clinical experiences have suggested a possible reduced sensitivity of BDG for candidemia due to *C. parapsilosis*.[69,78,79] Therefore, some caution in discontinuing antifungals based on a negative BDG may be considered in centers with a high prevalence of candidemia due to *C. parapsilosis*, although there is also a need for large, prospective, confirmatory studies to definitely confirm this hypothesis. In contrast with this high NPV, the PPV is usually low (less than 20%) although it may increase with a second test as reported by Martín-Mazuelos and colleagues who found that BDG > 80 pg/mL in two consecutive measurements had a PPV of 35%.[80]

A disadvantage of the BDG test reported by many authors is its suboptimal specificity due to multiple, possible causes of false-positive results (e.g., hemodialysis, transfusions of blood and/or blood derivatives, treatment with immunoglobulins or albumin, bacteremia, treatment with β-lactams, use of non-BDG-free laboratory equipment).[65,81–93] However, it is also true that the frequency of false-positive results has likely been reduced in recent years, owing to the availability of modern dialysis membranes not releasing BDG, glucan-free laboratory material, surgical gauzes and blood products without or with a very few amount of BDG, and the evidence of a reduced number of false-positive results in patients with bacteremia and/or treated with β-lactams than previously suggested.[94–99] Furthermore, not all studies reporting a low BDG specificity were conducted in ICU patients deemed to be at risk of candidemia and with a consistent clinical picture (i.e., those in whom its PPV is maximized), but some also included other patients with a low likelihood of candidemia.[75]

In an attempt to balance together advantages (early diagnosis) and disadvantages (false-negative and false-positive results) of using serum BDG in ICU patients at risk of candidemia, Giacobbe and colleagues conducted a posthoc analysis of a prospective, observational study evaluating the diagnostic performance of serum BDG in 186 septic ICU patients with *Candida* score ≥ 3.[75,100] The authors employed a desirability of outcome ranking (DOOR) method (i.e., to balance, on the basis of blood cultures results, the hypothetical benefits and harms of using a BDG-based strategy for deciding whether or not to administer early pre-emptive antifungals versus using an universal strategy based on the empirical administration to all patients at risk). According to the study results, the BDG-based strategy had a 67.8% probability (95% confidence intervals [CIs] 67.3– 68.3) of prompting a "more desirable" therapeutic decision than the empirical strategy.[100] However, as also recognized by the authors, several important issues, including arbitrariness in the definition of the ranked outcome and in the interpretation of results, should be resolved before reliably using DOOR methods for this purpose.[100]

Randomized controlled trials (RCTs) assessing the impact of BDG-based pre-emptive decisions (early treatment, discontinuation) have provided some conflicting, or perhaps, still incomplete evidence. In the EMPIRICUS RCT, empirical and not pre-emptive therapy was evaluated, but some information regarding the possible usefulness of BDG testing can be garnered from the subgroup of patients with positive serum BDG. Indeed, fungal infection-free 28-day survival in ICU patients with severe sepsis and positive serum BDG (>80 pg/mL) was higher in BDG-positive patients treated with empirical micafungin (58/91, 64%) than BDG-positive patients receiving placebo (47/84, 56%), with a trend toward a potentially beneficial effect (hazard ratio [HR]: 1.41; 95% CI: 0.85–2.23).[101] Conversely, a similar trend was not observed when the endpoint was limited to 28-day mortality (with or without fungal infection) (HR: 0.95; 95% CI: 0.55–1.75).[101] In an unblinded, single-center RCT, Rouzé and colleagues

assessed the percentage of early discontinuation for reasons other than death in patients with risk factors for IC and receiving empirical antifungals for a consistent clinical presentation.[102] Patients were randomized in two groups: (1) biomarker strategy (discontinuation of empirical antifungals in case of negative BDG, mannan (Mn), and antimannan tests); (2) routine strategy (14 days of therapy in patients improving after antifungal treatment according to the investigator's judgment). Early discontinuation of antifungals occurred more frequently in the biomarker strategy group (29/54, 54%) than in the routine strategy group (1/55, 2%) (odds ratio [OR]: 63; 95% CI: 8–486).[102] No differences were detected in subsequent probable/proven IC, subsequent antifungal treatments, length of ICU stay, and mortality.[102] Other RCTs evaluating the impact of BDG results on early therapeutic choices are ongoing or have been recently completed (NCT02734550, NCT03117439, NCT03090334, and NCT03538912).[103] Their results are awaited to ultimately firmly delineate the impact of BDG results on pre-emptive therapeutic choices in ICU patients with suspected candidemia.

Mannan and Antimannan

The polysaccharide Mn is one of the major components of the *Candida* cell wall, and can be found in serum during candidemia or other forms of IC.[104,105] Since the presence of circulating antimannan antibodies (A-Mn) may correlate with a reduction in circulating Mn antigens,[106] the diagnostic performance of combined Mn/A-Mn testing was evaluated and deemed preferable to either Mn or A-Mn.[105,107,108] However, the PPV of the A-Mn component may be low due to previous *Candida* infections or *Candida* colonization,[20,109,110] and also variable diagnostic performances of the combination Mn/A-Mn have been reported across different studies.[111–117]

With regard to experiences restricted to ICU populations, in a retrospective case–control study of 43 ICU patients with candidemia and 67 controls, Mn/A-Mn testing showed 59% sensitivity and 65% specificity for the diagnosis of candidemia.[73] In another study among 233 ICU patients with severe abdominal conditions, 31 developed IC (11 candidemia; 20 intra-abdominal candidiasis).[117] The diagnostic performances of Mn and A-Mn were evaluated separately. Mn showed 43% sensitivity, 67% specificity, 17% PPV, and 89% NPV, whereas A-Mn showed 26% sensitivity, 89% specificity, 27% PPV, and 89% NPV.[117] In the previously cited RCT conducted by Rouzé and colleagues, decisions regarding continuation or discontinuation of antifungals were based on a combination of BDG and Mn/A-Mn testing, but their separated impact was not evaluated.[102] In the discussion, the authors reported that the decision of continuing antifungals was only based on Mn/A-Mn in three cases.[102]

Other Antigen/Antibody-Based Tests

The *C. albicans* germ tube antigen (CAGTA) test is able to detect specific antibodies for a fungal hyphal protein (namely, Hwp1), which is expressed by *Candida* spp. during biofilm formation and tissue invasion.[118,119] Although the hyphal protein was initially found in *C. albicans* (hence the name of the test), the CAGTA assay can be positive also in IC caused by other *Candida* species.[20,117,120–122] Experience in the use of CAGTA for IC is limited compared with BDG and Mn/A-Mn. According to the results of a recent meta-analysis of seven studies,[117,119,120,122–125] the pooled sensitivity and specificity of CAGTA for the diagnosis of IC were 65% (95% CI: 59–73) and 76% (95% CI: 58–88).[126] An important heterogeneity in specificity was detected.[126] Notably, in one study comparing the diagnostic performance of CAGTA in 29 patients with candidemia plus deep-seated candidiasis versus 21 patients with isolated candidemia, sensitivity was 69 and 5% in the former and in the latter, respectively.[119]

Some tests for detecting *Candida* protein antigens have been hypothesized or developed, but their applicability in clinical practice remains low because of low sensitivity, possibly linked to rapid clearance, formation of immune complexes, and low serum concentrations.[127–135] Suboptimal performances and lack of standardization are also important limitations of tests based on the detection of the *Candida* sugar alcohol D-arabinitol in serum.[128,133,136,137]

Combinations of Available Antigen/Antibody Tests

Some authors have tried to combine the use of available tests, to improve their usefulness in guiding pre-emptive therapeutic decisions. Martínez-Jiménez and colleagues evaluated the combined use of different, possible combinations of antigen/antibody markers (BDG, Mn, A-Mn, CAGTA) for differentiating candidemia (31 patients) from bacteremia (50 patients).[124] The best combinations found by the authors were BDG plus CAGTA (97% sensitivity, 84% specificity, 79% PPV, 98% NPV) and Mn plus CAGTA (94% sensitivity, 86% specificity, 81% PPV, 96% NPV). Since the prevalence of candidemia in the study sample was quite high (38%), the authors also extrapolated their results to lower prevalences of candidemia (5–10%), showing a NPV of approximately 100% for both BDG plus CAGTA and Mn plus CAGTA.[124] Subsequently, the same authors conducted a prospective study in which they measured BDG and CAGTA serum levels in 63 ICU and 37 non-ICU patients receiving empirical antifungals in the suspicion of IC, to evaluate the potential for using the BDG/CAGTA combination to guide safely discontinuation of antifungals when both the markers are negative.[121] In the overall study population, the NPV of the combination was 97%, reaching 100% in the subgroup of ICU patients.[121] Another experience regarding the combined use of BDG and CAGTA is that of León and colleagues, in which the combination (with the criterion for positivity being set to positivity of at least one of the two markers) showed 90% sensitivity, 42% specificity, 19% PPV, and 97% NPV for the diagnosis of IC in 233 ICU patients with severe abdominal conditions.[117] A lower discriminatory ability was observed for combinations involving Mn and/or A-Mn.[117]

With the aim of reducing costs of combined testing, and also to explore combinations that may be available in a higher number of laboratories, Giacobbe and colleagues assessed the performance of serum BDG combined with the widely used serum procalcitonin (PCT) test for

differentiating between candidemia and bacteremia in a retrospective cohort of 166 ICU patients (73 with candidemia and 93 with bacteremia).[71] The rationale was based on the fact that serum PCT usually remains within the normal concentration range or is only slightly elevated in patients with candidemia, differently from bacteremia, during which high serum PCT concentrations are frequently measured.[138–143] Interestingly, while the NPV for candidemia observed by combining a positive BDG with low PCT levels (<2 ng/mL) was similar to that of a positive BDG alone (95 vs. 93%, respectively), the PPV of the combination was considerably higher than that of BDG alone (96 vs. 79%, respectively). Notably, PPV and NPV of PCT alone (66 and 84%, respectively) were markedly low compared to both those of BDG alone and those of the BDG/PCT combination.[71]

Rapid Tests Based on Polymerase Chain Reaction

The possibility of rapidly identify *Candida* spp. in the blood or serum of patients with candidemia by means of PCR-based techniques has been extensively studied in the last decades, prompted by the inherent advantages of increased sensitivity compared with blood cultures, very rapid turnaround time, and rapid identification at the species level.[20,118] In a meta-analysis of 54 studies, pooled sensitivity and specificity for the diagnosis of IC (mainly candidemia) of PCR methods were 95 and 92%, respectively.[144] However, performance of both in-house and commercial PCR varied markedly across studies,[144–148] and no test has been validated for the diagnosis of candidemia through dedicated, large, multicenter experiences. In view of these considerations, PCR-based tests, although promising, have still to be included in diagnostic guidelines and standardized definitions of candidemia.[38,40,149]

Several studies have been recently published regarding the diagnostic performance of the T2Candida panel (T2 Biosystems, Lexington, MA), which is Food and Drug Administration (FDA)-cleared for the diagnosis of candidemia. The test is based on the mechanical lysis of cells, with subsequent amplification of DNA by means of PCR and target-specific primers (which enable the identification of the five most frequent *Candida* species). The amplified products are detected by measuring the agglomeration of amplicons-induced supermagnetic particles.[150,151] FDA clearance was based on the results of the DIRECT study, conducted in 1,801 hospitalized patients in whom blood cultures were ordered according to local standards of care.[151] The T2Candida panel demonstrated 91% sensitivity (95% CI: 87–94) and 99% specificity (99–100%). The median time to positive results (including species identification) and to negative results was 4.4 ± 1.0 hours and 4.2 ± 0.9 hours, respectively. A 99% NPV was estimated for a population with 10% prevalence of candidemia.[151] In a study conducted in 126 ICU patients at high risk of IC and with sepsis despite 3 days of broad-spectrum antibiotics, the sensitivity and specificity of the T2Candida panel for proven IC were 55 and 93%, respectively, with 50% PPV and 93% NPV.[152] In another study conducted among 46 patients with severe sepsis or septic shock and multiple risk factors for candidemia, the T2Candida panel showed 100% sensitivity (95% CI: 2.5–100), 92% specificity (95% CI: 78–98), 25% PPV (95% 1–81), and 100% NPV (95% CI: 90–100).[153] Of note, some authors have also suggested that a positive T2Candida test could be a potential marker of poor outcome in patients receiving empirical antifungal therapy for suspected IC.[154] In the future, it is likely that cumulative evidence from different real-life experiences will allow to precisely delineate the positioning of the T2Candida panel within diagnostic algorithms, and to maximize its cost-effectiveness (also considering the local prevalence or *Candida* species not included in the panel).[155–157]

Susceptibility Testing

Once *Candida* species responsible for candidemia are identified from blood cultures, detection of acquired resistance could be important for adjusting initially inadequate therapies and for allowing safe de-escalation to oral azole therapy whenever indicated by the patient's clinical conditions, although it should be noted that the guidelines of the Infectious Diseases Society of America (IDSA) recommend routine susceptibility testing for azole and echinocandin resistance in *C. glabrata*, while less value is attributed to routine susceptibility testing of other *Candida* species.[149] Some authors have nonetheless suggested that routine susceptibility testing of all *Candida* isolates from sterile sites could be important for registering resistance trends and for detecting the local emergence of resistance.[42,158] In resource-limited settings, susceptibility testing of *Candida* species may be limited to breakthrough infections, treatment failures, or in the presence of limited therapeutic options.[158]

Reference microbroth dilution methods suggested by the European Committee on Antimicrobial Susceptibility Testing (EUCAST) and the Clinical and Laboratory Standards Institute (CLSI), although excellent for detecting resistance, are not easy to implement in routine laboratory workflows, in which the most frequently used methods are commercial microbroth dilution tests, semiautomated broth dilution, and agar diffusion.[20] In the future, further development and validation of MALDI-TOF-based detection of resistance could help in reducing time to phenotypical susceptibility testing. Molecular methods may not be available in many laboratories, and have the limitations of identifying only already known determinants and of being of little use for detecting azole resistance, since involved genes may mutate at several locations.[41,159–162] Nonetheless, they may be of help for rapidly detecting known determinants of echinocandin resistance.[161,163–168]

Treatment

Because delayed treatment is associated with high morbidity and mortality,[3,26] many strategies have been implemented aiming to minimize the negative impact of candidemia in critically ill patients.[15,28,169] Apart from the prophylactic use of antifungal drugs for a few clinical scenarios,[170–172] ICU physicians may adopt an empirical approach relying on signs and symptoms, fungal biomarkers, and specific risk factors for IC in the absence of any identified pathogen.[173] Targeted therapy is based on microbiological evidence of an IC (e.g., a

positive blood culture for *Candida* species or positive cultures of a normally sterile site).[174] Moreover, once candidemia is diagnosed, an adequate source control of the infection (catheter removal, drainage, debridement) should be also performed as soon as possible.[3,27]

Antifungal Agents

Over the past decade, there has been a considerable research in antifungal drugs against *Candida*. To date the antifungal drugs most commonly used for the treatment of candidemia are the echinocandins (caspofungin, micafungin, and anidulafungin), azoles (fluconazole and voriconazole), and amphotericin B.[175] Doses of antifungals commonly used to treat candidemia are shown in ►**Table 2**.

Caspofungin, micafungin, and anidulafungin are echinocandins for which only intravenous formulation is available. Echinocandins target the fungal cell wall and act by inhibiting BDG synthesis, showing fungicidal activity against most *Candida* species including biofilm-forming and azole-resistant strains.[176] Intrinsic resistance to echinocandins is anecdotal but acquired resistance has been increasingly reported, especially in *C. glabrata*.[177,178] In addition, echinocandins do not achieve therapeutically effective concentrations in some tissues (e.g., eyes, central nervous system, urine) and their pharmacokinetic/pharmacodynamic (PK/PD) properties are poorly known for critically ill patients.[179]

Echinocandins appear to be as effective as and better tolerated than amphotericin B formulations[180,181] and, in two randomized trials, more effective than azoles.[182,183] Particularly, in one of these trials including 245 patients with IC (89% of them with candidemia only) anidulafungin treatment resulted in superior combined clinical and microbiological response compared with fluconazole (at 2 weeks 65 vs. 49%), although no differences were observed at 60-day mortality rates.[182] The use of echinocandins is further supported by a quantitative review of RCTs (1,915 patients, seven studies) showing that treatment with echinocandins led to decreased mortality (OR: 0.65; 95% CI: 0.45–0.94) and increased treatment success (OR: 2.33; 95% CI: 1.27–4.35).[184] Moreover, a recent propensity-score-adjusted multivariable analysis of critically ill patients with proven candidemia showed that empirical therapy with echinocandins instead of fluconazole led to lower 30-day (OR: 0.32; 95% CI: 0.16–0.66; $p = 0.002$) and 90-day mortality (OR: 0.50; 95% CI: 0.27–0.93; $p = 0.014$).[185] However, in a prospective study conducted in 29 hospitals in Spain with less severe patients (only 30% being in the ICU), empirical treatment with fluconazole was not associated with increased 30-day mortality compared with echinocandins in patients with candidemia.[174] There has been concern about the use of echinocandins as primary therapy against *C. parapsilosis* because of higher in vitro minimum inhibitory concentrations (MICs). A retrospective study on 307 episodes of *C. parapsilosis* candidemia demonstrated no difference in 30-day mortality between patients receiving an echinocandin as compared with fluconazole.[186]

Because of their efficacy, tolerability, broader spectrum, fungicidal activity, and fewer drug–drug interactions, echinocandins are currently recommended as first-line therapy in the treatment of IC in critically ill patients (►**Table 2**)[17,149,187] and are also preferred in noncritically ill patients with previous exposure to azoles and/or evidence of colonization with a *Candida* strain with reduced susceptibility to azoles.

Azoles (fluconazole and voriconazole) work by inhibiting the 14-α-demethylase enzyme which mediates the conversion of lanosterol to ergosterol in the fungus wall. This class is metabolized by P450 cytochromes, which can result in drug–drug interactions. Fluconazole is used in the treatment of candidemia as a de-escalation therapy with a significantly lower cost compared with the echinocandins. Fluconazole also remains a well-tolerated treatment of noncritically ill candidemic patients with no risk factors for azole-resistant strains.[17,149,187] Other azoles such as posaconazole, itraconazole, and isavuconazole are not approved for systemic *Candida* infections.

Amphotericin B is a polyene that acts by binding to the ergosterol in the fungal membrane. Owing to its toxicity,

Table 2 Recommended adequate doses of antifungal drugs for empirical or targeted treatment of candidemia[a]

Drugs	Adequate dose	Comment
Caspofungin	70 mg loading dose followed by 50 mg daily	Recommended as first-line therapy[17,149,187]
Anidulafungin	200 mg loading dose followed by 100 mg daily	
Micafungin	100 mg daily. No loading dose is required	
Fluconazole	12 mg/kg loading dose followed by 6 mg/kg daily	Recommended as an acceptable alternative to an echinocandin as initial therapy[17,149,187] Recommended for de-escalation therapy[17,149,187]
Voriconazole	3–4 mg/kg orally twice daily modified according to TDM	Recommended for de-escalation therapy[17,149,187]
L-AmB	3 mg/kg daily	Recommended as a reasonable alternative if there is intolerance, limited availability, or resistance to other antifungal agents[17,149,187]
ABLC	5 mg/kg daily	Not recommended
ABCD	3–4 mg/kg daily	Not recommended

Abbreviations: ABCD, amphotericin B colloidal dispersion; ABLC, amphotericin B lipid complex; L-AmB, liposomal amphotericin B.
[a]Adequate doses refer to patients with normal renal and hepatic function and those with no drug–drug interactions.

amphotericin B deoxycholate has now been replaced by better-tolerated polyenes including liposomal amphotericin B (L-AmB), amphotericin B lipid complex (ABLC), and amphotericin B colloidal dispersion (ABCD). L-AmB is widely used and has favorable pharmacokinetics along with relatively high intracellular penetration in the cerebral spinal fluid and in the eye. Both L-AmB and ABLC achieve therapeutically effective concentrations in the epithelial lung fluid of critically ill patients.[188] L-AmB is used as a first-line therapy for disseminated forms of *Candida* species infection, and as a second-line therapy for IC,[179] especially when *C. glabrata* candidemia from urinary tract source is documented.

A few more antifungals are currently under investigation for the treatment of candidemia and IC, including new compounds belonging to known classes or molecules with novel mechanisms of action.[189] Rezafungin (previously CD101; Cidara Therapeutics, Inc.) is a novel long-acting echinocandin characterized by a spectrum of activity that is comparable to the other echinocandins but also a distinct safety PK/PD profile that enables high plasma drug exposure and extended interval dosing.[190,191] In vitro, rezafungin has demonstrated potent activity against a broad range of *Candida* spp., including echinocandin- and azole-resistant strains,[192] but interlaboratory variation was observed thus warranting further investigation.[193] A multicenter, randomized, double-blind phase 2 trial evaluating the efficacy and safety of rezafungin once weekly compared with caspofungin in patients with candidemia has been recently finished (NCT023734682).

SCY-078 is a semisynthetic, triterpenoid, antifungal glucan synthase inhibitor currently in development for the treatment of invasive and mucocutaneous fungal diseases.[194] SCY-078 has shown good bioavailability and has been studied as oral and intravenous formulations with once daily administration.[194] The drug is currently in phase 3 clinical development for the treatment of IFD.

Prophylaxis

The concept of prophylaxis, introduced almost 40 years ago, refers to the administration of antifungal drugs to patients with risk factors for IC without clinical signs or symptoms of infection.[149,169] Although the benefits of antifungal prophylaxis are well established in neutropenic patients (e.g., hematological patients) or in solid organ transplant, especially in high-risk liver transplant patients,[170–172] its utility in non-immunocompromised, critically ill patients with sepsis and no confirmed fungal infection is still controversial[52,195] and is not currently recommended by the critically ill patients study group of ESCMID.[17]

Over the last decade, several studies[196–199] have focused on the prevention of fungal infections in ICU patients administering echinocandins, azoles, and oral nystatin. Despite the large number of publications, the quality of evidence still remains low in many studies, leading to uncertainty with regard to the reduction of mortality, reduction of IC, or the risks of fungal colonization.[199] Since the universal administration of antifungal prophylaxis remains an inefficient strategy that may increase subsequent azole-resistance or non-*albicans* candidemias,[200,201] it should be avoided in critically ill patients, and its use should be eventually restricted to selected ICU patients at highest risk (>10%) of IC[149,202] (surgical patients with anastomotic leakage after abdominal surgery or early re-intervention of the digestive tract).

Empirical Approach

Although prompt initiation of appropriate antifungal therapy has been associated with a reduction in mortality,[3,26–28,184] it is often delayed because of the low sensitivity of blood cultures, the time needed for blood cultures to turn positive, and the possibility of negative blood cultures also in patients with proven disease. To overcome this problem, several studies have looked to identify strategies for initiating empirical treatment based on risk factors, positive culture collected from nonsterile sites (respiratory tract, urine), clinical scoring systems, and surrogate markers of infection.

Previous studies also looked at prediction models to identify patients at highest risk for IC development. As discussed in the "Risk Prediction Models" section, these studies are frequently based on risk scores (i.e., *Candida* score, *Candida* colonization index, Ostrosky score) with very low PPV[203,204] that can lead to unnecessary antifungal treatment in a large number of patients. For example, in a prospective observational study performed in 36 ICUs, antifungal treatment was empirically administered according to *Candida* score to 180 out of 1,017 patients included in the study (17%), but only 5% of those really developed candidemia.[205]

Surrogate markers that have been evaluated in critically ill patients include BDG, Mn/A-Mn, PCR testing, and T2Candida. BDG appears to be more sensitive than *Candida* colonization scores or indices, reaching a sensitivity of approximately 90% when performed twice weekly. On the other hand, PPV of the test is very low[74,85,206,207] with a high percentage of false-positive results. According to its diagnostic performance, BDG seems to be more useful in excluding rather than diagnosing IC in the ICU setting.[72,121,124] Other studies analyzed the role of Mn/A-Mn testing,[114,208] real-time PCR[209] T2Candida[154] for implementing or discontinuing empirical antifungal therapy, but recommendations for their clinical use cannot be made because of the lack of robust data in critically ill patients.[17]

Limited clinical studies have evaluated the efficacy of empiric strategies. Three multicenter randomized clinical trials[52,101,204] evaluated empirical antifungal therapy for fungal infection suspicion in high-risk patients. None of the studies demonstrated a benefit with early antifungal therapy and no differences were observed in terms of resolution of fever, major adverse events, and mortality. Recently, Timsit et al[101] compared the outcome of a 14-day empirical course of micafungin with placebo in a prospective randomized multicenter trial including 260 nonneutropenic critically ill patients with ICU-acquired sepsis, multiple *Candida* colonization, and MOF. Although empirical use of micafungin was associated with a lower rate of new IFD diagnosis in comparison to placebo (4/128 patients [3%] vs.

15/123 [12%]; $p = 0.008$), there were no differences between the two arms regarding death and IFD free at 28 days (HR: 1.35; 95% CI: 0.87–2.08).

Despite these results, the fact is that the empirical approach remains a common practice both inside and outside ICU[154] and its role in high-risk patients still remains to be determined. In our opinion, further studies aimed to specify criteria for early initiation of antifungal therapy in critically ill patients are needed.

Until such studies will be available, empiric antifungal therapy should be considered only in patients with septic shock and MOF who have more than one extra-digestive site (i.e., urine, mouth, throat, upper and lower respiratory tracts, skin folds, drains, operative site) with proven *Candida* species colonization.[17]

Once empirical treatment is started, an echinocandin regimen should be preferred especially in hemodynamically unstable patients or those previously exposed to an azole, and in those colonized with azole-resistant *Candida* species.[17] Daily clinical revaluation should be performed, and treatment should be stopped earlier (within 4–5 days of antifungal treatment) in patients who do not clinically improve or in those with no positive cultures or positive surrogate markers.[72,121] Otherwise, a 14-day course of empirical therapy may be administered.[210]

Definitive Therapy

Regarding the treatment of proven infections, the last IDSA and European guidelines[17,149,187] recommend first-line treatment for *Candida* spp. infection with an echinocandin (e.g., caspofungin, anidulafungin, or micafungin), rather than fluconazole. Evidence supporting this recommendation is mainly based on the increasing prevalence of fluconazole-resistant *Candida* spp.[169,211,212] and from previously described clinical trials in which echinocandins showed a significantly higher efficacy in comparison to azoles for the treatment of candidemia.[182,183] Interestingly, when antifungal treatment was specifically assessed in the critically ill patients with septic shock due to candidemia, the administration of echinocandin was also associated with better survival in association with a prompt and adequate source control of the infection.[27]

Despite growing evidence of the superiority of echinocandins, fluconazole still remains an acceptable alternative for candidemic patients who are not critically ill or at risk of fluconazole resistance. Moreover, fluconazole represents together with voriconazole the drugs of choice for de-escalation therapy according to disease severity and susceptibility testing results.[17,149,187]

Regarding this issue, the optimal timing for de-escalating or switching to oral treatment in patients with candidemia has not been provided. In most trials, step-down therapy to azoles is permitted after 10 days of treatment. In a recent non-comparative trial, step-down to an oral azole, was allowed after 5 days of intravenous treatment.[210] Although early de-escalation has no impact survival[213] and has been associated with a significant decrease in antifungal use,[210] recent studies showed that only 20 to 40% of patients with fluconazole-susceptible strains have their treatment de-escalated from echinocandin to fluconazole in daily clinical practice.

As for duration of therapy, follow-up blood cultures should be performed every 24 to 48 hours until negativity and candidemia is usually treated for 14 days from the first negative blood culture. Treatment duration is prolonged in patients with evidence of deep-seated infections; thus, it is recommended to systematically perform a transoesophageal echocardiography and fundoscopy to all patients with a positive blood culture,[17,149,187] irrespective of clinical signs or symptoms of metastatic infection or predisposing factors.[214] Once a deep-seated candidemia is diagnosed, the duration of treatment depends on the site of infection and on the quality of the source control.

Source Control

Source control includes all measures to control invasive infection (i.e., debridement, device removal, compartment decompression) and restore optimal function of the affected site.[215] An adequate source control of the infection has been shown to be a major determinant of outcome, more so than early adequate antifungal treatment,[211,216] and should never be considered as "covered" by the only antifungal therapy. Although CVC removal remains a controversial issue,[15,217] CVC withdrawal should be attempted in all patients with candidemia.[149,187] Moreover, all surgical and radiological approaches for obtaining an adequate source control of the infection must be systematically discussed, especially in patients with intra-abdominal infection[210] or those with a candidemia from urinary tract.[218] Importantly, physicians should always keep in mind that efficacy of source control is time-dependent[219,220] and adequate procedures should therefore be performed as rapidly as possible especially in patients with septic shock.[3]

Pharmacodynamics Issues

A growing evidence support the idea that, in critically ill patients receiving treatment for IC, standard antifungal dosing is frequently associated with suboptimal drug concentration and poor outcome.[221,222] For example, in a prospective point prevalence study performed in 68 ICUs, at least 30% of patients treated with fluconazole did not reach the PK/PD target exposure, a factor associated with worse outcome.[221] The main reason for this observation relies on the pathophysiological changes associated with critical illness that can modify serum drug exposures so that they are significantly lower than values reported for healthy subjects or for non-ICU patients.[101,223] A weight-based dose regimen is probably more suitable for patients with a larger volume of distribution such as ICU patients. In a study conducted in 20 ICU adults treated with standard caspofungin dosages, a low AUC0–24 (79 mg h/L) was seen in 10 patients while an AUC0–24 of 98 mg h/L was considered appropriate.[224] The AUC0–24 was significantly and positively correlated with the caspofunginmg/kg/day ($p < 0.011$). dose in The interest of a higher than 70 mg loading dose of caspofungin warrants further research. A high variability of micafungin plasma concentrations has also been observed in

ICU patients, 18% not reaching the AUC/MIC ratio of 5,000.[225] Patients with sequential organ failure assessment score of <1, weighing more than 100 kg, and receiving 100 mg micafungin daily are at risk for inappropriate micafungin exposure and potentially inadequate antifungal treatment. Finally, ICU patients treated with echinocandins for non-*albicans* *Candida* may be also at risk for suboptimal concentrations. However, to the best of our knowledge, no studies have specifically analyzed the patient outcome according to a dose-optimization approach. Further studies are needed to clarify this issue.

Conclusions

Candidemia is associated with a significant morbidity and mortality, especially in ICU patients. Treatment of this infection is often started late because diagnosis can be challenging. New diagnostic techniques should be introduced into daily clinical practice with the aim of shortening diagnostic time. Until such tests will be available, empirical antifungal treatment should be carefully administered according to the clinical condition of the patients, risk factors, local epidemiology, and site of the infection. Further data are needed to help better define the role of surrogate markers in high-risk patients, and thus to guide empirical antifungal therapy. Administering the correct drug is of paramount importance in ICU patients but data regarding adequate dose remain limited, with current evidence suggesting that dosing should be individualized according to patients' characteristics. Further research should be conducted to define how often blood cultures should be taken in critically ill patients with candidemia and to establish the adequate timing for de-escalating. Finally, future studies are also needed to analyze the adequate duration of antifungal therapy, especially in those patients with noncomplicated disease.

Conflict of Interest

In the past five years M. Bassetti has participated in advisory boards and/or received speaker honoraria from Achaogen, Angelini, Astellas, AstraZeneca, Bayer, Basilea, Cidara, Gilead, Melinta, Menarini, MSD, Nabriva, Paratek, Pfizer, Roche, The Medicine Company, Shionogi, Tetraphase, VenatoRX, and Vifor. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript.

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