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What has changed in the treatment of invasive candidiasis? A look at the past 10 years and ahead

Matteo Bassetti[1]*, Elda Righi[1], Philippe Montravers[2] and Oliver A. Cornely[3]

[1]Infectious Diseases Clinic, Department of Medicine University of Udine and Azienda Sanitaria Universitaria Integrata, Presidio Ospedaliero Universitario Santa Maria della Misericordia, Udine, Italy; [2]Paris Diderot Sorbonne Cite University, and Anesthesiology and Critical Care Medicine, Bichat-Claude Bernard University Hospital, HUPNSV, AP-HP, INSERM UMR 1152, Paris, France; [3]Cologne Excellence Cluster on Cellular Stress Responses in Aging-Associated Diseases (CECAD), Department I of Internal Medicine, Clinical Trials Centre Cologne (ZKS Köln), University of Cologne, Cologne, Germany

*Corresponding author. Clinica Malattie Infettive, Azienda Sanitaria Universitaria Integrata, Presidio Ospedaliero Universitario Santa Maria della Misericordia, Piazzale Santa Maria della Misericordia 15, 33100 Udine, Italy. Tel: +39 0432 559355; Fax: +39 0432 559360; E-mail: mattba@tin.it matteo.bassetti@uniud.it

The treatment of invasive candidiasis has changed greatly in the past decade and must continue to evolve if we are to improve outcomes in this serious infection. A review of recent history may provide insights for the future. The morbidity and mortality of invasive candidiasis remain difficult to measure despite an obvious clinical burden. Current treatment guidelines now recommend echinocandins as first-line empirical treatment, with fluconazole as an acceptable alternative for selected patients, reflecting the efficacy demonstrated by echinocandins and increasing resistance observed with fluconazole. The selection of antifungal therapy now must consider not only resistance but also the shift in predominance from *Candida albicans* to non-*albicans* species, notably *Candida glabrata*. The recent emergence of *Candida auris* has been met with great interest, although the longer-term implications of this phenomenon remain unclear. The broad goal of treatment continues to be administration of safe, efficacious antifungal therapy as soon as possible. Diagnostic methods beyond traditional blood culture present an opportunity to shorten the time to an accurate diagnosis, and earlier treatment initiation based on prophylactic and empirical or pre-emptive strategies seeks to ensure timely therapeutic intervention. In addition, there are novel agents in the antifungal pipeline. These developments, as well as ongoing studies of dosing, toxicity and resistance development, are important items on the current research agenda and may play a role in future changes to the treatment of invasive candidiasis.

Introduction

The challenge of invasive candidiasis extends well beyond the past 10 years,[1] as does the history of its treatment.[2,3] However, our most recent experience in the management of this serious fungal infection provides a useful context for understanding current standards of treatment and areas of research focus in the future. This review discusses key changes and trends that have had an impact on where we are today, as well as ongoing developments that may influence the future of treatment for invasive candidiasis.

Morbidity and mortality, then and now

Morbidity

Denominator choice is essential for understanding and interpreting results from epidemiological studies of candidaemia and invasive candidiasis. Frequently used denominators are the total number of admissions, or (in specific subpopulations of in-hospital patients) the number of admissions per observed ward or clinical entity, or the attack rate per number of patient days at risk. The difficulty with diagnosing invasive candidiasis, e.g. the inability to obtain a biopsy in many patients, leads to categories of lower diagnostic certainty. Unproven cases add to the inaccuracy of estimating case numbers of invasive candidiasis.[4] Delayed diagnosis impacts current strategies,[5] and successful clinical trials evaluating treatment early in the course of disease are difficult to design.[6,7]

The incidence of invasive candidiasis in a population-based study including ICU and non-ICU wards was 0.61 per 1000 admissions in Petah-Tikva, Israel, between 2007 and 2014.[8] Focusing on ICU patients, higher rates are expected. Between 2006 and 2008, a European study conducted in 14 countries found a median rate of 9 candidaemias per 1000 ICU admissions (range 3–28) and regional incidence differences, with Finland having the lowest rate and Italy and Spain having the highest.[9] The candidaemia rate per 10000 ICU patient-days per year was increasing (from 1.25 to 3.06) in an Italian tertiary care hospital between 1999 and 2003.[10] The US American TRANSNET study reported an invasive candidiasis incidence rate of 3.8% among solid organ transplant recipients.[11]

Recently, the fungaemia rate in 145030 European in-hospital cancer patients has been determined to be 0.23%. The highest rate in that study occurred in HSCT recipients (1.55%), whereas patients with solid tumours had a lower risk (0.15%).[12]

Mortality

Since echinocandins became recommended as first-line treatment for candidaemia,[13–16] attributable mortality rates would have been expected to decline following widespread echinocandin use. This, however, is difficult to prove and remains a pressing topic in the current research agenda.[17,18]

Candidiasis is associated with high crude mortality rates, reaching up to 60%, although attributable mortality is difficult to establish due to the presence of confounders such as a patient's underlying conditions and septic shock.[7] Various studies have attempted to calculate *Candida*-attributable mortality and have reported highly variable rates (5%–70%). Patients in large, well-designed, randomized clinical trials that enrolled between 1989 and 2006 had an average mortality rate of 31%.[19–26] That mortality rate may reflect the lower end because of the general selection bias of prospective trials. In 1988, Wey *et al.*[27] reported crude and attributable in-hospital mortality rates of candidaemia of 57% and 38% in a case–control study. A follow-up study from the same hospital analysed 108 matched pairs between 1997 and 2001 and found practically unchanged crude and attributable mortality rates of 61% and 49%, respectively.[28] An EORTC study on 249 cancer patients treated at 30 tertiary care cancer centres in Europe and the Middle East between 1992 and 1994 demonstrated a 39% overall mortality at 30 days.[29] European cancer patients treated between 2005 and 2009 had a virtually unchanged 36% death rate at 4 weeks after diagnosis of candidaemia.[12] In an ICU population ($n = 200$) studied between 1992 and 2000, researchers from the Netherlands found a generally high mortality rate (43%) in their patients, which did not significantly differ from mortality in those with candidaemia (48%).[30] In an epidemiological candidaemia study conducted in the Paris area from 2002 to 2014, the risk of death was particularly higher in those admitted to the ICU and those with haematological cancer or solid tumours. Crude death rates in ICU patients had significantly increased over the 11 year observation period, i.e. from 18% to 58%.[31] When comparing general medical and surgical ward patients with those on an ICU within the same hospital, the highest 30 day mortality rates were found in the ICU (75%), followed by medical (63%) and surgical wards (39%).[8]

Overall, mortality is not decreasing. Rates depend on the clinical setting and range from 40% to 60% at 30 days post diagnosis of candidaemia.

Microbiological context

There is a vast body of literature on the epidemiology of candidiasis. One essential aspect is the relative frequency of individual species. The relative distribution of *Candida* spp. is clinically important since it drives initial antifungal choice when the microbiologist reports yeast in a (blood) culture.[32] That laboratory result is the first step in establishing the diagnosis of invasive candidiasis and its most common form, i.e. candidaemia.[5] Since mortality in untreated candidaemia increases by the hour,[33] clinicians strive to hit early and hit hard.[14] For many years a drug of choice in that clinical scenario was fluconazole.[34]

Candida spp. distribution varies with the patient population characteristics as well as by region and hospital, and even between individual wards.[35] These factors render it difficult to document a shift from fluconazole-susceptible species to less-susceptible species.[36] Usually, the proportion of *C. albicans* is addressed as part of the whole. Species shifts within the individual patient are well documented and depend on the duration of exposure to antifungals.[37,38]

In the 1990s and early 2000s, the variable epidemiology of candidaemia was described by the following exemplary studies. In a nationwide Swiss study conducted from 1991 to 2000, 1137 candidaemias were observed. Incidence rates were stable and *C. albicans* accounted for 66% of the episodes, without changes over time.[39] A study from a German tertiary care hospital found a stable species distribution from 1995 to 2004. While the overall number of candidaemias almost doubled, *C. albicans* accounted for 57.1% of 296 blood culture isolates, and no trend in favour of non-*albicans* species was seen.[40] The European Confederation of Medical Mycology (ECMM) conducted a surveillance study enrolling 2089 candidaemia cases throughout Europe from 1997 to 1999. *C. albicans* accounted for 56% of isolates.[35] From 1999 to 2003, 182 episodes of candidaemia among patients in a northern Italian ICU occurred. Analyses revealed an overall increase in the incidence of candidaemia and a decrease in the proportion of *C. albicans* to <30%. Interestingly, the prophylactic and empirical use of fluconazole inversely correlated with the species shift.[10] A similar decline in the proportion of *C. albicans* was found in a recent population-based study from Israel.[8] A study from Northern Ireland focused on 151 candidaemias diagnosed from 2001 to 2006 and found an increasing proportion of *C. albicans* over time.[41] A meta-analysis of such epidemiological studies presents an unusual but potentially interesting approach. Recently such a study was attempted, but the full publication is pending. The analysis compared epidemiology before and after 2004 and found a general decrease in *C. albicans* as a cause of candidaemia, which was more pronounced in ICU settings, where it exceeded 10%. Still, the overall *C. albicans* proportion remained >50%.[42] In line with these findings, a US study on solid organ transplant recipients recently reported a rate of *C. albicans* of 46%.[11]

Developments that are more recent show the emergence of *Candida auris* since 2012. Simultaneous reports from Asia, Africa and South America posed the question of phylogenetic relatedness. Whole-genome sequencing of 54 patient isolates, as well as the isolate of the first reported case (an ear infection) from Japan, demonstrated that clades differed between geographical regions and that within a region isolates were clonal. *C. auris* is of particular interest because of generally high rates of antifungal resistance, including a 7% rate of echinocandin resistance.[43,44] In the first hospital outbreak of *C. auris* in the UK, which was reported in 2016 and had been ongoing since 2015, all isolates had high-level resistance to fluconazole and exhibited variable amphotericin B susceptibility, but the majority were echinocandin susceptible.[45] Recent cases of *C. auris* infection in continental Europe and ongoing transmission in the USA have been reported and have attracted great attention.[46–48] However, at this point in time, it remains enigmatic if and how *C. auris* will influence future management strategies for invasive candidiasis.[49]

Table 1. Non-culture based diagnostics[15,134]

Method or marker	Sensitivity/ specificity	Potential advantages	Potential limitations
Assays before identification and susceptibility results			
Candida PCR	95%/92% (suspected); 85%/38% (probable)	• shorter time to diagnosis • species identification • detection of resistance markers • detection of deep-seated candidiasis	• cost, inconvenience • lack of universally standardized methods (e.g. specimen type) or performance validation
Mannan-Ag and anti-mannan Ab	58%/93% (mannan-Ag); 59%/83% (anti-mannan Ig); 83%/86% (combined)	• best when used together and for detecting *C. albicans*, *C. glabrata* or *C. tropicalis*	• limited sensitivity/specificity when used individually and for detecting *C. parapsilosis* and *C. guilliermondii* • uncertain reliability in immunocompromised hosts, uncertain utility for deep-seated candidiasis
BDG	75%–80%/80%	• pan-fungal marker for patients at risk for other systemic infections (e.g. with *Aspergillus* spp. or *Pneumocystis jirovecii*, in HSCT recipients) • detection of deep-seated candidiasis • high negative predictive value • can detect infection days or weeks in advance of culture-based diagnosis	• prophylactic or empirical antifungal treatment may impact test performance • lower sensitivity for *C. parapsilosis* • false-positive results higher for patients in ICU, with colonization, other systemic infections, multiple therapeutic interventions; may require more than one consecutive positive result
CAGTA	77%–89%/91%–100%	• high negative predictive value (93.9%) • unaffected by colonization or antifungal use	• limited experience/data
T2MR	91.1%/99.4% per assay	• shorter time to diagnosis • high specificity • low limit of detection	• limited experience/data
Assays after identification and susceptibility results			
MALDI-TOF	>90%	• rapid results (within minutes) • ability to identify genus, species, strain and potential resistance patterns	• lack of experience/data

Diagnostic advances

Considering the importance of timely initiation of antifungal treatment, non-culture-based diagnostics have shown promising performance for the early detection of invasive candidiasis. Several tests are available that can be separated in a chronological approach into assays for the periods before and after microbiological identification and susceptibility testing results (Table 1). Their applicability to ICU patients remains debated in many instances. Most reports focus on fungal identification, whereas the impact on clinical outcome remains under-evaluated.

Before identification and susceptibility testing results

These tests are used as an early warning in patients suspected of having invasive candidiasis and/or to help in the decision-making process for initiating antifungal therapy. Their use for antifungal stewardship remains minimally investigated. A major trend in recent years is the emergence of combined approaches using different biomarkers or repeated measures of several markers.[50–54]

Candida PCR

No officially standardized PCR test is yet available and the usefulness of PCR as an early marker of invasive candidiasis is a subject of debate.[55,56] Many limitations have been pointed out, including costs and the labour-intensive nature of its use. Reports in ICU patients have demonstrated good sensitivity, specificity and predictive values.[57,58] The comparison of the capacities of PCR testing for detection of bacterial DNA compared with fungal DNA has demonstrated a lower sensitivity for fungal infection.[59] The value of PCR compared with other techniques remains a subject of debate. Some authors have reported better results with PCR, especially in deep-seated candidiasis,[51,58] whereas others have observed lower discriminating capacities.[54] Overall, the value of

PCR compared with other techniques remains to be clearly established.

Mannan antigen (mannan-Ag) and anti-mannan antibodies (anti-mannan-Ab)

The value of these markers of the *Candida* cell wall has been assessed in ICU and immunocompromised patients.[54,60] The sensitivity and specificity of mannan-Ag have been disappointing in several studies.[54,61] The combination of mannan-Ag and anti-mannan-Ab assays significantly increases the sensitivity and specificity of the test.[62] The best sensitivity results have been reported with *C. albicans* and *C. glabrata*,[62] whereas disappointing results have been reported in *C. parapsilosis* and *C. guilliermondii* infections.[52] The use of mannan-Ag/anti-mannan-Ab assays has not been rigorously assessed in patients with deep-seated candidiasis, such as intra-abdominal *Candida* infections.[63]

1,3-β-D-Glucan (BDG)

This pan-fungal marker for invasive fungal infections, except zygomycetes and *Cryptococcus neoformans*, has been proposed as a marker for the early detection of invasive candidiasis. Several false-positive results have been reported for other fungal and bacterial infections and with many therapeutic interventions, including antibiotics, haemodialysis, surgical gauze, blood products and intravenous immunoglobulins.[64–66] The conventional cut-off value for the diagnosis of invasive candidiasis is 80 pg/mL, but several thresholds have been discussed.[54] The sensitivity of the test seems to vary by *Candida* species, with the lowest sensitivity being reported for *C. parapsilosis*. Therefore, test results for this species in particular should be carefully evaluated.[67] BDG positivity can anticipate the diagnosis of invasive candidiasis by a median of 5–8 days before culture-based diagnosis.[68,69] Repeated measurements have been proposed to increase the diagnosis accuracy and the best results have been obtained when two consecutive analyses were positive.[68,70] The high negative predictive value of the test allows its use to exclude invasive candidiasis.[70,71] The decline in BDG concentrations in successfully treated patients suggests its use as a surrogate for clinical response, but this approach is debated,[68,70,72] in particular because of persistent BDG levels of >80 pg/mL for several weeks after initiation of therapy.[68,73,74] A relationship between BDG and high-grade *Candida* spp. colonization has been evidenced in several studies.[54,68,74] Two consecutive BDG samples of ≥80 pg/mL were able to differentiate invasive candidiasis from high-grade colonization.[69]

Candida albicans germ tube antibodies (CAGTA)

The detection by indirect immunofluorescence assay of CAGTA is a recent and promising approach. A positive CAGTA test corresponds to a serum titre of ≥1/160.[75] In the ICU setting, the test has been assessed in patients having significant BDG concentrations (≥259 pg/mL) associated with a positive CAGTA value (sensitivity 90.3%, negative predictive value 93.9%).[50] The promise of the combined approach has been confirmed using a lower BDG cut-off (≥80 pg/mL) in three cohorts of patients with a large proportion of ICU cases and severe abdominal cases.[53,54,69] Significant CAGTA titres were observed in patients with invasive candidiasis treated with systemic antifungals for various types of *Candida*, including *C. albicans*, *C. parapsilosis* and *C. glabrata*.[69] In patients receiving antifungals, no significant changes in the CAGTA kinetics were observed.[69] A positive CAGTA test in a patient with candidaemia seems to be suggestive of deep-seated candidiasis.[76] The high sensitivity and negative predictive value of the combination BDG/CAGTA could be a reliable tool for evaluating the discontinuation of empirical antifungal therapy.[53]

T2 magnetic resonance

The nanodiagnostic method of T2 magnetic resonance (T2MR) is another recent development of interest. T2MR utilizes whole-blood samples to detect and identify *Candida* spp. and can produce results on a scale of hours versus days with culture-based testing. In a clinical trial of T2MR sensitivity and specificity, the mean time to species identification was 4.4 h, with a 91.0% overall rate of sensitivity per patient.[77] There was high specificity overall and for non-*albicans* species (99.9% for *C. krusei*/*glabrata*, 99.3% for *C. parapsilosis*). The study also reported a low limit of detection (1 cfu/mL) for *C. krusei*/*C. tropicalis*, which may be useful in cases where fungal burden is low (e.g. gastrointestinal infection, patients receiving antifungal therapy).

After identification and susceptibility testing results

MALDI-TOF

The promise of these tools is to expedite the selection of appropriate therapy by providing prescribers with identification of the organisms and their potential resistance patterns. Several techniques are available and used routinely for identification of microorganisms from isolated colonies, obtained by culture, in a few minutes with an accuracy rate of >90%.[78,79] Clinical evaluations of these tests have shown decreased time to organism identification and improved time to effective anti-infective therapy.[80]

In summary, the two approaches of early detection of patients at risk using biomarkers and early identification of *Candida* using rapid tests (PCR, T2MR, MALDI-TOF) complement one another. Combinations of these tools in bundles and repeated assessments could be hypothesized to speed up the management of these high-risk cases in the near future. However, the added value of these combined techniques remains to be evaluated.

Approaches to prophylactic, pre-emptive and empirical treatment

Over the last decade, early antifungal agents have been prescribed in non-neutropenic adult patients admitted to the ICU for various purposes corresponding to prophylaxis or pre-emptive or empirical therapies.

Prophylaxis strategy is usually defined as administration of antifungal agents to patients with risk factors for invasive candidiasis without clinical signs and symptoms of infection.[81,82] The concept, initiated almost 40 years ago, remains an important issue in routine practice, as illustrated in European observational studies where prophylaxis was reported in 10%–16.6% of the patients or units.[83,84] Over the last decade, 10 articles have focused on the prevention of fungal infection in ICU patients in randomized controlled trials involving echinocandins, intravenous or oral fluconazole and oral nystatin.[85] However, the quality of evidence is low in

many studies, leading to uncertainty with regard to the reduction of mortality, reduction of invasive candidiasis, or the risks of fungal colonization or resistance development with wide-scale use.[85] Despite the large number of publications, it is not yet possible to identify among the critically ill patients those who deserve prophylaxis, or determine the agent to select, when to start it, at what dose, how long to use it or what is the best monitoring regime for this procedure. The current IDSA guidelines do not provide specific recommendations, only suggesting use of fluconazole or echinocandins in high-risk patients in adult ICUs with high rates (5%) of invasive candidiasis, without clear definitions of the target population or durations of prophylaxis.[15] Nevertheless, research and clinical experience have continued to explore strategies for antifungal prophylaxis, not only in the ICU but also in haematology/oncology and transplant infectious disease. Evidence regarding prophylaxis in these settings is reviewed separately in this Supplement.[86,87]

Various definitions have been proposed for pre-emptive therapy over the last 10 years.[14,82,85] Consequently, the concept of pre-emptive strategy has been an area of confusion as treated patients have been described by some authors as having received empirical therapy while others refer to pre-emptive or presumptive therapy.[81] In addition to the differing nomenclature, tools for detecting the target population are not clearly defined, although the use of biomarkers has been suggested to guide the prescriptions.[71,88,89] These poorly defined topics could explain the downward trend in the number of recent publications, as illustrated by the absence of recommendation for pre-emptive therapy in Canadian guidelines[90] and in the 2016 updated IDSA guidelines.[15] The only two recently published randomized, placebo-controlled trials evaluating pre-emptive therapy with echinocandins in ICU patient populations were unable to provide conclusive evidence that this policy was effective in preventing invasive candidiasis.[6,91] Both studies were conducted in patients at higher risk of infection; cardiovascular and gastrointestinal surgery were among the top reasons for ICU admission in one study,[91] and all patients required surgery for intraabdominal infection in the other.[6] Two other studies, one using the term 'prophylaxis'[92] and the second 'empiric',[7] could also be assimilated to pre-emptive therapy but neither study demonstrated a benefit with early antifungal therapy. Interestingly, pre-emptive therapy remains widely used in ICU patients, accounting for between 18.2% and 28% of antifungal therapy in European ICUs.[83,84]

Empirical therapy requires complex alignment between appropriateness (of dose and spectrum of activity) and timing. As noted previously, early intervention is known to benefit mortality and is a goal of treatment.[14,33] However, more work is needed to specify criteria for starting empirical antifungal therapy in non-neutropenic critically ill patients. Empirical treatment is usually considered in patients with risk factors for invasive candidiasis and no other known cause of fever, based on the clinical assessment of risk factors, serological markers for invasive candidiasis and/or culture data from non-sterile sites.[82] Early initiation of antifungal therapy is increasingly popular, corresponding to between 45% and 65% of all the prescriptions in European ICUs,[83,84,93] raising questions of whether warnings about toxicity, cost and resistance emergence[83,94] are going unheeded. The lack of published randomized controlled trials demonstrating the efficacy of empirical therapy, with any drug, limits broad recommendations on appropriateness and timing. Amidst these research challenges, the potential benefits for high-risk ICU patients with sepsis continue to be debated and explored.[7,92,95,96] In a retrospective cohort of patients with invasive candidiasis, early empirical treatment has been reported to achieve better clinical stability.[97] A better prognosis with empirical therapy has been reported in bloodstream infections but only in combination with catheter removal,[98] and this benefit has not been reported in *Candida* peritonitis.[99]

Treatment experience and guidelines

Recent updates to treatment guidelines reflect the changes and trends being described. Key recommendations from the IDSA and ESCMID are summarized in Table 2.[14,15] As previously mentioned, the benefit of empirical or pre-emptive therapy to *Candida*-related mortality remains unclear, especially among critically ill patients hospitalized in the ICU. Furthermore, challenges in the use of antifungal prophylaxis include correct selection of the appropriate high-risk populations, in order to avoid overtreatment that might impact fungal ecology and select resistance.[100] A double-blind placebo-controlled trial did not support the use of antifungal empirical therapy in high-risk, critically ill patients presenting with ICU-acquired sepsis, *Candida* spp. colonization and multiple organ failure. In this patient population, treatment with micafungin did not increase fungal infection-free survival compared with placebo.[91] Empirical therapy with micafungin in high-risk hosts, however, was associated with a decrease in the incidence of proven disease.[7]

The 2016 updated guidelines from the IDSA recommend first-line treatment for *Candida* spp. infection with an echinocandin (e.g. caspofungin, anidulafungin or micafungin), rather than fluconazole, based on the increasing prevalence of *Candida* spp. with decreased susceptibility to fluconazole, especially in critically ill patients.[14,15,63,81,90]

Evidence to support the use of an echinocandin as first-line therapy in the treatment of candidiasis has been provided from clinical trials and observational studies. A randomized trial comparing anidulafungin with fluconazole for the treatment of candidaemia and invasive candidiasis in non-neutropenic patients showed a significantly higher efficacy with the use of anidulafungin compared with fluconazole (76% versus 60%; $P < 0.01$).[13] Multivariate analyses also confirmed the superiority of anidulafungin compared with fluconazole for infections due to fluconazole-susceptible *C. albicans* and over a broad range of APACHE II scores.[13,101] Although two prospective studies found no correlation between antifungal treatment type and prognosis,[99,102] a quantitative review of randomized trials gathering 1915 patients from seven studies reported that treatment with an echinocandin was a factor in decreased mortality and a factor in increased success.[19] In the ICU setting, emerging evidence supports the superiority of this antifungal class.[103,104] In this group, however, complex pathophysiological changes may affect echinocandin concentration, and further studies to assess the clearance and correct dosing of antifungals are warranted to avoid suboptimal concentrations.[105–107]

A recent large, randomized trial comparing a new azole, isavuconazole, with caspofungin confirmed higher rates of success for the group of patients treated with the echinocandin (71.1% versus 60.3%, respectively). This result was not limited to critically ill patients and also applied to subjects with low APACHE II scores.[16]

Table 2. Key IDSA/ESCMID recommendations by treatment strategy[14,15]

Strategy	Case	Recommendation		Notes
		antifungal	SoR/QoE[a]	
Targeted	confirmed infection	iv echinocandin (caspofungin, anidulafungin, micafungin)	strong/I;[14] strong/high[15]	For 14 days after candidaemia; may need longer durations for deep-seated infections. Consider local epidemiology.
		fluconazole	marginal/I;[14] strong/high[15]	Option if not critically ill and no prior azole. At higher doses for susceptible *C. glabrata* or *C. parapsilosis*.
		L-AmB	moderate/I;[14] strong/low[15]	Similar efficacy but higher toxicity. Consider in cases of intolerance, limited availability, or resistance to other agents.
		voriconazole	moderate/I;[14] strong/ moderate[15]	Little advantage over fluconazole, except additional mould coverage. Note DDIs, renal impairment, and potential TDM. For susceptible *C. glabrata*.
	catheter-related	remove catheter	strong/II;[14] strong/low[15]	If catheter removal is not possible, echinocandin or L-AmB or ABLC.
Prophylaxis	risk of IA candidiasis	fluconazole	moderate/I[14]	Following abdominal surgery with recurrent GI perforation or anastomotic leakage.
	ICU, high-risk (non-transplant)[b]	fluconazole	marginal/I;[14] weak/ moderate[15]	
		iv echinocandin	marginal/II;[14] weak/low[15]	
Empirical	febrile, at risk of infection[c], with no microbiological evidence	same as for targeted, echinocandin or fluconazole preferred	marginal/II;[14] strong/ moderate[15]	Select antifungal based on local epidemiology and DDI risk for the individual patient.
Pre-emptive	microbiological evidence but unproven IFI	echinocandin or fluconazole[d]	marginal–strong/II[14]	Marginal SoR with positive BDG test; Strong SoR with positive culture.
Step-down from iv treatment	clinically stable with susceptible isolate and negative blood cultures	fluconazole, voriconazole (for *C. krusei*)	moderate/II;[14] strong/ moderate[15]	From 5 to 10 days after starting echinocandin treatment (e.g. may step down earlier if *C. parapsilosis* is identified).

ABLC, amphotericin B–lipid complex; DDI, drug–drug interaction; IFI, invasive fungal infection; SoR, strength of recommendation; QoE, quality of evidence; TDM, therapeutic drug monitoring.
[a]As defined by ESCMID and IDSA guidelines for non-neutropenic adult patients, where QoE was defined either numerically (I indicates ≥1 properly designed, randomized, controlled trial and II indicates ≥1 well-designed clinical trial without randomization, cohort or case-controlled analytical studies, multiple time series or dramatic results of uncontrolled experiments) or descriptively (i.e. high, moderate, low or very low as a composite estimate of effect based on study design and plausible confounding/bias, such as inconsistency, imprecision, dose response, or effect size).
[b]As defined by ESCMID based on study populations that included critically ill patients with expected ICU stay of ≥3 days, ventilation for ≥3 days, and other risk factors (for example, parenteral nutrition, dialysis).
[c]Critically ill, with risk factors or surrogate markers for invasive candidiasis, prior azole exposure and/or culture from non-sterile sites.
[d]Author recommendation, consistent with published guideline cited.

In a retrospective study, echinocandin use as well as prompt antifungal therapy and adequate source control were associated with increased survival in patients with septic shock due to *Candida* spp.[108]

In a retrospective cohort study analysing patients infected with *C. glabrata*, treatment failure was associated with ICU admission, whereas echinocandin therapy was associated with complete clinical response at day 14.[109]

In the trial comparing anidulafungin with fluconazole, a trend towards lower mortality was demonstrated for patients treated with anidulafungin, although the difference between the two treatment arms was not significant (23% versus 31%, $P = 0.13$).[13] Treatment with fluconazole, however, did not show a significant association with mortality, either as empirical or definitive therapy or in patients with septic shock, compared with echinocandins in a prospective multicentre study.[110] Two cohort studies did not demonstrate significantly increased survival rates with echinocandin treatment compared with fluconazole treatment in *C. glabrata* infections.[109,111] Overall, the results appear conflicting and difficult to compare since many trials were not powered for mortality

differences when comparing different antifungal regimens. More data are needed to confirm the association of a specific antifungal regimen with improved outcomes.

Several studies have highlighted that prompt administration of adequate antifungal therapy correlates with increased survival rates.[33,112] For this reason, early diagnosis followed by timely administration of antifungal treatment currently represents a priority to target *Candida* spp. infections. The implementation of this approach, along with updated recommendations on antifungal use for the treatment of candidiasis, has been reviewed in recently published guidelines.[14,15]

Fluconazole has been the drug of choice for the treatment of candidiasis for over two decades owing to its favourable tissue penetration, pharmacokinetics and its low cost. Fluconazole was initially compared with amphotericin B deoxycholate (dAmB), demonstrating no significant differences in treatment outcomes for patients with candidaemia but lower toxicity than amphotericin B (AmB).[20] Over the years, newer compounds, such as voriconazole and caspofungin, showed comparable efficacy and reduced toxicity compared with dAmB, which has currently been replaced by new formulations of polyenes such as liposomal amphotericin B (L-AmB).[22,23] All new antifungal drugs, in particular echinocandins, have been compared with a standard regimen for the treatment of candidiasis in at least one randomized controlled trial. Micafungin was shown to be as effective as both L-AmB and caspofungin in randomized controlled trials.[25,26]

The ESCMID guidelines published in 2012 no longer consider fluconazole to be the drug of choice for invasive candidiasis, and recommend the use of echinocandins as first-line empirical treatment.[14] The 2016 IDSA guidelines also prioritize echinocandins as first-line treatment prior to species identification and susceptibility testing (AI, strong recommendation). Supporting evidence for these recommendations has been published in various studies and settings, including the ICU.[103,104] Favourable characteristics of echinocandins compared with fluconazole include fungicidal activity, a broader spectrum of activity, an excellent safety profile, and few drug–drug interactions.[15,19] However, despite growing evidence of the superiority of echinocandins and the emergence of resistance to fluconazole, especially among non-*albicans* strains of *Candida*, fluconazole is still widely used in clinical practice for the treatment of candidiasis. As reported in the 2016 IDSA guidelines, fluconazole remains an acceptable empirical alternative for patients who are not critically ill or at risk of fluconazole resistance, and represents the drug of choice for step-down therapy according to disease severity and susceptibility testing results.[15] Other alternatives include voriconazole, which offers little advantage over fluconazole as initial therapy, and L-AmB, which can be used in case of intolerance or limited availability of other antifungals or in case of resistance.[15] Fluconazole susceptibility testing is recommended for all clinically relevant *Candida* spp. isolates, whereas for echinocandins testing is suggested if the patient was previously treated with an echinocandin for infections caused by *C. glabrata* or *C. parapsilosis*.[15] Voriconazole can be used as step-down therapy in infections due to *C. krusei*.[15]

Areas of uncertainty remain even in the current guidelines, including the overall duration of antifungal therapy and the optimal treatment for deep-seated candidiasis, such as intra-abdominal candidiasis.

The optimal duration of intravenous therapy for candidaemia and invasive candidiasis has not been extensively studied. 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.[113] Early de-escalation, however, did not seem to impact survival.[114] Candidaemia is usually treated for 14 days from the first negative blood culture, requiring daily blood cultures to be performed until negativity. Treatment duration is prolonged in deep-seated infections and endocarditis; thus it is recommended to rule out these infections using CT scans, transoesophageal echocardiography and fundoscopy.[14]

Owing to the fact that candidaemia is easier to recognize and diagnose compared with deep-seated candidiasis, current guidelines mainly focus on the management of candidaemia, and trials on abdominal candidiasis are lacking.[14,63] Risk factors for intra-abdominal candidiasis include recent surgery, necrotizing pancreatitis and anastomotic leaks.[63] Empirical antifungal treatment with echinocandins or L-AmB should be considered in the critically ill or in patients with previous exposure to azoles and risk factors for *Candida* spp. infection. Despite the lack of randomized trials, antifungal therapy for patients with complicated intra-abdominal infection is recommended when *Candida* sp. is grown from cultures.[63] Fluconazole can be adopted for targeted therapy of non-critically ill patients who do not have previous exposure to azoles and are not colonized with a strain with reduced susceptibility to azoles.[63]

New antifungal agents

Over the past two decades, a range of antifungals has been developed and demonstrated therapeutic efficacy in severe fungal infections. Various antifungal classes are currently available for the treatment of candidiasis, including polyenes such as L-AmB, azoles (fluconazole, isavuconazole and voriconazole) and echinocandins (anidulafungin, caspofungin and micafungin). A few more antifungals are currently under investigation for the treatment of candidaemia and invasive candidiasis, including new compounds belonging to known classes or molecules with novel mechanisms of action (Table 3).[115]

The echinocandins belong to a class of semisynthetic lipopeptides that inhibit the synthesis of the β-(1,3)-D-glucan component of the cell wall of fungi. Echinocandins are characterized by fungicidal activity, excellent tolerability, few drug–drug interactions and low resistance rates compared with fluconazole.[116] Echinocandins are effective in the treatment of *C. albicans* and against non-*albicans* infections, biofilms and also azole-resistant strains.[117] Limitations in the use of currently approved echinocandins include the absence of an oral formulation and the need for daily administration.

Rezafungin (previously CD101; Cidara Therapeutics, Inc.) is a novel long-acting echinocandin[118] characterized by a spectrum of activity that is comparable to the other echinocandins but also a distinct safety–pharmacokinetic/pharmacodynamic (PK/PD) profile that enables high plasma drug exposure and extended interval dosing.[119–121] Rezafungin acetate is currently in development for once-weekly intravenous administration and has also been studied as a subcutaneous formulation.[122] *In vitro*, rezafungin has demonstrated potent activity against a broad range of *Candida*

Table 3. Antifungal agents in development

Candidate	Class	Current development	Potential
T-2307	arylamidine	Phase 1, TBD	Activity against echinocandin-resistant *Candida spp.*
Rezafungin acetate[120,121,123,125,135,136]	echinocandin	Phase 2;[128] iv, sc	Once-weekly dosing. PK/PD enables high plasma drug exposure. Subcutaneous formulation
SCY-078[129,130]	triterpene	Phase 3;[131] oral	Novel antifungal class. Under study for treatment of refractory fungal disease

TBD, to be determined.

spp., including echinocandin- and azole-resistant strains.[123] In caspofungin-resistant isolates containing *FKS* mutations, which correlate with clinical failure or poor response to therapy,[124] rezafungin demonstrated similar efficacy compared with micafungin and high plasma drug exposure that suggested possible advantage in preventing the emergence of resistant strains.[120] Rezafungin efficacy in burden reduction was comparable to that of micafungin in a neutropenic murine model of disseminated candidiasis. In that study, the rezafungin elimination half-life ranged from 29.8 to 52.0 h.[121] In healthy subjects, a dose–escalation study[125] including single or multiple doses administered weekly (from 50 to 400 mg for up to 3 weeks) demonstrated that rezafungin was safe and well tolerated, with only mild adverse events. Half-lives were up to 130 h (400 mg dose) with reduced accumulation (30%–55%) and minimal renal elimination.[125] Preclinical studies determined that the rate of rezafungin protein binding is similar to that of anidulafungin (~98% in human plasma).[121,126] The long elimination half-life, coupled with the prolonged efficacy of rezafungin[121] and its concentration-dependent killing as an echinocandin, fit the PK/PD profile of drugs that are most effective in larger doses, administered infrequently.[106,120,127] A multicentre, randomized, double-blind Phase 2 trial is currently ongoing to evaluate the efficacy and safety of rezafungin once weekly compared with caspofungin in patients with candidaemia and invasive candidiasis.[128]

SCY-078, a derivative of enfumafungin, is a semisynthetic, triterpenoid, antifungal glucan synthase inhibitor, currently in development for the treatment of invasive and mucocutaneous fungal diseases.[129] SCY-078 represents the first compound of the triterpene class of antifungals and is currently in Phase 3 clinical development for the treatment of invasive fungal diseases. SCY-078 has shown good bioavailability and has been studied as oral and intravenous formulations with once daily administration.[129] High *in vivo* activity against *C. albicans* and non-*albicans* strains has been shown in animal models.[129] Pre-clinical pharmacokinetic studies demonstrated a high volume of distribution at steady state (4.7–5.3 L/kg), suggesting extensive tissue distribution.[130] An open-label study to evaluate the efficacy and safety of SCY-078 in patients with refractory fungal diseases is currently ongoing.[131]

Among antifungal drugs with novel targets of action, the new arylamidine T-2307 has shown promising activity against *C. albicans* and *C. glabrata* both *in vitro* and *in vivo* and is currently in Phase 1 of development.[132,133] For 17 strains of echinocandin-resistant *C. glabrata*, T-2307 showed a mean MIC value of 0.0083 mg/L and maintained *in vivo* efficacy in mice infected with resistant strains, showing reductions in fungal burden greater than those with caspofungin.[133] Although the compound is still in early-phase development, these findings appear promising and support the potential use of T-2307 against echinocandin-resistant *Candida* spp.

In summary, although various antifungal classes are currently in use, several aspects such as toxicity, type of formulation and drug–drug interactions limit their employment in daily clinical practice. Furthermore, drug-resistant fungi are now emerging. Therefore, new antifungals for the treatment of severe *Candida* infection, including resistant strains, are awaited with widespread interest.

Conclusions

During the past 10 years, the treatment of invasive candidiasis has been influenced by changes in the epidemiological landscape, drug development and the pursuit of more timely intervention, by way of both earlier diagnosis and earlier initiation of therapy. The morbidity and mortality associated with invasive candidiasis remain difficult to estimate yet are largely unchanged, underscoring the need for continued efforts in the improved use of existing modalities and the development of new, safe and efficacious options.

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