

TREATMENT AND PROPHYLAXIS OF INVASIVE CANDIDIASIS WITH ANIDULAFUNGIN, CASPOFUNGIN AND MICAFUNGIN – REVIEW OF THE LITERATURE

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Abstract

Working by a distinct cell wall-specific mechanism of action, the echinocandin class of antifungals has substantially expanded the range of available treatments for invasive *Candida* infections. Anidulafungin, caspofungin and micafungin were investigated versus drugs from earlier antifungal classes in large clinical trials that demonstrated their excellent clinical and microbiological efficacy in the primary treatment of invasive candidiasis. Therefore, and supported by a number of favourable pharmacological characteristics, the echinocandins rapidly became established in guidelines and clinical practice as primary treatment options for moderately to severely ill patients with invasive candidiasis. This article reviews the relevant clinical evidence that forms the basis for the use of echinocandins in the management of invasive candidiasis, and discusses their current role in the context of recent guideline recommendations and treatment optimization strategies.

INTRODUCTION

Candida spp. are prominent fungal pathogens causing invasive infections predominantly in neutropenic and severely ill non-neutropenic patients. Most patients with invasive candidiasis have candidemia without evidence of deep tissue or organ involvement. Despite efforts to advance treatment options and modalities, the mortality associated with invasive candidiasis is still high. Published figures of crude mortality reside in the range of 30-60%, attributable mortality is estimated at 25-40% [1-6].

As several investigators have shown, mortality of candidemia is directly correlated with the delay of initiation of adequate antifungal therapy [7, 8]. Thus, early treatment with a reliably active and safe drug is mandatory to achieve the optimum clinical outcomes. However, this is a difficult requirement to meet as the predominant challenges encountered in the management of invasive candidiasis include a lack of well-performing methods for early detection of infection and several shortcomings of the azole and polyene antifungals, the former mainstays of invasive candidiasis therapy. These include gaps in the antifungal spectrum and a multitude of drug interactions for the azoles, and nephrotoxicity or acute toxicity associated with the polyene antifungals.

Beginning in 2002, the introduction of three echinocandin antifungals has significantly expanded the historically limited armamentarium of drugs available for the treatment of invasive candidiasis. Working by a distinct cell wall-specific mechanism of action, anidulafungin, caspofungin and micafungin are characterized by excellent antifungal activity against *Candida spp.* and *Aspergillus spp.*, low toxicity, few or negligible drug-drug interactions and pharmacokinetic independence of renal (and mostly hepatic) function. Therefore they rapidly became established in guidelines and clinical practice as primary treatment options for severely ill patients with invasive candidiasis. After a brief overview of the epidemiology and characteristics of invasive candidiasis, this article reviews current published data on the use of echinocandins in the management of invasive *Candida* infections.

INVASIVE CANDIDIASIS

As pointed out above, invasive *Candida* infections are important opportunistic infections. In the recent EPIC II survey performed in 667 European intensive care units, *Candida spp.* were involved in 18.5% of cases with nosocomial infections [9]. According to another recent survey at the intensive care units of 310 German hospitals [10], fungal pathogens were involved in every fifth patient with infection, in the subset of university hospitals *Candida spp.* were detected in 24% of the infections.

In a large survey with 24,000 cases of bloodstream infections in US hospitals [4], *Candida spp.* were the fourth most common pathogen involved in sepsis at an incidence of 4.6 cases per 10,000 admissions. A multi-institutional survey performed by the European Confederation of Medical Mycology in several European countries reported incidences of 2.0-3.8 cases of candidemia per 10,000 admission and 0.30-0.41 cases per 10,000 patient hospital days. The majority of the cases was diagnosed on surgical and intensive care wards (48.2% and 40.2%, respectively), 22.5% of the patients had solid tumors, 17.4% received steroids and 12.3% had hematological malignancies [11].

This distribution reflects the predisposing factors identified by several authors [12], including neutropenia, cancer chemotherapy, colonization with *Candida spp.*, exposure to broad spectrum antibiotics, indwelling central venous catheters, hemodialysis or re-

nal failure, high APACHE score, mechanical ventilation, prior surgery, particularly gastro-abdominal surgery [13], gastrointestinal perforation and higher age. Another important risk group are solid organ transplant recipients receiving immunosuppressants [14]. Premature birth is a major predisposing factor in neonates [12]. For intensive care patients, the rate of invasive fungal infections increases with the duration of stay, particularly >7 days [15].

Among patients with malignant haematological diseases, the highest rates of invasive *Candida* infections are found in patients with neutropenia due to induction chemotherapy for acute leukemia or myelodysplastic syndrome and in recipients of allogeneic blood stem cell transplants in the early post-transplant phase and in periods of graft-versus-host disease (GVHD) [16, 17].

While the majority of invasive *Candida* infections are blood stream infections, organ involvement after hematogenous dissemination, peritonitis and endocarditis [18] are important manifestations of disease. *Candida* endophthalmitis may develop in patients with delayed pathogen clearance from the blood stream (persistent candidemia).

ANTIFUNGAL ACTIVITY OF ECHINOCANDINS IN CLINICALLY RELEVANT *CANDIDA SPP.*

The echinocandins are semisynthetic lipopeptides derived from natural metabolites produced by three different fungi [19]. Their almost identical central hexapeptide structure carries substance-specific lipophilic N-acyl side chains. This may be the basis of some differences in terms of antifungal activity, pharmacokinetics, metabolism, tissue distribution and interactions.

In contrast to azole and polyene antifungals, the echinocandins inhibit the synthesis of 1,3-beta-D-glucan, an essential polysaccharide component of the cell wall in *Candida spp.* and *Aspergillus spp.* In *Candida spp.*, the deprivation of this major structural element leads to disruption of the cell wall and subsequent cell lysis, accounting for the fungicidal activity against many *Candida* isolates at adequate concentrations [20]. The echinocandins show rather similar *in vitro* antifungal activity with largely overlapping minimal inhibitory concentration ranges for clinically relevant species [21]. MICs against *C. albicans*, *C. glabrata*, *C. tropicalis* and *C. krusei* are usually significantly lower than those observed for *C. parapsilosis* or the rare species *C. guilliermondii*. However, this divergence apparently does not translate into clearly significant differences in clinical activity. In a recent meta-analysis, the treatment success rate in 202 patients with *C. parapsilosis* infection from five studies was very similar for echinocandins and non-echinocandin drugs (76.3% vs. 73.0%) [22].

Recently proposed modifications of clinical interpretive breakpoints for echinocandin susceptibility testing of *Candida spp.* reflect this fact: *C. parapsilosis* breakpoints are at least three dilution steps higher than those of other *Candida* species, based on the fact that isolates carrying resistance mechanisms are associated with much higher MIC levels in *C. parapsilosis* vs. other species [23].

Despite increasing use over the last decade, resistance against echinocandins still remains rare and is largely restricted to *de novo* emergence in patients with longer treatment duration [24]. This is reassuring, given the fact that point mutations in the target enzyme subunit may suffice for resistance induction [25]. Cross-resistance among echinocandins is the rule, while caspofungin-resistant isolates remaining susceptible to anidulafungin and/or micafungin have been observed [26, 27].

PHARMACOKINETIC PREMISES

Due to a lack of oral bioavailability, the echinocandins are exclusively parenteral drugs administered via intravenous infusion over 1-2 hours. Recommended infusion rates should not be exceeded to avoid systemic infusion reaction.

Anidulafungin and micafungin show linear dose-plasma exposure relationships while caspofungin exhibits some degree of non-linearity in the clinically useful range [28, 29]. All echinocandins exhibit some degree of enrichment versus plasma in organs relevant to invasive candidiasis (liver, kidneys, spleen, lungs). In animal models, micafungin enriches 2-3 fold in these organs [30], caspofungin mainly targets the liver and to a lesser extent the kidneys [31] while anidulafungin exhibits rather uniform enrichment (9-12 fold) in all four organs [32]. None of the echinocandins reaches adequate levels in the cerebrospinal fluid, intraocular compartments or urine, making them less suited for treatment of infections involving these sites [33-35].

Anidulafungin is exclusively degraded by spontaneous chemical processes and possibly by nonspecific peptidases in the plasma [36], whereas the other echinocandins are metabolized to some extent in the liver via N-acetylation or by the catechol-O-methyltransferase [37]. This may entail dose adjustment, restrictions of use or drug interactions.

DOSAGE CONSIDERATIONS

Anidulafungin is used at a uniform dosage of 100 mg/d (preceded by one 200 mg loading dose on day 1) [38] for all patients regardless of body weight, organ functions, age, or comedications [39-41]. Anidulafungin can be used at the same dose in patients with all levels of hepatic insufficiency [40].

Caspofungin dosage must be adjusted according to body weight and liver function. In addition, patients on treatment with inducers of hepatic metabolism must receive higher doses [42]. The standard dosage is 50 mg/d (after an initial loading dose of 70 mg on day 1). Patients weighing >80 kg should receive 70 mg/d as maintenance dose. Larger doses of caspofungin (150 mg/d) have been used in a clinical trial on invasive candidiasis. No significant differences or toxicity or efficacy vs. standard doses were noted [43]. Moderate liver insufficiency (Child-Pugh Score 7-9) requires a reduction of the maintenance dose to 35 mg/d [44]. Caspofungin should not be used in patients with severe hepatic insufficiency (Child-Pugh Score >9) [29].

Micafungin dosage is dependent of the purpose of treatment (therapy vs. prophylaxis) [45, 46] and body

weight [47]. Therapeutic use requires double the dosage compared to prophylactic treatment. In patients weighing ≤ 40 kg micafungin must be dosed per kg body weight (2 mg/kg d or 1 mg/kg d for prophylaxis), whereas heavier patients receive a fixed dosage of 100 mg/d (or 50 mg/d for prophylaxis). The dosage may be doubled in patients with insufficient initial response.

Micafungin doses are independent of organ functions. However, the drug should not be used in patients with severe liver insufficiency due to a lack of data [47].

DRUG-DRUG INTERACTIONS

Generally, the echinocandins are characterized by a low potential of drug-drug interactions, a feature that is clearly a novelty in the field of antifungals that notoriously involved multiple pharmacokinetic (azoles) [48] or problematic pharmacodynamic interactions (polyenes) [49].

Primarily owing to the absence of any hepatic metabolism [36], no clinically relevant interactions have been described for anidulafungin [50-52], the drug may thus be used at a fixed dose regardless of any comedications [41].

Due to its hepatic metabolism, caspofungin maintenance dosages should be increased to 70 mg/d in patients concomitantly receiving enzyme inducers such as rifampicin, dexamethasone, phenytoin, or carbamazepine [42]. Other potential interactions of caspofungin involve immunosuppressants: the comedication of caspofungin and ciclosporin A has been associated with liver function abnormalities in healthy volunteers, therefore patients receiving both drugs should be monitored for liver damage, whereas a retrospective review of patients treated with the combination did not find evidence of enhanced clinically significant hepatotoxicity [29, 53]. In addition, caspofungin increases the trough levels of tacrolimus [54]; plasma level monitoring and appropriate dose adjustments are required [29].

Micafungin increases the exposure of amphotericin B requiring risk/benefit analysis and close monitoring of amphotericin B toxicity. In addition micafungin increases the exposures of itraconazole, sirolimus and nifedipine, requiring monitoring and dose reduction as appropriate [47].

CLINICAL TRIALS ON TREATMENT OF INVASIVE CANDIDA INFECTIONS

The discussion in this section is mainly focussed on well-conducted large, prospective trials. Studies with small patient numbers or retrospective trials were not included due to their limited evidence level and ambiguities of clinical interpretation.

PIVOTAL TRIALS

The clinical efficacy and safety of all three echinocandins was investigated in randomized double-blinded multicenter trials primarily involving non-neutropenic adult patients with candidemia (Table 1) [45, 55-57].

Two studies used prevalidated comparator regimes – anidulafungin was studied versus fluconazole [55] and caspofungin was tested versus conventional amphotericin B [56]. An earlier randomized study had established the therapeutic noninferiority of fluconazole versus amphotericin B [58]. Micafungin, however, was initially investigated vs. liposomal amphotericin B that had not been studied in a randomized trial for this indication [57]. Regulatory authorities therefore requested a second study of micafungin versus caspofungin [45].

All but one study had a primary endpoint of combined clinical-microbiological response at the end of intravenous therapy in the modified intention-to-treat (MITT) population, i.e. patients with initial detection of *Candida spp.* in blood or other physiologically sterile sites, and receipt of at least 1 dose of study medication. The trial of micafungin vs. liposomal amphotericin B [57] primarily analyzed patients treated for at least 5 days which lead to numerically high success levels in both groups by elimination of patients with early discontinuation or failure. The MITT analysis for non-inferiority was a secondary endpoint in this trial. With the exception of the micafungin vs. liposomal amphotericin B trial, all studies allowed for a switch to oral fluconazole after at least 10 days of intravenous study treatment.

All three trials involving caspofungin and micafungin the non-inferiority of the experimental drug vs. comparator: caspofungin was as effective as amphotericin B and micafungin was non-inferior to liposomal amphotericin B and caspofungin. There were no significant mortality differences between the respective study arms [45, 56, 57].

The trial of micafungin vs. caspofungin [45] involved two micafungin dose regimens (100 mg/d and 150 mg/d) that showed similar efficacy, establishing 100 mg/d as the standard dose in this indication. The global success rates in patients with *C. glabrata* infections were approximately 20% higher in the micafungin vs. caspofungin groups, whereas the difference was not statistically significant.

In contrast to the other trials, the protocol of the study comparing caspofungin vs. amphotericin B deoxycholate [56] defined a change of therapy due to toxicity as failure. This caused an inherent imbalance in favour of caspofungin since the well-known nephrotoxicity of amphotericin B necessitated the discontinuation of this study drug in a high proportion of patients (16.5% versus 2.8% in the caspofungin arm).

The trial of anidulafungin versus fluconazole [55] was the first randomized study in invasive candidiasis to establish a significant difference in the primary endpoint favouring a new drug versus an established option. The global success rate at the end of intravenous therapy was 76% for anidulafungin vs. 60% for fluconazole. The difference was statistically significant (95% confidence interval 3.9-27.0). According to the same criteria, anidulafungin had significantly higher success rates at the end of all therapy and at the follow-up visit 2 weeks after the end of therapy. The higher global efficacy of anidulafungin may be due to a faster clearance of the pathogens from the blood

Table 1. Results in the MITT populations of pivotal trials of echinocandins for therapy of invasive fungal infections [45, 55-57].

	Anidulafungin	Caspofungin	Micafungin	
Comparator	Fluconazole	Amphotericin B deoxycholate	Liposomal amphotericin B	Caspofungin ****
Patient number (MITT), n	127 / 118	109 / 115	247 / 247	191 / 188
Candidemia, %	91 / 87	82.6 / 79.1	84.2 / 85.8 ***	85.3 / 85.6
Infection with <i>C. non-albicans</i> , %	36 / 41 *	64.4 / 45.9 [p = 0.0009]	62.4 / 58.9 ***	54.5 / 60.6
Neutropenia, %	2.4 / 3.4	12.8 / 8.7	11.9 / 7.9 ***	11.5 / 5.9
Switched to oral fluconazole, %	26.0 / 28.0	24.8 / 34.8	Not allowed	20.9 / 21.2
Global success at end of IV therapy, %	75.6 / 60.2 [p = 0.01]	73.4 / 61.7 [p = n.s.]	74.1 / 69.6 [p = n.s.]	76.4 / 72.3 [p = n.s.]
Global success at end of all therapy, %	74.0 / 56.8 [p < 0.02]	72.5 / 61.7 [p = n.s.]	74.1 / 69.6 [p = n.s.]	74.9 / 70.2 [p = n.s.]
Global success at 2 weeks follow up, %	64.6 / 49.2 [p < 0.02]	63.6 / 53.8 [p = n.s.]	Not reported	54.5 / 50.5 [p = n.s.]
Global success at 6 weeks follow up, %	55.9 / 44.1 [p = n.s.]	56.6 / 47.5 ** [p = n.s.]	Not reported	46.6 / 42.6 [p = n.s.]
Microbiological success at end of IV therapy, %	88.1 / 76.2	Not reported	Not reported	88.5 / 84.0
Time to negative blood cultures, days (<i>C. albicans</i>)[59]	2 / 5	Not reported	3 / 4 ***	2 / 2
Persistent infection, %	6.3 / 14.4 [p = n.s.]	8.3 / 8.7 [p = n.s.]	8.9 / 8.4 *** [p = n.s.]	5.8 / 9.6 [p = n.s.]
Mortality rate (ITT), %	22.8 / 31.4 [p = n.s.]	34.2 / 30.4 [p = n.s.]	40 / 40 [p = n.s.]	29.0 / 26.4

* Patients with *C. krusei* infection were excluded from the trial.

** Follow-up at 6-8 weeks after end of all therapy.

*** In the per-protocol set.

**** Column excludes results of micafungin 150 mg arm.

stream that was obtained e.g. for *C. albicans* after a median of 2 days in patients receiving anidulafungin vs. 5 days in the fluconazole arm [59]. Persistent *Candida* infection at the end of intravenous therapy was observed in 6.3% vs. 14.4% of patients. The robustness of these data was shown by the analysis of subpopulations with risk factors for an unfavourable outcome: anidulafungin achieved higher success rates in intensive care patients, patients with single and multiple organ failure and/or severe sepsis, higher age, and retained central venous catheters [60].

The results of this trial established that anidulafungin – and potentially the echinocandins in general – may provide a relevant clinical benefit versus the long-standing standard candidemia drug fluconazole. This advantage may be used to the benefit of more severely ill patients in clinical routine, a notion that is reflected in current guideline recommendations on the treatment of invasive *Candida* infections.

FURTHER STUDIES

The database of anidulafungin was recently expanded in a non-comparative multicenter phase IIIb trial (ICE study) [61] exclusively involving adult intensive care patients with invasive *Candida* infection and at least 1 additional risk factor, e.g. abdominal surgery, organ

transplant, or neutropenia. 29% of the 170 patients had invasive infections involving non-bloodstream body sites. Patients were allowed to switch to oral fluconazole or voriconazole after at least 10 days of intravenous therapy. The success rates at the end of intravenous therapy and further time points were comparable to the results of the pivotal trial, confirming the efficacy of anidulafungin for severely ill patients with invasive candidiasis including those with tissue or organ involvement (Fig. 1).

Another multicenter study investigated the use of caspofungin as primary or salvage treatment in invasive candidiasis involving non-bloodstream body sites. Patients with peritonitis, intraabdominal abscesses, chronic-disseminated candidiasis, or multilocular invasive candidiasis received the standard 50 mg/d caspofungin dose, patients with osteomyelitis, septic arthritis, or endocarditis were treated with a higher dosage (100 mg/d) [62]. These dosages could be escalated to 100 mg/d or 150 mg/d, respectively, in cases with inadequate response. The overall success rate was 81%, ranging from 33% (1/3) for endocarditis to 100% (4/4) for osteomyelitis or septic arthritis. Overall mortality was 23% at 12 weeks. The elevated dosage of 100 mg/d was well tolerated.

Colombo et al. [63] analyzed the data of 212 patients with *C. non-albicans* infections (predominantly

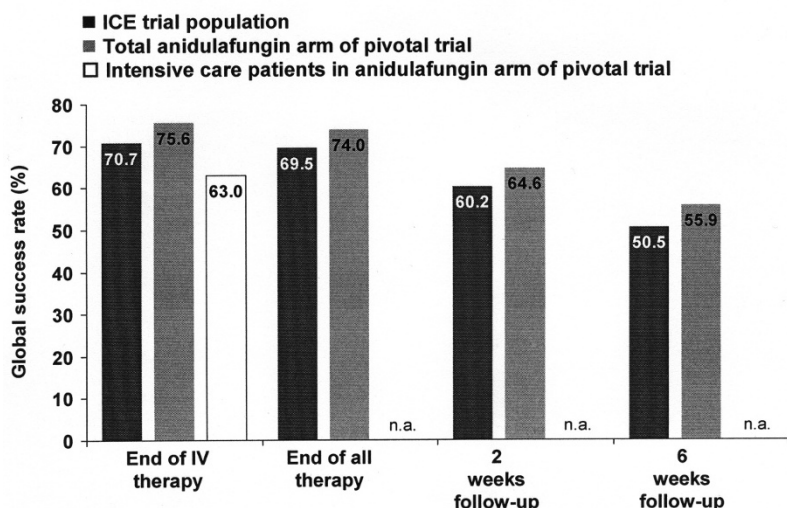


Fig. 1. Global success rates in the anidulafungin ICE trial in intensive care patients and the previous pivotal trial [55, 60, 61].

C. parapsilosis, *C. tropicalis*, *C. glabrata* or *C. krusei*) from the caspofungin clinical trials database, indicating response rates in the range of infections with *C. albicans* (at least 70%).

A recent randomized trial compared caspofungin at elevated dosage (150 mg/d) versus standard-dose therapy in patients with proven invasive *Candida* infections, mostly candidemia [43]. Both dosages were equally well tolerated as shown in the primary safety analysis. No significant differences between the study arms were observed in terms of clinical or microbiological response rates in the secondary efficacy analysis. However, the trial was not sufficiently powered to establish either therapeutic noninferiority or superiority of any treatment arm. A numerically higher response rate of *C. parapsilosis* infections in the high-dose arm (17/21 vs. 11/18) may indicate a benefit in patients with this pathogen species but requires further study due to the lack of statistical significance.

EXPERIENCE IN NEUTROPENIC PATIENTS

The therapeutic use of echinocandins in neutropenic patients with invasive *Candida* infection has not been studied in dedicated prospective trials. The echinocandin arms of the pivotal invasive candidiasis trials included comparatively small numbers of patients with neutropenia at baseline (3-50 patients, or 2.4%-13.3%) [45, 55-57]. Keeping the limited database in mind, the pooled response rate for neutropenic patients reported in the trial of micafungin vs. caspofungin was in the same range as in non-neutropenic patients (68% vs. 74%), without significant differences between the study arms [45]. Micafungin achieved a similar response rate in neutropenic patients as did liposomal amphotericin B (75% vs. 80% in the per protocol set of the trial) [57]. Caspofungin was similarly effective as amphotericin B deoxycholate in neutropenic patients (50% vs. 40% successfully treated patients) [56].

Betts et al. [64] published a compiled analysis of neutropenic patients treated in 4 studies of the caspofungin clinical trials program. Overall success rate in the 27 patients with invasive candidiasis was 68%, 15 of 17 successfully treated patients achieved a complete response.

DEESCALATION TO AZOLES

Based on the results of the pivotal trials of echinocandins that all but one [57] allowed for a switch from intravenous echinocandin to (oral) therapy with fluconazole after 10 days, a step down to an oral azole agent appears feasible after pathogen clearance and clinical stabilization [65]. No detrimental effects of this step down were observed in the approximately 20-35% of the study patients using this option [45, 55, 56].

This approach may provide economic benefits and helps to avoid changes of fungal epidemiology and selection of echinocandin resistance via reduced overall exposure to this class of drugs [66].

Prerequisites for a step down to an azole include clinical improvement, resolution of fever, negative blood culture, documented sensitivity of the initial isolate to the intended drug (particularly in patients with *C. glabrata* infection) and, in the case of oral medication, adequate gastrointestinal function. Pivotal trials that allowed a transition to an oral azole (fluconazole) required 10 days of intravenous therapy [45, 55, 56]. The candidiasis guideline committee of the Infectious Diseases Society of America (IDSA) estimates that 3-5 days of echinocandin therapy followed by oral fluconazole or voriconazole is reasonable while pointing out that few data support this approach [67]. Therefore, the minimum required duration of an initial echinocandin therapy remains uncertain.

CATHETER MANAGEMENT

As biofilms forming on the surfaces of intravenous catheters may serve as a source or reservoir in *Candida* blood stream infections, current guidelines recommend the removal of catheters in patients with documented candidemia if at all possible [67]. However, as cited by the IDSA guideline panel this recommendation is based primarily on experience in patients receiving antifungals other than echinocandins [67].

Azoles, for that matter, exhibit very little or no useful activity against *Candida spp.* in biofilms [68, 69]. But as echinocandins have been shown to exert potent antifungal activity against biofilm-dwelling *Candida*

cells [68-72], the use of this class of drugs may put the urgency of early catheter removal into perspective. Interestingly, additive effects of neutrophils and anidulafungin on *C. parapsilosis* and *C. albicans* biofilms were recently reported [73, 74].

Analyzing data from the two above-mentioned pivotal trials of micafungin vs. caspofungin or liposomal amphotericin B, respectively, Nucci et al. [75] did not find a clinical benefit of early catheter removal. In their multivariate analysis, early catheter removal within 24 or 48 hours of treatment initiation was not associated with higher treatment success or lower mortality. In two of the pivotal trials, response rates of patients with retained catheters were similar to those with catheter removal [56, 57]. In the study of micafungin vs. caspofungin, patients who underwent catheter removal or replacement *at any time* had significantly higher response rates than those with remaining catheters in place [45]. This result of an unadjusted analysis may have been influenced by imbalances of the severity of underlying diseases between the two catheter status subgroups. In the trial of anidulafungin vs. fluconazole, the response rates of patients with retained catheter were higher in the anidulafungin group, whereas the number of patients was small (4 vs. 11 patients) [55].

With due caution, it may be concluded that an echinocandin could be preferred over fluconazole as initial therapy for patients in whom early catheter removal appears to be unfeasible or associated with inappropriate risks or complications. Deescalation to an azole appears inadequate in these patients.

However, it should be noted that the guideline panel of the European Conference on Infections in Leukemia (ECIL-3) strongly recommends catheter removal in all infections involving *C. parapsilosis* probably because this species is particularly prone to biofilm formation and generally less susceptible to echinocandins vs. other species [76].

EXPERIENCE IN PEDIATRIC PATIENTS WITH INVASIVE *CANDIDA* INFECTIONS

Limited available data on the use of echinocandins for treatment of invasive *Candida* infections in pediatric patients include prospective clinical trials for caspofungin and micafungin. Both agents are licensed for the treatment of invasive candidiasis in children (>12 months of age for caspofungin).

Caspofungin was studied in a multicenter trial that involved 37 patients (age: 3 months to 17 years) with invasive *Candida* infections, mostly candidemia [77]. In 30 patients with primary therapy, complete responses were observed in 81% of cases. Five of 7 patients receiving caspofungin for salvage therapy were successfully treated. The response rates were largely independent of age, but the small sample size does not allow valid conclusions regarding this aspect. Two out of five neutropenic patients were successfully treated. In 4 patients, the dosage was escalated from 50 to 70 mg/m² due to inadequate treatment response, with successful outcome in 3 of them.

The efficacy of micafungin in pediatric patients with invasive candidiasis was investigated in a subpop-

ulation of the above-mentioned double-blind, randomized trial. This substudy [78] compared micafungin (2 mg/kg) with liposomal amphotericin B (3 mg/kg) as first-line therapy of invasive candidiasis in 106 children and adolescents <16 years of age; 57 patients were ≤2 years old, 19 patients were premature infants. Successful outcomes were observed in 73% of patients of the micafungin group versus 76% of those treated with liposomal amphotericin B. Treatment success was independent of neutropenia or prematurity status. Adverse events leading to discontinuation of study drug were significantly less frequent in the micafungin group.

Pediatric patients aged ≥6 months were included in a randomized trial investigating prophylaxis of invasive fungal infections in recipients of blood stem cell transplants [46]. A total of 84 pediatric patients (<16 years), mostly receiving allogeneic hematopoietic stem cell transplantation (HSCT) were analyzed. Proven or probable breakthrough infections occurred in 1 of 39 pediatric patients in the micafungin group (no *Candida* infections) and 3 of 45 in the fluconazole group (including 1 candidemia).

Published clinical experience with anidulafungin in children is limited to date [79]. Clinical trial data of anidulafungin in pediatric patients with invasive candidiasis have not been presented yet; a non-comparative trial enrolling 60 patients with invasive candidiasis is ongoing [80].

Echinocandins, i.e. currently caspofungin and micafungin, provide valuable and well-tolerated treatment options for pediatric patients with *Candida* infections.

PROPHYLAXIS OF INVASIVE CANDIDIASIS

Prophylactic use of systemic antifungals is an established practice in hematological and selected non-hematological patients at high risk of invasive candidiasis or other invasive fungal infections [81, 82]. Several studies have explored the use of echinocandins in this indication.

Clinical experience in the prophylactic treatment with caspofungin includes hematological patients and liver transplant recipients. Mattiuzzi et al. [83] performed an open-label randomized comparison of caspofungin versus itraconazole in 192 patients receiving chemotherapy for malignant haematological diseases. Seven patients in the caspofungin arm developed invasive fungal infections (including 2 with candidemia), compared to 5 in the itraconazole arm (including 4 with candidemia). The limited size of the trial precluded definitive conclusions about the relative prophylactic efficacy of both drugs. Chou et al. [84] reported on a retrospective analysis of 123 blood stem cell recipients (117 with allogeneic HSCT; 50 of whom developed GVHD) who had received caspofungin (35-50 mg/d) over a median duration of 73 days for prophylaxis of invasive fungal disease. Nine patients (7.3%) developed breakthrough invasive fungal infections including 2 with *Candida* infections). The authors concluded that caspofungin appears to be an effective option for primary antifungal prophylaxis in the highly immunosuppressed stem cell transplant patient population. Fortun et al. [85] described a

prospective trial in 71 liver transplant recipients receiving prophylactic caspofungin for at least 21 days, the observation period spanned 100 days. Two patients developed breakthrough fungal infection including one *C. albicans* surgical wound infection.

Micafungin was investigated in a large phase III randomized double blind trial versus fluconazole for prophylaxis in 882 allogeneic HSCT recipients of all ages during the neutropenic phase for up to 42 days. Seven breakthrough infections occurred in the micafungin arm (including 4 candidemias) versus 11 in the fluconazole group (including 2 candidemias) [46]. Based on the results of this trial, micafungin was licensed for prophylaxis of invasive *Candida* infections in allogeneic HSCT patients.

The prophylactic use of anidulafungin has not been investigated as yet.

Thus, randomized trials on prophylaxis with echinocandins indicate their potential usefulness in the prevention of *Candida* infection in hematological high risk patients. However, study data in non-hematological patients are insufficient to support prophylactic treatment with echinocandins in non-study settings for this population. In addition, their routine prophylactic use would expose high numbers of patients to these agents for prolonged periods of time with potential untoward consequences, e.g. selection of resistance in the exposed patients, and shifts in the local epidemiology towards less echinocandin-susceptible strains. Given the restricted options for the treatment of patients after exposure to echinocandins and/or selection of low-susceptibility strains, particularly *C. glabrata* and *C. krusei*, the widespread use of these agents appears unjustified, let alone the burden of intravenous application and high cost.

SAFETY AND TOLERABILITY

The echinocandins have generally favourable safety and tolerability profile (Table 2). Most observed adverse events (AEs) are mild to moderate in nature. The most frequent adverse events include infusion reactions (predominantly phlebitis and fever), liver enzyme

abnormalities, mild hypokalemia, gastrointestinal symptoms, skin rash and headache [29, 41, 91].

Infusion reactions such as fever or rigors that may occur more often with caspofungin versus the other echinocandins [86] may be managed by reducing the rate of infusion. Phlebitis may be avoided by infusion via a central venous catheter [54] after early replacement in the course of therapy. Liver enzyme abnormalities are generally mild and were mostly less common or similarly frequent as in the comparator groups of randomized trials [55-57].

Echinocandins are rated as pregnancy category C drugs and should not be used in pregnant women [87-89]. As these drugs may be secreted in the milk, breastfeeding should be avoided.

In the pivotal trial of anidulafungin vs. fluconazole, the total adverse event rates were similar in both arms [55]. Anidulafungin was associated with significantly lower incidence of hepatic enzyme abnormalities (1.5% vs. 7.2% of patients; p = 0.03). Two patients experienced treatment-related serious AEs in the anidulafungin arm (1 patient with atrial fibrillation, 1 with seizures). The most frequent treatment related AEs (all grades) were hypokalemia (3.1%), diarrhea (3.1%) and elevated ALT levels (2.3%). There was 1 treatment discontinuation (<1%) due to an adverse event [90].

As expected, caspofungin was significantly better tolerated than amphotericin B deoxycholate in the pivotal invasive candidiasis trial [56]. Drug-related infusion reactions, laboratory abnormalities and nephrotoxic events were significantly less frequent in the caspofungin group: 20% (vs. 49%) of patients had an infusion-related event (mostly chills, fever or phlebitis/thrombophlebitis), 11% (vs. 26%) developed hypokalemia requiring supplementation, 24% (vs. 54%) developed laboratory abnormalities (mostly liver function test changes) and 8% (vs. 25%) had a nephrotoxic effect. Three percent (vs. 23%) discontinued study treatment due to adverse events.

Micafungin showed a generally similar safety and tolerability profile versus liposomal amphotericin B in the first phase III trial in invasive candidiasis [57]. 5% (vs. 9%) of patients discontinued therapy due to an

Table 2. Frequencies of drug-related adverse events observed in patients receiving echinocandins [86].

Adverse reaction, % of patients	Anidulafungin	Caspofungin	Micafungin
Phlebitis	< 1	3.5-25	1.6
Fever	< 1	4-40	1-14
Abdominal pain	< 2	3.6	1
Nausea / vomiting	1 / < 1	1-6 / 2-4	2-7 / 1-5
Diarrhea	3.1	3.6	1.6
Headache	1.3	4-15	2-17
Rash / pruritus	1 / < 2	1-10 / < 2	1-12 / < 1
Leukopenia	< 1	6.2	1.6
Neutropenia	1	1.9	1.2
Thrombocytopenia	< 2	3.1	< 1
Hypokalemia	3-10	2-10	1.2
Liver function test abnormalities	3-5	1-15	1-8

adverse event. The most frequent micafungin-related AEs were infusion related reactions (17%), fever (8%), hypokalemia (7%) and nausea (5%). Drug-related laboratory abnormalities mostly included moderate liver function test abnormalities (2-7%). The second pivotal trial comparing micafungin vs. caspofungin reported similar overall drug-related AE profiles in the two micafungin and the caspofungin arms [45]. The types of adverse events were not reported per treatment group in the publication. Adverse events in the total population predominantly included liver function test abnormalities, nausea, constipation, hypokalemia and rash; 2-4% of patients withdrew from the trial due to adverse events.

As a unique aspect of micafungin, foci of altered hepatocytes and hepatocellular tumours were observed after prolonged exposure in preclinical animal experiments, with a threshold for tumour induction in the range of human therapeutic exposure [91]. While the clinical relevance of these findings remains unclear, the European Medicines Agency restricted the use of micafungin to situations where other antifungals are inappropriate. Treatment should be discontinued in patients with elevation of liver enzymes on therapy to avoid adaptive liver cell regeneration and potential subsequent tumour formation. Taking a divergent view on the apparent preclinical tumorigenicity of prolonged exposure to micafungin, the Food and Drug Administration did not impose this kind of restriction [92].

RECOMMENDATIONS IN GUIDELINES

Based on the results of the described clinical trials, an expert group of the Infectious Disease Society of America [67] recommends echinocandins as the preferred treatment in moderately to severely ill non-neutropenic adult patients with suspected or documented candidemia before pathogen species identification. In particular, the IDSA committee recommends the use of anidulafungin, caspofungin or micafungin at an evidence level of A-I. Fluconazole should be restricted to less severely ill patients without recent exposure to an azole antifungal, and those patients without an elevated risk of involvement of *C. glabrata* or *C. krusei* (such as cancer patients or elderly patients) [93-95]. For infections with documented involvement of *C. glabrata*, the IDSA panel recommends an echinocandin, whereas fluconazole is preferred for documented *C. parapsilosis* infections. In terms of prophylaxis, micafungin at 50 mg/d is considered an option for allogeneic stem cell recipients with neutropenia (evidence level A-I).

On a conference in 2009, European Conference on Infections in Leukemia (ECIL-3) panel issued similar guidance [76, 96]: echinocandins or liposomal amphotericin B are recommended with the highest assigned

evidence level for treatment of candidemia before species identification in the general patient population and in hematologic patients. Azoles should not be used in patients with previous azole prophylaxis, and fluconazole is restricted to non-severely ill patients. After species identification, echinocandins or liposomal amphotericin B are treatments of choice in patients infected with *C. albicans*, *C. glabrata*, and *C. krusei*. Fluconazole should not be used for *C. glabrata* and *C. krusei* infections. There is no guidance provided on preferred treatments for *C. parapsilosis* infections.

In their guidelines for hematological patients, the Infectious Diseases Working Party (AGIHO) of the German Society of Hematology and Oncology (DGHO) prefers an echinocandin to fluconazole for initial therapy of invasive candidiasis in unstable or neutropenic patients. This recommendation is based on the increasing incidence of infections with *Candida* spp. with primary resistance or reduced susceptibility to fluconazole and its lower efficacy versus anidulafungin [55, 97].

While the optimum treatment duration has not been specifically studied, the guideline panels recommended a duration of therapy for candidemia without obvious metastatic complications of at least 2 weeks after documented eradication of *Candida* species from the bloodstream plus resolution of symptoms attributable to candidemia plus resolution of neutropenia, if applicable [67, 76, 96, 97].

ROLE OF THE ECHINOCANDINS IN THE MANAGEMENT OF INVASIVE *CANDIDA* INFECTIONS

The echinocandins combine a number of features required for the optimization of primary therapy of invasive *Candida* infections, providing enhanced opportunities of effective and safe treatment over the azole antifungals, particularly fluconazole that is still used as primary therapy in the majority of patients with candidemia (Table 3; Fig. 2) [98].

In contrast to the azoles they are fungicidal against most *Candida* strains [20], potentially allowing for more rapid clearance of the pathogen from the infection sites. While fungicidal activity may prove advantageous in severely ill patients, particularly those with severe sepsis, this could not yet be demonstrated in clinical studies since the proportion of critically ill patients in the only available trial of an echinocandin vs. an azole in this indication was below 20%. At least for anidulafungin, a significantly higher success rate in the primary endpoint of a randomized trial versus fluconazole indicates potential therapeutic advantages of echinocandins over azoles in the treatment of candidemia

Table 3. Agents used for the treatment of candidemia as reported in the PATH alliance database [98].

N = 2019 patients	Fluconazole	Echinocandins	Lipid-formulation amphotericin B	Voriconazole	Amphotericin B deoxycholate
Patients treated, %	67.7	48.9	10.0	6.7	2.2

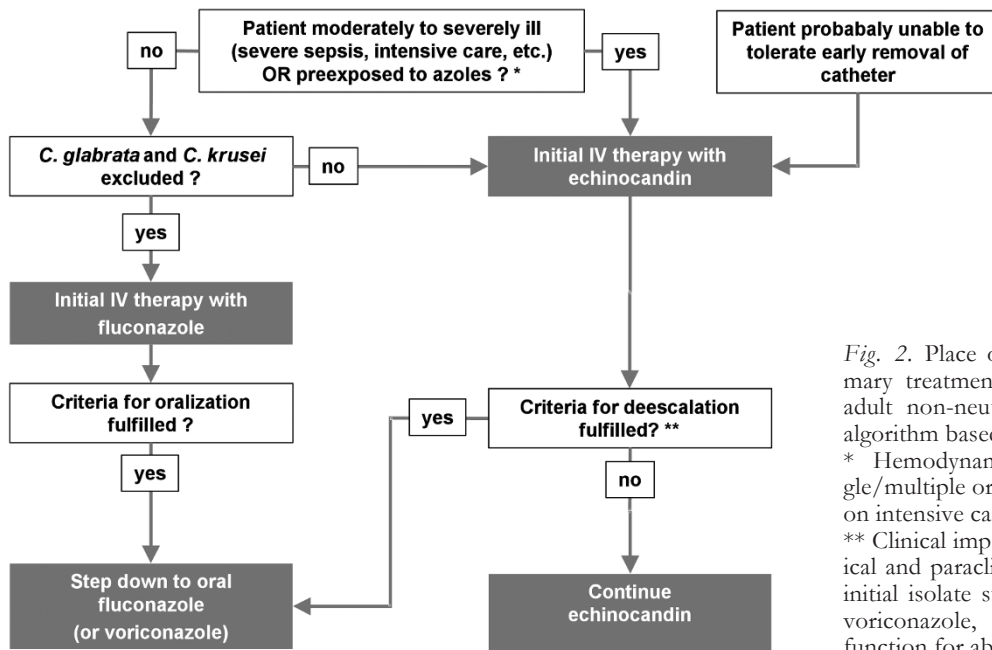


Fig. 2. Place of echinocandins in the primary treatment of invasive candidiasis in adult non-neutropenic patients. Modified algorithm based on current guidelines [67]. * Hemodynamic instability and/or single/multiple organ failure, i.e. most patients on intensive care units. ** Clinical improvement, resolution of clinical and paraclinical signs of inflammation, initial isolate susceptible to fluconazole or voriconazole, adequate gastrointestinal function for absorption.

[55]. Also evidence of a shortened median time to blood culture negativity vs. fluconazole appears to point in that direction [59].

Being fully active against *C. glabrata* and *C. krusei*, the fungal Achilles' heels of fluconazole, the echinocandins provide an important measure of additional therapeutic reliability in situations where treatment must be started in absence of species identification or even before availability of blood culture results, particularly in elderly patients with high rates of *C. glabrata* infection [94], and for hematologic and solid cancer patients in whom very high rates of fluconazole-resistant isolates have been described in a recent candidemia survey [95]. Again, this is particularly relevant in patients with severe sepsis or septic shock with a narrow time window of opportunity for initiation of effective therapy to preserve optimum chances of survival [99, 100].

Elevated inhibitory concentrations observed in *C. parapsilosis* are causing some concern, but several aspects may alleviate these concerns: (i) a meta-analysis revealed no disadvantage for echinocandins vs. other therapies; [22] (ii) *C. parapsilosis* is considered as a less virulent compared to e.g. *C. albicans* and is associated with lower mortality rates [98], (iii) recently proposed resistance breakpoints for *C. parapsilosis* are several steps higher than for the other clinically relevant *Candida* species [23]; and (iv) current guidelines recommend echinocandins for primary therapy in the absence of species information [67, 76, 97].

Organ dysfunctions are common in patients developing invasive fungal infections. Being pharmacokinetically independent of renal function, the echinocandins need no dose adjustment in patients with all grades of renal insufficiency or renal replacement therapies, quite different from fluconazole that needs complex dose adjustments in patients with impaired renal function and hemodialysis or hemofiltration [101]. In fact, renal impairment was identified as a significant predictor of inadequate fluconazole dosing [102].

In patients with liver dysfunction, anidulafungin and micafungin may be administered without dose adjustments [41, 47]. Anidulafungin can be used in patients with severe hepatic insufficiency [41]. The other echinocandins should not be used in this population for lack of data.

The low propensity of echinocandins for drug interactions may allow for substantial simplification of treatment in severely ill patients receiving multiple comedications. Being inhibitors and substrates of hepatic enzymes, the azoles are associated with a multitude of interactions [103] complicating patient management and potentially jeopardizing treatment success. This issue is avoided with anidulafungin and greatly reduced to interactions with few immunosuppressive drugs with the other echinocandins.

Activity against biofilms is another feature that favours the echinocandins over azoles as agents of choice in patients with catheter-associated candidemia particularly in situations where early removal of catheters appears unfeasible. Even in patients whose catheters are removed within the first two days of therapy, echinocandins may suppress fungal burden more effectively during this critical initial treatment phase when the potentially fungus-shedding device is still present.

Prophylactic use of echinocandins currently is an option for selected hematological patients in whom azoles are inappropriate due to tolerability issues or unmanageable drug interactions. Mind that anidulafungin and caspofungin are not licensed for prophylaxis and micafungin is not licensed for prophylaxis of mould infections, a predominant concern in hematological patients [29, 41, 47].

In conclusion, echinocandins provide safe, uncomplicated and highly active therapy for invasive *Candida* infections with potentially superior efficacy versus fluconazole and better tolerability compared to formulations of amphotericin B, making them the agents of choice for moderately to severely ill patients with invasive candidiasis.

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