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New antifungal agents for the treatment of candidaemia

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Abstract

Suspected or proven invasive candidiasis is an important indication for antifungal drugs and a leading cause of death. Prompt initiation of effective therapy has a marked effect on survival, but the indiscriminate application of different risk factor-based prediction models is massively increasing the number of patients treated unnecessarily. Fluconazole resistance levels are <5% in most European centres and the use of low doses is still common. Candins are fungicidal, have efficacy against device-related infections, have few interactions and are well tolerated. Accordingly, the use of newer, more expensive drugs must be carefully balanced in each case. Campaigns directed towards stewardship in antifungal drug use must take into consideration the choice of the drug, the dose and route of administration, and the length of therapy. Early microbiological information and medical education may contribute to better use of these important drugs. We review the characteristics of the new antifungals used for the treatment of candidaemia.

Keywords:

Candidaemia

Echinocandins

Voriconazole

Anidulafungin

Micafungin

Caspofungin

1. Introduction

Candida spp. are the most common cause of nosocomial invasive mycosis. Although the fourth most frequently isolated microorganism from blood cultures, it is the leading cause of related mortality, which remains near 40% in most series.

Different studies demonstrate that the rate of candidaemia is increasing. Figures from our institution demonstrate that the incidence of candidaemia per 100 000 inhabitants has increased from 1.7 episodes in 1985 to 12.5 in 2006 ($P < 0.0001$) [1]. This trend has been confirmed by other authors. A large series summarizing 10 319 418 cases of sepsis from a sample of non-federal acute care hospitals in the USA showed that cases of fungaemia increased by 207% from 1979 through 2000 [2].

It is estimated that 33–55% of candidaemia episodes occur in intensive care units, but many hospital departments are affected by the problem. In a recent European study the proportions of surgical and critical patients affected were 44.7% and 40.2%, respectively [3].

The cost of a candidaemia episode has been estimated at US\$44 000 for adults and US\$28 000 for neonates [4,5]. However, the exponential increase in hospital expenditure on antifungal drugs (fourfold increase since 2001) is not justified by the increase in the number of proven infections. The reasons are multiple, but a change in the way drugs are prescribed and the use of newer antifungal drugs, sometimes in combination, are part of the problem. The cost of treating a candidaemic episode with fluconazole is around €240, and with an echinocandin is over €6000. The change in the way drugs are prescribed relates to the observation that at least 70% of drugs prescribed are part of a pre-emptive strategy [6]. Drugs are frequently started after using one of the available predictive scores (Ostrosky 1 or 2, Candida score, etc.) [6–

9], without taking into account that, although their negative predictive value is high, their positive predictive value is <15%.

Candidaemia can be treated with several classes of drug (azoles, candins or polyenes), the choice of which depends on the local epidemiology, the percentage of strains resistant to fluconazole, the origin of the infection, and the patient's co-morbidities, among others [10]. Although non-albicans strains have clearly increased, in most European centres the rate of resistance to fluconazole is <5% [3,11,12]. Rapid detection of resistance directly from blood samples may help in this decision [13]. Newer antifungal drugs may, however, confer advantages, such as more rapid sterilization of blood cultures, more efficacy in critically ill patients or activity in device-related infections. All these aspects have to be further investigated. We summarize here the most important characteristics of the echinocandins and voriconazole – the newer drugs for the treatment of candidaemia.

2. In vitro antifungal activity of echinocandins and voriconazole

During the past decade, the antifungal armamentarium against *Candida* spp. invasive infections has been extended by the introduction of a new family of very effective antifungal agents, the echinocandins. The new triazoles – voriconazole and posaconazole – also have high in vitro activity against *Candida* spp. isolates, although they are less commonly used for the initial treatment of invasive candidiasis [14].

The echinocandins target the fungal cell wall and act by inhibiting 1,3- and 1,6- β -D-glucan synthesis, showing fungicidal activity against *Candida* spp. [15]. Pfaller et al. demonstrated the potent in vitro activity of the echinocandins against invasive *Candida* isolates (minimum inhibitory concentration [MIC₉₀] for *Candida* spp.:

0.25 µg/ml for caspofungin, 1 µg/ml for micafungin and 2 µg/ml for anidulafungin) [16].

Despite this practically uniform susceptibility there are some slight differences in the antifungal susceptibility of different species to these agents. Most isolates of *C. albicans*, *C. glabrata*, *C. tropicalis* and *C. krusei* have a modal MIC ≤0.06 µg/ml. By contrast, *C. parapsilosis* and *C. guilliermondii* yield systematically lower susceptibility (MIC₉₀ 1–2 µg/ml). Fluconazole-resistant strains are susceptible to echinocandins [17].

Although observed infrequently to date, some *Candida* isolates are resistant to echinocandins. The mechanisms are not completely established. The echinocandins are rarely affected by the efflux pumps, however, mutations in the *FKS1* gene encoding the target enzyme (FKS1) may lead to decreased susceptibility to these agents [18–24]. Resistance to one of the echinocandins confers resistance to the others. The Etest seems to be more efficient than the microdilution procedure for detecting these mutants.

3. Clinical efficacy, pharmacokinetics and toxicity of the echinocandins and voriconazole

The new guidelines published by the Infectious Diseases Society of America in 2009 [25] recommend the use of one of the three candins as initial therapy for the treatment of candidaemia in non-neutropenic adult patients (A-I) if the patient has been recently exposed to azoles, is colonized by a resistant strain or is haemodynamically unstable (shock). In Europe, micafungin and caspofungin are also indicated for candidaemia in neutropenic (A-III) patients and in children and neonates.

We will briefly review the most important clinical trials that led to these indications and mention some key characteristics of each drug.

3.1. Caspofungin

3.1.1. Clinical data

Caspofungin showed comparable clinical efficacy but less toxicity than amphotericin B deoxycholate for the treatment of invasive candidiasis in a non-inferiority trial including adult patients (Table1) [26]. The study recruited patients aged >18 years with *Candida* isolated from blood cultures or other sterile sites, and with clinical evidence of infection. Patients were stratified according to APACHE score (Acute Physiology and Chronic Health Evaluation) and the presence or absence of neutropenia. They were assigned to receive caspofungin (70 mg loading dose followed by 50 mg per day) or amphotericin B (0.6–1.0 mg/kg per day).

[Table 1 here]

A total of 224 patients were analysed, most of whom had candidaemia. *C. albicans* and *C. parapsilosis* were the species most frequently isolated. Patients treated with caspofungin showed favourable response/mortality rates of 73.4%/34.2% vs. 67.7%/30.4% in patients treated with amphotericin B deoxycholate. The outcome was worse in patients with neutropenia or an APACHE score >20, but there was no difference according to the *Candida* species. Caspofungin showed higher efficacy than amphotericin B against *C. parapsilosis* (70% vs. 65%), but five of the nine patients with persistent candidaemia were infected by *C. parapsilosis*. More than half of the patients included in each group had a central venous catheter at the time of the diagnosis, and the management of the catheters did not differ significantly between groups.

Another study suggested that higher doses of caspofungin did not improve clinical efficacy [27]. A total of 197 adult patients with invasive candidiasis were randomized to receive caspofungin at 150 mg vs. 50 mg per day. The rates of response were 77.9% and 71.6%, respectively and treatment was well tolerated at both dosages. Although non-fungaemic invasive candidiasis is considered a poor prognostic factor, Cornely et al. reported overall success in 81% of patients with proven non-fungaemic invasive candidiasis receiving caspofungin; outcomes were similar across different *Candida* species [28].

In order to get a better understanding of the clinical efficacy of caspofungin for the treatment of candidaemia caused by non-albicans *Candida* species, Colombo et al. performed a retrospective analysis including 212 patients treated with caspofungin [29]. At the end of caspofungin therapy, the rate of success ranged from 70% (*C. krusei*) to 100% (*C. lusitanae*). Of interest, a favourable outcome was achieved in 74% of patients with candidaemia caused by *C. parapsilosis*.

Zaoutis et al. evaluated the safety, tolerability and efficacy of caspofungin in 38 children (aged from 3 months to 17 years) with invasive candidiasis (92% with candidaemia) in a prospective multicentre open-label study [30]. Most patients were receiving caspofungin as the primary treatment, were carrying an intravenous catheter (79%), were receiving broad-spectrum antibiotics (74%) or were immunosuppressed (55%). A favourable outcome was achieved in 81.1% [64.8–92%] of patients. Of interest, seven of the eight patients infected by *C. parapsilosis* had a favourable outcome. Adverse events were common (clinical 23.7%; laboratory 39.5%), however, none of them required treatment discontinuation [30,31].

3.1.2. Pharmacokinetics and adverse events

As with the other candins, caspofungin is not absorbed after oral administration and is only available for intravenous infusion. Caspofungin showed pharmacokinetic linearity, with clearance from plasma and $t_{1/2\beta}$ values independent from the dose [32]. Adjustment of doses in patients aged ≥ 65 years, or in those with renal insufficiency, is not required as renal clearance of caspofungin is very slow [32]. It is highly protein-bound (96%) and cannot be removed by haemodialysis. However, in patients with moderate liver disease (Child–Pugh 7–9) the recommended dose of caspofungin is 35 mg per day.

Serum levels >1 $\mu\text{g/ml}$, a concentration that exceeds the MIC at which 90% of clinically relevant isolates of *Candida* are inhibited, are achieved through therapy with daily doses of 50 mg plus a loading dose of 70 mg [32,33]. Caspofungin is spontaneously degraded and further metabolism implies hydrolysis and *N*-acetylation. Caspofungin is not an inhibitor of cytochrome P450 and not a substrate of the P protein; however, ciclosporin increases the caspofungin area under the curve by 35% and they should be used together with caution. By contrast, caspofungin decreases the plasma concentration of tacrolimus. Interference with rifampicin, efavirenz, phenytoin, dexamethasone and carbamazepine has also been described.

Adverse events related to the administration of caspofungin are common, occurring in around half of patients. However, they are usually mild (headache, chills, fever, local tolerability, nausea and vomiting) and require treatment discontinuation in a small proportion of patients (2.6%) [26,32]. Caspofungin showed a significantly lower rate of adverse events requiring discontinuation than amphotericin B [26].

3.2. Anidulafungin

3.2.1. Clinical data

Anidulafungin is a semi-synthetic lipopeptide derivate of *Aspergillus nidulans*. The clinical efficacy of anidulafungin vs. fluconazole for the treatment of invasive candidiasis was assessed in a randomized double-blind non-inferiority trial [34]. The study included 245 adult patients (only 12 solid transplant recipients). Clinical efficacy was assessed as the global, clinical and microbiological response at the end of the intravenous treatment given for a minimum of 10 days. *C. krusei* species were excluded from this study.

A global response was achieved in 75.6% of patients who received anidulafungin, compared with 60.2% in patients who received fluconazole. Of interest, 29 patients were infected by *C. parapsilosis*, and those receiving anidulafungin had significantly lower eradication rates (69%) than those treated with fluconazole (88%). Global mortality was also lower for patients receiving anidulafungin (23%) than for patients receiving fluconazole (31%), but the difference did not reach statistical significance.

As with other echinocandins, the clinical efficacy of high doses of anidulafungin has been assessed in a randomized double-blind study, which included 68 patients with candidaemia or invasive candidiasis treated with different doses of anidulafungin (50 mg, 75 mg and 100 mg per day). The success rates at follow-up were 72%, 85% and 83%, respectively, and at 2 weeks after the end of therapy were 84%, 90% and 89%, respectively. Although there was a trend to achieve higher success rates at doses >50 mg, the authors did not find statistically significant differences [35].

There are practically no data in special populations yet. One multicentre study included 12 neutropenic paediatric patients aged 2–17 years, in whom the safety of

anidulafungin was evaluated. Patients were treated with anidulafungin 0.75 or 1.5 mg/kg of body weight per day; two patients had drug-related adverse effects (fever and facial erythema) [36].

3.2.2. *Pharmacokinetics and adverse events*

Anidulafungin has good tissue penetration and a prolonged post-antibiotic effect. Its metabolism is markedly different from the other echinocandins, its clearance appearing to be primarily due to slow non-enzymatic chemical degradation by plasma peptidases in serum to an inactive metabolite, with no evidence of hepatically mediated metabolism. Anidulafungin has been shown to be eliminated in the faeces, predominantly as degradation products, and only a small fraction (10%) as unchanged drug. Faecal elimination likely occurs via biliary excretion [37]. As a consequence, anidulafungin has no interaction with other drugs metabolized in the liver and it can be safely used in patients with hepatic and/or renal insufficiency. A retrospective study evaluated anidulafungin in 35 patients with hepatic dysfunction (70%) and candidaemia or invasive candidiasis. Ten patients were solid or hematopoietic stem cell transplant recipients. A favourable outcome was assessed in 77% of 13 patients who were evaluated [38]. No dosage adjustment is necessary, even in patients undergoing haemodialysis.

Since it has no hepatic metabolism via cytochrome P450, it is ideal for transplant recipients receiving calcineurin inhibitors, although more data are needed. Dowell et al. conducted a study in healthy volunteers and observed that anidulafungin did not alter the metabolism of ciclosporin or voriconazole [39,40]. In another retrospective study there was no interaction with metronidazole [38].

The most common adverse events related to the use of anidulafungin were hypokalaemia, hypotension, nausea, vomiting, constipation and pyrexia (5–13%) [35]. Anidulafungin has fewer side effects than fluconazole [34,41].

3.3. *Micafungin*

3.3.1. *Clinical data*

Micafungin was approved by the US Food and Drug Administration in 2005 to treat oesophageal candidiasis and for prophylaxis of *Candida* infections in hematopoietic cell transplant recipients. In 2008 the indications were expanded to include the treatment of invasive candidiasis or candidaemia in adults, neutropenic patients and in children and neonates.

The clinical efficacy of micafungin as first-line treatment of invasive candidiasis or candidaemia was demonstrated in a double-blind randomized multinational non-inferiority study that compared micafungin (100 mg per day) with liposomal amphotericin B (3 mg/kg per day) [42]. A total of 115 centres and 531 adult patients were included, of which 57 were neutropenic and 90 were solid organ transplant recipients. The end point was clinical and mycological response (complete or partial) at the end of treatment. Overall treatment success rates in the modified intention-to-treat population receiving micafungin or liposomal amphotericin B were 74.1% and 69.6% (95% CI 4.5; -3.5 to 12.4), respectively. Neutropenic patients were included, 32 treated with micafungin and 25 with liposomal amphotericin B. The success rates in this population were 59.4% and 56% (95% CI 4.9; -3 to 12.8), respectively.

One study to date has compared two candins – micafungin and caspofungin. This study was a randomized double-blind multinational study in adult patients with candidaemia and invasive candidiasis, stratified by APACHE II score. Caspofungin

was given to 188 patients at 50 mg per day and micafungin to 191 patients at 100 mg per day and to 199 at 150 mg per day. The study included 16 solid organ transplant patients. The end point was clinical and microbiological success at the end of blinded intravenous treatment. Patients continued with intravenous treatment for a minimum of 10 days. Treatment success was similar in the three groups (76.4%, 71.4% and 72.3%, respectively). The higher dose of micafungin was not associated with a better outcome [43].

A study including paediatric patients compared micafungin (2 mg/kg per day) with liposomal amphotericin B (3 mg/kg per day) as first-line treatment of invasive candidiasis [44]. The study included 98 patients <16 years old (including neonates) with clinical signs of systemic *Candida* infection and with one or more positive *Candida* cultures from blood or another sterile site. The primary end point was clinical and mycological response at the end of therapy. Forty-eight patients received micafungin (response rate 72%) and 50 patients received liposomal amphotericin B, 76% reaching a clinical response. There were no differences in overall mortality at 3-month follow-up (25% vs. 24.1%) or in the related mortality rates (7.7% vs. 5.6%).

One study including four premature infants retrospectively analysed the efficacy and tolerability of micafungin for treating *Candida* infections. All patients responded to the treatment and no side effects were reported [45].

There is evidence that micafungin is effective for the treatment of invasive candidiasis in transplant recipients. An open-label non-comparative study was performed in 13 countries and included 126 patients. Micafungin was given as first-line therapy in 72 patients and as salvage therapy in 54 patients. Eighteen (14.3%) were bone marrow transplant recipients, 29 (23%) had neutropenia and 4 (3.2%)

patients had received a solid organ transplant. Global response at the end of therapy was 83.3% (95% CI 76–89); the response to micafungin as first-line therapy 87.5%; and the responses to salvage therapy 79.3% (combined with another antifungal drug) and 76% (alone) [46]. A study that included 18 transplant patients showed therapeutic efficacy in all of them with excellent tolerance (only one had an increase in sirolimus levels) [47].

Micafungin is fungicidal and has demonstrated in vitro and in vivo efficacy against yeast embedded in biofilms. The in vitro effectiveness of micafungin in the reduction or control of fungal biofilms associated with silicone medical devices has been demonstrated. Micafungin was able to induce a significant and persistent reduction in the yeast metabolic activity of intermediate and mature biofilms of *Candida albicans* when used in catheter lock solutions (5 mg/L) [48]. This effect may be essential, since not removing the intravenous catheter has been a consistently poor prognostic factor. This may not hold true if micafungin is used. Nucci et al, in a post hoc analysis of two prospective phase 3 micafungin trials [42,43] showed that prompt removal of a baseline central venous catheter by 24 or 48 h after treatment initiation with micafungin was not associated with overall treatment, 28-day survival, or 42-day survival [49]. This is clearly one of the most promising areas in the field, and good-quality prospective data are warranted.

3.3.2. Pharmacokinetics and adverse events

Micafungin is the only candin that does not need a loading dose. The recommended daily dose is 100 mg/day. Micafungin shows linear pharmacokinetics, with a long elimination $t_{1/2}$ for once-daily doses. It has hepatic metabolism mediated by the action of an arylsulfatase and catechol-O-methyltransferase; it is metabolized to a lesser

extent by the cytochrome P450 isoenzymes. It has a low clearance of 0.197 mL/min per kg, an elimination half life of 13.9 h and the urinary recovery is <1% [50].

Micafungin is a weak substrate of cytochrome P3A4 [51], and may increase levels of sirolimus (up to 21%), nifedipine (up to 18%) and itraconazole (up to 22%). By contrast, no changes were observed in plasma levels of other drugs such as tacrolimus, mycophenolate, ciclosporin, fluconazole, prednisone and voriconazole [52–55].

Undre et al. studied the pharmacokinetics of micafungin in eight subjects with severe hepatic dysfunction, and although the intrinsic clearance was higher than in the control group, the difference was not statistically significant and it was concluded that no dose adjustment was necessary [56]. In experimental animals, hepatic tumours were reported after 3 months of treatment with high doses of the drug. This effect has not been detected in humans.

It is a well-tolerated drug and the discontinuation of treatment was requested only in 3.0–4.9% of patients, compared with 9% of patients treated with liposomal amphotericin. The most common adverse effects are nausea, vomiting, diarrhoea, phlebitis, fever and hypokalaemia. The largest difference, compared with liposomal amphotericin B, is the lower renal toxicity associated with micafungin [42].

In paediatric patients, adverse effects were fever, vomiting, diarrhoea, anaemia, thrombocytopenia and hypokalaemia, and additionally in this population the proportion of treatment withdrawals was inferior to that of liposomal amphotericin B (3.8% vs. 16.7%, $P = 0.005$) [44]. No dosage adjustment is necessary in renal failure or haemodialysis [57,58]. During pregnancy it should be used with caution (category C).

3.4. Voriconazole

3.4.1. Clinical data

Voriconazole showed high in vitro antifungal activity against *Candida* isolates [59,60]. In 52 patients with invasive candidiasis intolerant of or refractory to other antifungal agents, voriconazole showed an overall rate of response of 56% (95% CI, 41–70) [61]. Voriconazole efficacy has been assessed in non-neutropenic patients with candidaemia. Patients were randomized to receive voriconazole ($N = 283$) or amphotericin B followed by fluconazole ($N = 139$). Voriconazole was not inferior to amphotericin B/fluconazole (success rates 65% and 71%, respectively) in the primary efficacy analysis [62].

3.4.2. Pharmacokinetics and adverse events

Voriconazole is available in both oral and parenteral formulations. The oral bioavailability of voriconazole is 100%; it is not affected by gastric pH but it decreases when the drug is administered with food. Oral voriconazole can be used as sequential therapy for completing therapy in patients with fluconazole-resistant strains [63].

Cerebrospinal fluid and vitreous penetration of voriconazole is excellent [64]. The corresponding maximum plasma concentration found in serum was 1.88 mg/L (200 mg), 4.84 mg/L (300 mg) and 5.27 mg/L (400 mg) when determined after 7 days of oral dosing. The plasma protein binding of voriconazole is moderate (58%).

Because of the potential for cyclodextrin accumulation among patients with significant renal dysfunction, intravenous voriconazole is not recommended for patients with a creatinine clearance <50 mL/min; however, oral voriconazole does not require dosage adjustment. Voriconazole is the only triazole requiring dosage

reduction for patients with mild-to-moderate hepatic impairment. It shows wide variability in serum levels, which must be monitored. Drug–drug interactions are very common [25]. Adverse events and laboratory abnormalities are relatively common, although not usually severe. One of the most distressing adverse effects is visual disturbance.

4. New antifungals in development

Isavuconazole (BAL4815) is an experimental triazole currently in phase 3 trials for the treatment of fungaemia. It has shown excellent in vitro antifungal activity against different species of *Aspergillus*, *Mucorales*, *Candida*, *Cryptococcus* and other rare yeast pathogens [65–67]. To date, three clinical trials evaluating isavuconazole for the treatment and prevention of invasive fungal infections are in progress or have been completed. Unfortunately, clinical efficacy results are not yet available.

Aminocandin is a water-soluble echinocandin that has shown potent in vitro and in vivo activity against *Candida* and *Aspergillus* spp. [68]. However, no data on clinical efficacy in humans are available.

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References

1. Rodriguez-Creixems M, Alcala L, Muñoz P, Cercenado E, Vicente T, Bouza E. Bloodstream infections: evolution and trends in the microbiology workload, incidence, and etiology, 1985–2006. *Medicine (Baltimore)* 2008;87:234–49.
2. Martin GS, Mannino DM, Eaton S, Moss M. The epidemiology of sepsis in the United States from 1979 through 2000. *N Engl J Med* 2003;348:1546–54.
3. Tortorano AM, Kibbler C, Peman J, Bernhardt H, Klingspor L, Grillot R. Candidaemia in Europe: epidemiology and resistance. *Int J Antimicrob Agents* 2006;27:359–66.
4. Smith PB, Morgan J, Benjamin JD, Fridkin SK, Sanza LT, Harrison LH, et al. Excess costs of hospital care associated with neonatal candidemia. *Pediatr Infect Dis J* 2007;26:197–200.
5. Olaechea PM, Palomar M, Leon-Gil C, Alvarez-Lerma F, Jorda R, Nolla-Salas J, et al. Economic impact of *Candida* colonization and *Candida* infection in the critically ill patient. *Eur J Clin Microbiol Infect Dis* 2004;23:323–30.
6. Leon C, Ruiz-Santana S, Saavedra P, Galvan B, Blanco A, Castro C, et al. Usefulness of the "Candida score" for discriminating between *Candida* colonization and invasive candidiasis in non-neutropenic critically ill patients: a prospective multicenter study. *Crit Care Med* 2009;37:1624–33.
7. Ostrosky-Zeichner L, Sable C, Sobel J, Alexander BD, Donowitz G, Kan V, et al. Multicenter retrospective development and validation of a clinical prediction rule for nosocomial invasive candidiasis in the intensive care setting. *Eur J Clin Microbiol Infect Dis* 2007;26:271–6.

8. Ostrosky-Zeichner L, Pappas PG, Shoham S, Reboli A, Barron MA, Sims C, et al. Improvement of a clinical prediction rule for clinical trials on prophylaxis for invasive candidiasis in the intensive care unit. *Mycoses*. Epub 2009 21 Jul.
9. Paphitou NI, Ostrosky-Zeichner L, Rex JH. Rules for identifying patients at increased risk for candidal infections in the surgical intensive care unit: approach to developing practical criteria for systematic use in antifungal prophylaxis trials. *Med Mycol* 2005;43:235–43.
10. Muñoz P, Burillo A, Bouza E. Criteria used when initiating antifungal therapy against *Candida* spp. in the intensive care unit. *Int J Antimicrob Agents* 2000;15:83–90.
11. Guinea J, Pelaez T, Rodriguez-Creixems M, Torres-Narbona M, Muñoz P, Alcalá L, et al. Empirical treatment of candidemia in intensive care units: fluconazole or broad-spectrum antifungal agents? *Med Mycol* 2009;47:515–20.
12. Muñoz P, Fernandez-Turegano CP, Alcalá L, Rodriguez-Creixems M, Pelaez T, Bouza E. Frequency and clinical significance of bloodstream infections caused by *C. albicans* strains with reduced susceptibility to fluconazole. *Diagn Microbiol Infect Dis* 2002;44:163–7.
13. Guinea J, Recio S, Escribano P, Torres-Narbona M, Pelaez T, Sanchez-Carrillo C, et al. Rapid antifungal susceptibility determination for yeast isolates by use of E-test performed directly on blood samples from patients with fungemia. *J Clin Microbiol* 2010;48:2205–12.
14. Cuenca-Estrella M, Gomez-Lopez A, Mellado E, Buitrago MJ, Monzon A, Rodriguez-Tudela JL. Head-to-head comparison of the activities of currently available

antifungal agents against 3378 Spanish clinical isolates of yeasts and filamentous fungi. *Antimicrob Agents Chemother* 2006;50:917–21.

15. Canton E, Peman J, Valentin A, Espinel-Ingroff A, Gobernado M. In vitro activities of echinocandins against *Candida krusei* determined by three methods: MIC and minimal fungicidal concentration measurements and time-kill studies. *Antimicrob Agents Chemother* 2009;53:3108–11.

16. Pfaller MA, Boyken L, Hollis RJ, Kroeger J, Messer SA, Tendolkar S, et al. In vitro susceptibility of invasive isolates of *Candida* spp. to anidulafungin, caspofungin, and micafungin: six years of global surveillance. *J Clin Microbiol* 2008;46:150–6.

17. Messer SA, Diekema DJ, Boyken L, Tendolkar S, Hollis RJ, Pfaller MA. Activities of micafungin against 315 invasive clinical isolates of fluconazole-resistant *Candida* spp. *J Clin Microbiol* 2006;44:324–6.

18. Perlin DS. Resistance to echinocandin-class antifungal drugs. *Drug Resist Updat* 2007;10:121–30.

19. Garcia-Effron G, Katiyar SK, Park S, Edlind TD, Perlin DS. A naturally occurring proline-to-alanine amino acid change in Fks1p in *Candida parapsilosis*, *Candida orthopsilosis*, and *Candida metapsilosis* accounts for reduced echinocandin susceptibility. *Antimicrob Agents Chemother* 2008;52:2305–12.

20. Garcia-Effron G, Kontoyiannis DP, Lewis RE, Perlin DS. Caspofungin-resistant *Candida tropicalis* strains causing breakthrough fungemia in patients at high risk for hematologic malignancies. *Antimicrob Agents Chemother* 2008;52:4181–3.

21. Arendrup MC, Garcia-Effron G, Buzina W, Mortensen KL, Reiter N, Lundin C, et al. Breakthrough *Aspergillus fumigatus* and *Candida albicans* double infection

during caspofungin treatment: laboratory characteristics and implication for susceptibility testing. *Antimicrob Agents Chemother* 2009;53:1185–93.

22. Garcia-Effron G, Lee S, Park S, Cleary JD, Perlin DS. Effect of *Candida glabrata* FKS1 and FKS2 mutations on echinocandin sensitivity and kinetics of 1,3-beta-D-glucan synthase: implication for the existing susceptibility breakpoint. *Antimicrob Agents Chemother* 2009;53:3690–9.

23. Garcia-Effron G, Park S, Perlin DS. Correlating echinocandin MIC and kinetic inhibition of fks1 mutant glucan synthases for *Candida albicans*: implications for interpretive breakpoints. *Antimicrob Agents Chemother* 2009;53:112–22.

24. Arendrup MC, Garcia-Effron G, Lass-Flörl C, Lopez AG, Rodriguez-Tudela JL, Cuenca-Estrella M, et al. Echinocandin susceptibility testing of *Candida* species: comparison of EUCAST EDef 7.1, CLSI M27-A3, Etest, disk diffusion, and agar dilution methods with RPMI and isosensitest media. *Antimicrob Agents Chemother* 2010;54:426–39.

25. Pappas PG, Kauffman CA, Andes D, Benjamin DK Jr, Calandra TF, Edwards JE Jr, et al. Clinical practice guidelines for the management of candidiasis: 2009 update by the Infectious Diseases Society of America. *Clin Infect Dis* 2009;48:503–35.

26. Mora-Duarte J, Betts R, Rotstein C, Colombo AL, Thompson-Moya L, Smietana J, et al. Comparison of caspofungin and amphotericin B for invasive candidiasis. *N Engl J Med* 2002;347:2020–9.

27. Betts RF, Nucci M, Talwar D, Gareca M, Queiroz-Telles F, Bedimo RJ, et al. A multicenter, double-blind trial of a high-dose caspofungin treatment regimen versus a

standard caspofungin treatment regimen for adult patients with invasive candidiasis.

Clin Infect Dis 2009;48:1676–84.

28. Cornely OA, Lasso M, Betts R, Klimko N, Vazquez J, Dobb G, et al.

Caspofungin for the treatment of less common forms of invasive candidiasis. J

Antimicrob Chemother 2007;60:363–9.

29. Colombo AL, Ngai AL, Bourque M, Bradshaw SK, Strohmaier KM, Taylor AF,

et al. Caspofungin use in patients with invasive candidiasis caused by common non-*albicans Candida* species: review of the caspofungin database. Antimicrob Agents

Chemother 2010;54:1864–71.

30. Zaoutis TE, Jafri HS, Huang LM, Locatelli F, Barzilai A, Ebell W, et al. A

prospective, multicenter study of caspofungin for the treatment of documented

Candida or *Aspergillus* infections in pediatric patients. Pediatrics 2009;123:877–84.

31. Zaoutis T, Lehrnbecher T, Groll AH, Steinbach WJ, Jafri HS, Maertens J, et al.

Safety experience with caspofungin in pediatric patients. Pediatr Infect Dis J

2009;28:1132–5.

32. Stone JA, Holland SD, Wickersham PJ, Sterrett A, Schwartz M, Bonfiglio C, et

al. Single- and multiple-dose pharmacokinetics of caspofungin in healthy men.

Antimicrob Agents Chemother 2002;46:739–45.

33. Bartizal K, Gill CJ, Abruzzo GK, Flattery AM, Kong L, Scott PM, et al. In vitro

preclinical evaluation studies with the echinocandin antifungal MK-0991 (L-743 872).

Antimicrob Agents Chemother 1997;41:2326–32.

34. Reboli AC, Rotstein C, Pappas PG, Chapman SW, Kett DH, Kumar D, et al.

Anidulafungin versus fluconazole for invasive candidiasis. N Engl J Med

2007;356:2472–82.

35. Krause DS, Reinhardt J, Vazquez JA, Reboli A, Goldstein BP, Wible M, et al. Phase 2, randomized, dose-ranging study evaluating the safety and efficacy of anidulafungin in invasive candidiasis and candidemia. *Antimicrob Agents Chemother* 2004;48:2021–4.
36. Benjamin DK Jr, Driscoll T, Seibel NL, Gonzalez CE, Roden MM, Kilaru R, et al. Safety and pharmacokinetics of intravenous anidulafungin in children with neutropenia at high risk for invasive fungal infections. *Antimicrob Agents Chemother* 2006;50:632–8.
37. Damle BD, Dowell JA, Walsky RL, Weber GL, Stogniew M, Inskeep PB. In vitro and in vivo studies to characterize the clearance mechanism and potential cytochrome P450 interactions of anidulafungin. *Antimicrob Agents Chemother* 2009;53:1149–56.
38. Brielmaier BD, Casabar E, Kurtzeborn CM, McKinnon PS, Ritchie DJ. Early clinical experience with anidulafungin at a large tertiary care medical center. *Pharmacotherapy* 2008;28:64–73.
39. Dowell JA, Stogniew M, Krause D, Henkel T, Weston IE. Assessment of the safety and pharmacokinetics of anidulafungin when administered with cyclosporine. *J Clin Pharmacol* 2005;45:227–33.
40. Dowell JA, Schranz J, Baruch A, Foster G. Safety and pharmacokinetics of coadministered voriconazole and anidulafungin. *J Clin Pharmacol* 2005;45:1373–82.
41. Krause DS, Simjee AE, van Rensburg C, Viljoen J, Walsh TJ, Goldstein BP, et al. A randomized, double-blind trial of anidulafungin versus fluconazole for the treatment of esophageal candidiasis. *Clin Infect Dis* 2004;39:770–5.

42. Kuse ER, Chetchotisakd P, da Cunha CA, Ruhnke M, Barrios C, Raghunadharao D, et al. Micafungin versus liposomal amphotericin B for candidaemia and invasive candidosis: a phase III randomised double-blind trial. *Lancet* 2007;369:1519–27.
43. Pappas PG, Rotstein CM, Betts RF, Nucci M, Talwar D, De Waele JJ, et al. Micafungin versus caspofungin for treatment of candidemia and other forms of invasive candidiasis. *Clin Infect Dis* 2007;45:883–93.
44. Queiroz-Telles F, Berezin E, Leverger G, Freire A, van der Vyver A, Chotpitayasunondh T, et al. Micafungin versus liposomal amphotericin B for pediatric patients with invasive candidiasis: substudy of a randomized double-blind trial. *Pediatr Infect Dis J* 2008;27:820–6.
45. Kawaguchi C, Arai I, Yasuhara H, Sano R, Nishikubo T, Takahashi Y. Efficacy of micafungin in treating four premature infants with candidiasis. *Pediatr Int* 2009;51:220–4.
46. Ostrosky-Zeichner L, Kontoyiannis D, Raffalli J, Mullane KM, Vazquez J, Anaissie EJ, et al. International, open-label, noncomparative, clinical trial of micafungin alone and in combination for treatment of newly diagnosed and refractory candidemia. *Eur J Clin Microbiol Infect Dis* 2005;24:654–61.
47. Forrest GN, Rasetto F, Akpek G, Philosophe B. Safety and efficacy of micafungin in transplantation recipients. *Transplantation* 2006;82:1549.
48. Cateau E, Rodier MH, Imbert C. In vitro efficacies of caspofungin or micafungin catheter lock solutions on *Candida albicans* biofilm growth. *J Antimicrob Chemother* 2008;62:153–5.

49. Nucci M. Impact of early catheter removal during treatment of invasive candidiasis: analysis from two phase 3 micafungin trials. In: Abstracts of the 29th International Symposium on Intensive Care and Emergency Medicine; Brussels, Belgium; 2009, Abs P193.
50. Tabata K, Katashima M, Kawamura A, Kaibara A, Tanigawara Y. Population pharmacokinetic analysis of micafungin in Japanese patients with fungal infections. *Drug Metab Pharmacokinet* 2006;21:324–31.
51. Sakaeda T, Iwaki K, Kakumoto M, Nishikawa M, Niwa T, Jin JS, et al. Effect of micafungin on cytochrome P450 3A4 and multidrug resistance protein 1 activities, and its comparison with azole antifungal drugs. *J Pharm Pharmacol* 2005;57:759–64.
52. Keirns J, Sawamoto T, Holum M, Buell D, Wisemandle W, Alak A. Steady-state pharmacokinetics of micafungin and voriconazole after separate and concomitant dosing in healthy adults. *Antimicrob Agents Chemother* 2007;51:787–90.
53. Hebert MF, Townsend RW, Austin S, Balan G, Blough DK, Buell D, et al. Concomitant cyclosporine and micafungin pharmacokinetics in healthy volunteers. *J Clin Pharmacol* 2005;45:954–60.
54. Hebert MF, Blough DK, Townsend RW, Allison M, Buell D, Keirns J, et al. Concomitant tacrolimus and micafungin pharmacokinetics in healthy volunteers. *J Clin Pharmacol* 2005;45:1018–24.
55. Shimoeda S, Ohta S, Kobayashi H, Saitou H, Kubota A, Yamato S, et al. Analysis of the blood level of micafungin involving patients with hematological diseases: new findings regarding combination therapy with tacrolimus. *Biol Pharm Bull* 2005;28:477–80.

56. Undre N, Pretorius B, Botha FCJ, Davis HJ, Potgieter M A, Eltink C. Pharmacokinetics (PK) of micafungin in subjects with severe hepatic dysfunction (SHD). In: Abstracts of the 49th Interscience Conference on Antimicrobial Agents and Chemotherapy; San Francisco; 2009, A1-594.
57. Hirata K, Aoyama T, Matsumoto Y, Ogawa F, Yamazaki H, Kikuti A, et al. Pharmacokinetics of antifungal agent micafungin in critically ill patients receiving continuous hemodialysis filtration. *Yakugaku Zasshi* 2007;127:897–901.
58. Hebert MF, Smith HE, Marbury TC, Swan SK, Smith WB, Townsend RW, et al. Pharmacokinetics of micafungin in healthy volunteers, volunteers with moderate liver disease, and volunteers with renal dysfunction. *J Clin Pharmacol* 2005;45:1145–52.
59. Pfaller MA, Diekema DJ, Rex JH, Espinel-Ingroff A, Johnson EM, Andes D, et al. Correlation of MIC with outcome for *Candida* species tested against voriconazole: analysis and proposal for interpretive breakpoints. *J Clin Microbiol* 2006;44:819–26.
60. Pfaller MA, Messer SA, Boyken L, Rice C, Tendolkar S, Hollis RJ, et al. Use of fluconazole as a surrogate marker to predict susceptibility and resistance to voriconazole among 13,338 clinical isolates of *Candida* spp. Tested by clinical and laboratory standards institute-recommended broth microdilution methods. *J Clin Microbiol* 2007;45:70–5.
61. Ostrosky-Zeichner L, Oude Lashof AM, Kullberg BJ, Rex JH. Voriconazole salvage treatment of invasive candidiasis. *Eur J Clin Microbiol Infect Dis* 2003;22:651–5.
62. Kullberg BJ, Sobel JD, Ruhnke M, Pappas PG, Viscoli C, Rex JH, et al. Voriconazole versus a regimen of amphotericin B followed by fluconazole for

candidaemia in non-neutropenic patients: a randomised non-inferiority trial. *Lancet* 2005;366:1435–42.

63. Swoboda S, Lichtenstern C, Ober MC, Taylor LA, Storzinger D, Michel A, et al. Implementation of practice guidelines for antifungal therapy in a surgical intensive care unit and its impact on use and costs. *Chemotherapy* 2009;55:418–24.

64. Leveque D, Nivoix Y, Jehl F, Herbrecht R. Clinical pharmacokinetics of voriconazole. *Int J Antimicrob Agents* 2006;27:274–84.

65. Guinea J, Pelaez T, Recio S, Torres-Narbona M, Bouza E. In vitro antifungal activities of isavuconazole (BAL4815), voriconazole, and fluconazole against 1,007 isolates of zygomycete, *Candida*, *Aspergillus*, *Fusarium*, and *Scedosporium* species. *Antimicrob Agents Chemother* 2008;52:1396–400.

66. Guinea J, Hagen F, Pelaez T, Boekhout T, Tahoune H, Torres-Narbona M, et al. Antifungal susceptibility, serotyping, and genotyping of clinical *Cryptococcus neoformans* isolates collected during 18 years in a single institution in Madrid, Spain. *Med Mycol*. Epub 2010 Mar 18.

67. Seifert H, Aurbach U, Stefanik D, Cornely O. In vitro activities of isavuconazole and other antifungal agents against *Candida* bloodstream isolates. *Antimicrob Agents Chemother* 2007;51:1818–21.

68. Warn PA, Sharp A, Morrissey G, Denning DW. Activity of aminocandin (IP960; HMR3270) compared with amphotericin B, itraconazole, caspofungin and micafungin in neutropenic murine models of disseminated infection caused by itraconazole-susceptible and -resistant strains of *Aspergillus fumigatus*. *Int J Antimicrob Agents* 2010;35:146–51.

Table 1

Summary of trials in patients with invasive candidiasis (IC)

Antifungal	Clinical efficacy [reference]	Clinical indication	IDSA guidelines	Dosages and interactions	Adverse events
Caspofungin	Caspofungin is not inferior to amphotericin B deoxycholate	[26] Treatment of IC in adult patients	Initial therapy adult non-neutropenic (A-I) and neutropenic (A-III) patients with candidaemia, especially patients exposed to an azole or in severely ill patients	70 mg loading dose followed by 50 mg per day for 14 days	Adverse events common (approx. 50% of patients) but usually mild (headache, chills, fever, local tolerability, nausea, and vomiting) Treatment discontinuation in a small proportion of patients (2.6%)
	Caspofungin is effective for the treatment of IC in children	[30] Treatment of IC in children (12 months to 17 years)	In neonates, caspofungin should be used with caution (B-III)	70 mg/m ² loading dose followed by 50 mg/m ² per day for 14 days	
Anidulafungin	Anidulafungin is not inferior to fluconazole in patients with IC.	[34] Treatment of IC in adult patients	Initial therapy for treatment of adult non-neutropenic (A-I) and neutropenic (A-III) patients with candidaemia, especially patients exposed to an azole or in severely ill patients	200 mg loading dose followed by 100 mg per day No interaction with calcineurin inhibitors or azoles	Anidulafungin has fewer side effects than fluconazole (11 vs. 16 patients)
	Anidulafungin is safe and effective for treating IC	[35] Treatment of IC in adult patients with different doses (50, 75 and 100 mg)			Hypokalaemia, hypotension, nausea, vomiting, constipation and pyrexia (5–13%).
	Micafungin is not inferior to liposomal amphotericin B	[42] First-line treatment of IC or candidaemia in adult patients			2–3% nausea, vomiting, diarrhoea, phlebitis, fever and hypokalaemia 8% hepatic alteration
	Micafungin is not inferior to caspofungin	[43] Treatment of IC and candidaemia in adult patients			3% discontinue therapy due to an adverse treatment effect