Current Treatment Strategies for Disseminated Candidiasis

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The incidence of disseminated candidiasis has increased dramatically over the past several decades. Fortunately, in recent years, a variety of new antifungal agents have become available to treat these infections. On the basis of efficacy, safety, and cost considerations, fluconazole is the agent of choice for the empirical treatment of disseminated candidiasis in nonneutropenic, hemodynamically stable patients, unless a patient is suspected to be infected with an azole-resistant species (i.e., Candida glabrata or Candida krusei). For hemodynamically unstable or neutropenic patients, agents with broader species coverage, such as polyenes, echinocandins, or, possibly, voriconazole, are preferred for empirical treatment of candidemia. Modification of the initial, empirical regimen depends on the response to therapy and the subsequent identification of the species of the offending pathogen. Echinocandins or high-dose polyenes are preferred for the treatment of infections with C. glabrata or C. krusei. Central venous catheters should be removed from all patients who have disseminated candidiasis, if feasible, and antifungal therapy should be administered to all patients who have candidemia or proven candidiasis.

Candida organisms are opportunistic fungal pathogens that have become a major cause of nosocomial infections in the United States and worldwide. Candida species have become the third most common nosocomial bloodstream isolates and are exceeded in frequency only by coagulase-negative staphylococci and Staphylococcus aureus [1]. In the United States, the annual incidence of blood culture–confirmed candidemia reported in population-based surveys is ~10 cases/100,000 population [2, 3]. However, because blood cultures are insensitive for the diagnosis, up to half of the cases of disseminated candidiasis (defined as candidal infection in sterile target organs, with or without positive blood culture results) are never microbiologically confirmed. Therefore, estimates of disease frequency based on positive blood culture results are artificially low, and an annual incidence of >20 cases/100,000 population (≥60,000 cases/year in the United States) is likely to be more accurate [4].

Although Candida species are opportunistic pathogens, the majority of patients who develop disseminated candidiasis are not immunosuppressed in the classical sense [5]. Rather, the predominant risk factors for disseminated candidiasis are common iatrogenic and/or nosocomial factors (table 1). Given the increasing incidence of these risk factors in the aging population, as well as the increasingly intensive care administered to critically ill, hospitalized patients, disseminated candidiasis will likely continue to be a major cause of nosocomial infections in the coming years.

For decades, only one class of antifungal agents, the polyenes, was available for the treatment of disseminated candidiasis. However, with the advent of reliably active azoles, safer lipid formulations of amphotericin, and the novel echinocandin class of antifungals, clinicians are now in the enviable position of being able to choose from among multiple antifungal agents for the treatment of disseminated candidiasis. The purpose of the present review is to rationally compare the antifungal agents currently available for the treatment of these infections.

**ANTIFUNGAL OPTIONS FOR THE TREATMENT OF DISSEMINATED CANDIDIASIS**

Antifungal options available for the treatment of disseminated candidiasis are summarized in table 2.

**Polyenes.** Amphotericin B deoxycholate, which has been the reference standard for the treatment of disseminated candidiasis for 50 years [12], demonstrates rapidly cidal in vitro activity against virtually all strains of Candida albicans. However, there are increasing concerns about the activity of amphotericin B deoxycholate against other Candida species (see below). Furthermore, toxicities are frequently associated with amphotericin and may be severe. In an effort to reduce the
nephrotoxicity associated with amphotericin, the agent has been reformulated into various lipid-based derivatives, including liposomal amphotericin B and amphotericin B lipid complex. Unfortunately, the lipid formulations are considerably more expensive than amphotericin [13]. The effect of this increase in cost is significant, especially at hospitals with limited financial resources.

Nonrandomized trials have demonstrated that both liposomal amphotericin B and amphotericin B lipid complex are effective treatments for patients with disseminated candidiasis [14–16], and these drugs have been approved by the US Food and Drug Administration for use in patients with proven invasive candidiasis who are refractory to or intolerant of amphotericin B deoxycholate. Because the lipid-based formulations have superior side-effect profiles, their doses can be substantially increased. For example, published nonrandomized studies used lipid-based amphotericin at 3–7 mg/kg/day, which is up to 10-fold greater than standard doses of amphotericin B deoxycholate. Furthermore, it is now clear that liposomal amphotericin B doses up to, and possibly exceeding, 15 mg/kg/day are well tolerated [17]. This finding indicates that clinical trials may have underestimated the maximum efficacy of liposomal amphotericin B by testing lower doses of the drug.

Once the decision to use a lipid-based formulation of amphotericin has been made, there is little to guide the choice between liposomal amphotericin B and amphotericin B lipid complex. These agents have been compared in 2 head-to-head clinical trials, 1 involving patients receiving empirical treatment for neutropenic fever [6] and 1 involving patients with suspected or proven fungal infections [18]. Both studies found that the 2 agents had equivalent efficacies. One of the 2 studies found liposomal amphotericin B to be less nephrotoxic than amphotericin B lipid complex [6], whereas the second study found that these agents produced a similar nephrotoxicity [18]. Because very few patients with known candidemia were enrolled in these trials, recommendations regarding which agent is preferred for the treatment of disseminated candidiasis cannot be made on the basis of the available data.

**Azoles.** Although polyenes clearly have superior in vitro activity against *Candida* species compared with fluconazole, 2 large, multicenter, randomized studies have demonstrated unequivocally that fluconazole and amphotericin B deoxycholate have equivalent efficacies in nonneutropenic patients with candidemia [7, 8]. Fluconazole’s superior toxicity profile, its availability in both intravenously administered and highly bioavailable oral formulations, and the fact that its patent has recently expired, making the drug significantly less expensive than other agents, make fluconazole the preferred antifungal agent for the treatment of disseminated candidiasis in hemodynamically stable patients with susceptible isolates.

Itraconazole has similar activity against *C. albicans* isolates in vitro, compared with fluconazole [19]. A recent, small randomized study demonstrated that itraconazole and fluconazole had similar efficacies against candidemia in patients in a pediatric intensive care unit [20]. Nevertheless, because of both the paucity of available data on the use of itraconazole in patients with candidemia and the plethora of alternative agents for which more data are available, itraconazole cannot be considered to be a first-line agent for the treatment of candidemia at this time.

The activity of voriconazole against *Candida* species is superior to that of fluconazole, with MICs that are, on average, 8-fold lower than fluconazole MICs [21, 22]. A recent multicenter, international study has demonstrated that the efficacy of voriconazole is equivalent to that of standard antifungal therapy for disseminated candidiasis [9]. Kullberg et al. [9] randomized nonneutropenic patients with culture-proven candidemia to receive open-label voriconazole versus standard antifungal therapy. Standard antifungal therapy consisted of amphotericin B deoxycholate administered for ≥3 days, at which time the patient’s therapy could be switched to fluconazole or amphotericin B deoxycholate could be continued at the investigator’s discretion. Rates of cure in the modified intention-to-treat populations were equivalent in both arms. In secondary

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Table 1. Major risk factors for invasive *Candida* infections.

<table>
<thead>
<tr>
<th>Factor</th>
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<tr>
<td>Iatrogenic and/or nosocomial&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Colonization</td>
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<tr>
<td>Treatment with broad-spectrum antibiotics</td>
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<tr>
<td>Central venous catheter</td>
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<tr>
<td>Parenteral nutrition</td>
</tr>
<tr>
<td>Gastrointestinal or cardiac surgery</td>
</tr>
<tr>
<td>Prolonged hospital stay&lt;sup&gt;b&lt;/sup&gt;</td>
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<tr>
<td>Intensive care unit stay</td>
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<tr>
<td>Burns</td>
</tr>
<tr>
<td>Premature birth</td>
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<tr>
<td>Immunosuppression&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Neutropenia</td>
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<tr>
<td>Corticosteroid treatment</td>
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<tr>
<td>HIV infection&lt;sup&gt;d&lt;/sup&gt;</td>
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<tr>
<td>Diabetes mellitus</td>
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<sup>a</sup> Many iatrogenic and/or nosocomial factors are accompanied by poorly characterized immune defects (e.g., burn injuries and surgery down-modulate normal host defense mechanisms), as is diabetes mellitus.

<sup>b</sup> Mean time to onset of infection in a recent, large, prospective study was day 22 of hospitalization [1].

<sup>c</sup> HIV infection and diabetes mellitus predominantly predispose to mucocutaneous candidal infections, and diabetes is also a risk factor for disseminated disease; HIV infection is a cofactor for, but not an independent risk factor for, disseminated disease.

<sup>d</sup> Mean time to onset of infection in a recent, large, prospective study was day 22 of hospitalization [1].

<sup>e</sup> HIV infection and diabetes mellitus predominate in patients with culture-proven candidemia, and diabetes is also a risk factor for disseminated disease; HIV infection is a cofactor for, but not an independent risk factor for, disseminated disease.
Table 2. Therapeutic options for hematogenously disseminated candidiasis.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Advantage(s)</th>
<th>Disadvantage(s)</th>
<th>First-line treatment option?</th>
</tr>
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<tbody>
<tr>
<td>Polyene</td>
<td></td>
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<tr>
<td>Amphotericin B deoxycholate</td>
<td>50 years of experience; highly and rapidly cidal; broad species spectrum; inexpensive</td>
<td>Toxicity; “MIC creep” for Candida glabrata and Candida krusei</td>
<td>Yes</td>
</tr>
<tr>
<td>Amphotericin B lipid complex</td>
<td>Less nephrotoxic than amphotericin B deoxycholate; higher doses can be used</td>
<td>More expensive</td>
<td>Yes</td>
</tr>
<tr>
<td>Liposomal amphotericin B</td>
<td>Possibly the least nephrotoxic polyene [6]; higher doses can be used</td>
<td>More expensive</td>
<td>Yes</td>
</tr>
<tr>
<td>Azole</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fluconazole</td>
<td>Efficacy equivalent to that of amphotericin B deoxycholate [7, 8]; now available as a generic drug; very inexpensive (≈$1–2/day for the orally administered form of the drug)</td>
<td>Inadequate for many C. glabrata isolates and all C. krusei isolates; static in vitro (use cautiously in neutropenic hosts)</td>
<td>Yes</td>
</tr>
<tr>
<td>Itraconazole</td>
<td>In vitro spectrum similar to that of fluconazole</td>
<td>Minimal data available regarding use for candidemia; more expensive than fluconazole</td>
<td>No</td>
</tr>
<tr>
<td>Voriconazole</td>
<td>Efficacy equivalent to that of standard antifungal therapy (amphotericin B deoxycholate followed by fluconazole) [9]; markedly improved in vitro activity against all species, compared with fluconazole; active against many C. glabrata isolates and most C. krusei isolates</td>
<td>More expensive than fluconazole</td>
<td>Yes</td>
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<tr>
<td>Echinocandin</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Caspofungin</td>
<td>Efficacy equivalent to that of amphotericin B deoxycholate for treatment of invasive Candida infections [10]; active against all species; minimal adverse effects</td>
<td>Expensive; higher caspofungin MICs have been noted for some strains of Candida parapsilosis</td>
<td>Yes</td>
</tr>
<tr>
<td>Micafungin</td>
<td>In vitro activity similar to that of caspofungin; efficacy equivalent to that of liposomal amphotericin B for invasive candidiasis [11]; minimal adverse effects</td>
<td>Expensive; higher MICs have been noted for some strains of C. parapsilosis</td>
<td>Reasonable*</td>
</tr>
</tbody>
</table>


analyses, the times to sterilization of blood cultures were equivalent, as were the overall and Kaplan-Meier survival rates. Finally, voriconazole demonstrated a cure rate equivalent to that associated with standard antifungal therapy for patients infected with Candida glabrata. However, because of the use of fluconazole in the standard treatment arm, it cannot be stated with certainty that the efficacy of voriconazole was equivalent to that of polyene therapy for patients infected with C. glabrata.

**Echinocandins.** Caspofungin is a newly approved antifungal agent of a novel class of drugs called “echinocandins,” the mechanism of action of which is inhibition of β1,3-glucan synthase, a key enzyme in fungal cell-wall synthesis. In a randomized, double-blind, multicenter study, caspofungin was as effective as amphotericin B deoxycholate for the treatment of patients with invasive Candida infections, the large majority of whom had candidemia [10]. Many of the patients in this study had proven infection of target organs. The cure rates for all patients and for patients with C. glabrata infection, as well as the overall mortality rates, were equivalent in both treatment arms. Furthermore, in multiple studies, caspofungin has been shown to be extremely safe, with very low rates of associated adverse events. Hence, caspofungin is an acceptable first-line treatment option for disseminated candidiasis.

Micafungin is the second echinocandin to receive US Food and Drug Administration approval, and it was approved for the treatment of esophageal candidiasis. The in vitro activity of micafungin against Candida species is similar to that of caspofungin, including the higher MICs noted for some strains.
of *Candida parapsilosis*. In a nonrandomized trial of salvage therapy with micafungin involving 119 patients with candidemia [23], micafungin demonstrated an encouraging cure rate of 83%. Most recently, the results of a large, randomized, double-blind study that compared the use of micafungin (100 mg/day) with liposomal amphotericin B (3 mg/kg/day) in 531 patients with invasive candidiasis (mostly candidemia) have been presented at an international meeting [11]. Micafungin was found to be noninferior to liposomal amphotericin B overall (end-of-therapy response rate, 90% for both micafungin and liposomal amphotericin B) and when used against non- *albicans* species of *Candida*, including *C. glabrata* (end-of-therapy response rates, 83% and 80% for micafungin and liposomal amphotericin B, respectively) and *C. parapsilosis* (end-of-therapy response rates, 89% and 87% for micafungin and liposomal amphotericin B, respectively). On the basis of the data presented, and given the similarity of the structure, pharmacology, and in vitro candidacidal activity of micafungin to those of caspofungin, micafungin appears to be a reasonable first-line option for the treatment of candidemia in nonneutropenic patients. However, final judgment on the precise role of micafungin in the antifungal armamentarium may be reserved until publication of the peer-reviewed manuscript based on this trial occurs.

**MICROBIOLOGICAL CONSIDERATIONS**

*Non-albicans species of Candida are increasingly common.* Until the late 1980s, *C. albicans* caused the vast majority of cases of disseminated candidiasis. However, in recent series, *C. albicans* caused ∼50% of cases of hematogenously disseminated candidiasis, followed by *C. glabrata, C. parapsilosis,* and *Candida tropicalis,* each of which accounted for ∼10%–25% of cases. *C. glabrata* is typically the second most commonly recovered isolate in North America and much of Europe [24, 25], but it is less commonly recovered in Spain and Latin America [21, 25]. *C. parapsilosis* is typically the second most commonly recovered isolate in Latin America and Spain [21, 25]. Other species, including *Candida krusei* (associated with <5% of cases of hematogenously disseminated candidiasis), are more rare, except in clinical settings when *fluconazole* prophylaxis is widely used (e.g., at cancer treatment centers), where *C. krusei* may cause up to 10%–15% of cases of candidemia [26–28].

**Association between species and azole susceptibility.** The significance of species identification relates largely to the susceptibility of different *Candida* species to antifungal therapies and toazole antifungals in particular. In general, the incidence of resistance to *fluconazole* among *C. albicans* strains is extremely low, but azole resistance has been reported to develop in patients after receipt of multiple and/or prolonged courses of fluconazole therapy, including patients with advanced HIV infection and esophageal candidiasis and patients receiving prophylactic *fluconazole* in association with hematopoietic stem cell transplantation [29, 30].

Most non- *albicans* species of *Candida* are susceptible to *fluconazole*. In contrast, *C. krusei* is intrinsically resistant to *fluconazole* because of an altered cytochrome P-450 isoenzyme [31]. Almost all *C. krusei* isolates demonstrate in vitro resistance to *fluconazole* (MIC, ≥16 μg/mL) [32, 33]. This resistance cannot be overcome with the use of higher drug doses. Many *C. glabrata* isolates are also resistant to triazoles; however, the mechanism of resistance for this species is often drug efflux, and supranormal doses may overcome resistance in certain *C. glabrata* isolates [34]. Overall, the frequency of *fluconazole* resistance (MIC, ≥16 μg/mL) among *C. glabrata* strains is ∼20%–75% [32, 33, 35, 36]. However, the majority of these strains demonstrate “susceptibility–dose/delivery-dependent” resistance (MIC, 16–32 μg/mL) [19], rather than high-level resistance (MIC, ≥64 μg/mL), and these isolates may still respond to high doses of *fluconazole* in vivo [19].

*Voriconazole* has significantly greater in vitro activity against *C. glabrata* isolates and *C. krusei* isolates, compared with *fluconazole*, with ≥90% of *C. glabrata* and ≥98% of *C. krusei* isolates having voriconazole MICs of <2 μg/mL [24, 32, 33, 37]. In contrast to resistance to *fluconazole*, resistance to voriconazole is more frequent among *C. glabrata* isolates than it is among *C. krusei* isolates, because voriconazole binds much more effectively to the cytochrome P-450 isoenzyme in *C. krusei* than does *fluconazole* [38].

A recent case series has suggested that the in vitro activity of voriconazole translates into clinical success in patients infected with *C. krusei* [39]. When salvage therapy was used, 7 (70%) of 10 patients who had invasive *C. krusei* infections and who had experienced failure of previous antifungal therapy responded to voriconazole therapy. In contrast, the response rate for patients infected with *C. glabrata* was only 38%. Although the results of the head-to-head trial conducted by Kullberg et al. [9] were somewhat reassuring, demonstrating that voriconazole and standard antifungal therapy had equivalent efficacies against candidemia due to *C. glabrata*, it must be emphasized that patients in the study arm receiving standard antifungal therapy had therapy switched from amphotericin B deoxycholate to fluconazole after a mean of only 4 days. Hence, a significant component of standard antifungal therapy was fluconazole, and, in this context, it is impossible to determine whether voriconazole was as effective as amphotericin or whether it was merely as effective as fluconazole against *C. glabrata* isolates. Finally, it is of concern that *C. glabrata* breakthrough infections have been seen in high-risk stem cell transplant recipients receiving voriconazole prophylaxis [40]. The weight of evidence suggests that voriconazole is a reasonable choice as an alternative agent for the treatment of *C. krusei* infections; its usefulness in patients infected with *C. glabrata*...
remains unclear. In particular, until more data are available, voriconazole is probably best avoided for C. glabrata isolates with high-level resistance to fluconazole (MIC, \( \geq 64 \mu g/mL \)).

**Association between species and susceptibility to polyenes and caspofungin.** The treatment guidelines for Candida infections emphasize that there has been an alarming amphotericin “MIC creep” among C. glabrata isolates [19]. Furthermore, amphotericin has markedly delayed killing kinetics against C. glabrata and C. krusei in vitro, compared with its killing kinetics against C. albicans [41]. Therefore, the guidelines recommend use of amphotericin at \( \geq 0.7 \text{ mg/kg/day} \) or \( 1 \text{ mg/kg/day} \) for the treatment of infections caused by C. glabrata or C. krusei, respectively, despite the increased toxicity associated with this regimen. Although rarely encountered clinically, Candida lusitaniae strains may be resistant to amphotericin [42], and clinical failures have been noted in association with amphotericin therapy [19]. Fortunately, C. lusitaniae isolates remain susceptible to the azoles.

In contrast to polyenes and azoles, caspofungin has excellent in vitro activity against C. albicans, C. glabrata, C. krusei, and C. lusitaniae, and, in fact, against most Candida species [21, 43, 44]. However, caspofungin MICs are higher for C. parapsilosis than for other species, and, in the pivotal trial leading to the approval of caspofungin for the treatment of invasive Candida infections, 5 of 9 patients who had persistent fungemia despite receiving caspofungin therapy were infected with C. parapsilosis [10]. These data raise some concerns about the efficacy of caspofungin for the treatment of C. parapsilosis infections. Nevertheless, the overall response rates of patients infected with C. parapsilosis were the same for patients treated with caspofungin or amphotericin in the pivotal trial, thereby supporting the use of caspofungin for patients infected with C. parapsilosis. More data are needed to clarify this issue.

### Treatment Strategies

**Overview of treatment.** Consensus guidelines on the treatment of invasive candidiasis are available [19, 45], and they emphasize that all patients with candidemia and disseminated candidiasis should receive antifungal therapy and that percutaneous catheters should be withdrawn if possible. The exact duration of treatment of candidemia is not well established; however, it is recommended that treatment be continued for 14 days after the last positive blood culture result is obtained and the signs and symptoms of infection have resolved [19, 45]. Doses for first-line therapies are shown in table 3.

**Rational algorithm for the selection of empirical antifungal therapy for disseminated candidiasis.** The following factors should be considered in the selection of empirical antifungal therapy for patients with hematogenously disseminated candidiasis (figure 1): (1) the preference to use fluconazole for hemodynamically stable patients, because of the combination of impressive data on its efficacy in randomized studies, its highly favorable safety profile, and its very low cost; (2) the preference to avoid the use of fluconazole when there is an urgency to treat a broad range of species (e.g., for the treatment of hemodynamically unstable patients); and (3) the preference to avoid the use of fluconazole when an azole-resistant strain is likely to be the cause of the infection.

Patients who are hemodynamically unstable and/or otherwise demonstrate signs of severe sepsis require maximal therapy against the offending pathogen in the shortest possible time, because there is a high risk of a bad outcome occurring if empirical therapy that is inactive against the offending pathogen is initiated. Therefore, in a hemodynamically unstable patient, unless it is believed that the offending pathogen is very likely to be an azole-susceptible species, it is advisable to avoid the use of fluconazole. Furthermore, some clinicians may prefer to use a cidal agent (e.g., a polyene or echinocandin) for hemodynamically unstable patients, even if the offending pathogen is fluconazole susceptible, although there are no data to confirm that cidal agents are more effective than fluconazole for such patients.

Neutropenic patients are a second subset of patients for whom it may be advisable to avoid the use of anyazole therapy. The use of a static agent, such as fluconazole, for neutropenic patients with candidemia should be considered carefully, especially for neutropenic patients with sepsis. However, the practice of using fluconazole for hemodynamically stable neutropenic patients is becoming more popular, in general [19].

If a patient is neither hemodynamically unstable nor neutropenic, the next consideration in selecting antifungal therapy is the likelihood that an azole-resistant species is causing the patient’s infection. Patients who, on the basis of previous culture results, are known to be colonized with C. albicans or

<table>
<thead>
<tr>
<th>Drug, dose</th>
<th>Table 3. Doses of first-line agents for the treatment of hematomgenously disseminated candidiasis.</th>
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<tbody>
<tr>
<td>Amphotericin B deoxycholate</td>
<td>0.7 mg/kg/day iv for all species except Candida glabrata and Candida krusei</td>
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<tr>
<td></td>
<td>( \geq 0.7 \text{ mg/kg/day iv for C. glabrata} )</td>
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<tr>
<td></td>
<td>1 mg/kg/day iv for C. krusei</td>
</tr>
<tr>
<td>Amphotericin B lipid complex and liposomal amphotericin B</td>
<td>3–5 mg/kg/day iv</td>
</tr>
<tr>
<td></td>
<td>Consider higher doses (5–10 mg/kg/day) for C. glabrata or C. krusei</td>
</tr>
<tr>
<td>Fluconazole</td>
<td>400–800 mg/day (6–12 mg/kg/day) iv or po</td>
</tr>
<tr>
<td>Voriconazole</td>
<td>300 mg (4 mg/kg) twice per day for 2 doses, then 200 mg (3 mg/kg) twice per day iv or po</td>
</tr>
<tr>
<td>Caspofungin</td>
<td>70-mg load, then 50 mg every day iv</td>
</tr>
<tr>
<td>Micafungin</td>
<td>100 mg every day iv</td>
</tr>
</tbody>
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**NOTE.** iv, intravenously; po, by mouth.
other non-*glabrata* or non-*krusei* species of *Candida* are very likely to be infected with the colonizing species; fluconazole may be a reasonable choice for empirical antifungal therapy for such patients. In contrast, patients who are known to be colonized with *C. glabrata* or *C. krusei*, or patients who develop disseminated candidiasis in the face of fluconazole therapy that is ongoing or recent (within 30 days prior to the development of disseminated candidiasis), are highly likely to be infected with an azole-resistant *C. glabrata* or *C. krusei* strain. Fluconazole should be avoided as empirical therapy for such patients.

Once empirical therapy is chosen, modification of the regimen depends on the clinical course and on additional microbiological information (figure 2). For example, if nonazole therapy is initiated because of concern about an azole-resistant species, but the germ tube test result is positive for *C. albicans*, the patient's treatment may immediately be switched to fluconazole. If the germ tube test result is negative, but the organism is later determined to be a species other than *C. glabrata* or *C. krusei*, then therapy may reasonably be switched to fluconazole at that time.

More controversial is what to do if the patient starts receiving empirical fluconazole therapy but the offending pathogen is identified as *C. glabrata* several days later. The most important factor in making this decision is what has happened to the patient's condition in the intervening days. If the patient is responding to therapy with an improved temperature curve, a diminished WBC count, and/or an improved hemodynamic status, it is reasonable to continue fluconazole therapy despite the presence of *C. glabrata* [45], because it is known that a significant fraction of these strains are susceptible to fluconazole. It may be advisable to use a fluconazole dose of 800 mg/day for patients who are responding to therapy. In contrast, if the patient has not had an adequate response to therapy, switching therapy at this time is appropriate. Similarly, if the species

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**Figure 1.** Algorithm for the selection of empirical antifungal therapy for known or suspected cases of disseminated candidiasis. *For example, a patient colonized with *Candida glabrata* or *Candida krusei* or a patient who was recently exposed to fluconazole.*

**Figure 2.** Modification of empirical antifungal therapy for disseminated candidiasis. *Infection with other non-*glabrata* and/or non-*krusei* strains of *Candida* treated as if it was infection with *Candida albicans*, except that (1) an azole or echinocandin is preferred for the treatment of candidemia due to *Candida lusitaniae* and (2) echinocandins should be used with caution for the treatment of candidemia due to *Candida parapsilosis.*

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is not yet known but the patient’s condition is not improving during the first several days while the patient is receiving fluconazole therapy, it is reasonable to broaden coverage by switching to treatment with a polype, an echinocandin, or, possibly, voriconazole until species identification is completed.

Regardless of the clinical course, it is not advisable to use fluconazole for the treatment of patients infected with C. krusei [45]. As previously discussed in this article, an echinocandin or high-dose polye therapy is preferred for such patients, with voriconazole serving as an alternative agent.

Patients demonstrating suboptimal responses to what should be adequate antifungal therapy should be evaluated for several common causes of therapeutic failure. These causes include lack of removal of an intravenous catheter, presence of other endovascular niduses (e.g., an infected heart valve or infected endovascular grafts or dialysis shunts), seeding of a protected site (e.g., endophthalmitis, osteomyelitis, and hepatosplenic disease), or seeding of other prosthetic devices (e.g., artificial joints and peritoneal dialysis catheters). Patients with candidemia should undergo examination of dilated retinas to rule out endophthalmitis. As for central venous catheters, infected prosthetic materials should be removed, if feasible.

**Susceptibility testing should be considered in certain circumstances.** Fluconazole is the only first-line agent for the treatment of disseminated candidiasis for which standardized MIC breakpoints for susceptibility have been validated by clinical data [19]. MIC breakpoints for polyenes and for voriconazole have been proposed but have not yet been well validated clinically. Nevertheless, in certain clinical circumstances, susceptibility testing is advisable. For example, knowledge of the MIC for an isolate recovered from a patient with a marginal response to fluconazole or from a patient who has experienced relapse, reinfection, or breakthrough infection during or after recent fluconazole therapy can be useful to guide the selection of appropriate therapy. In addition, voriconazole susceptibility testing of C. krusei isolates may be useful in reassuring the clinician about the use of voriconazole for such patients. Although broad recommendations regarding the clinical usefulness of susceptibility testing are difficult to make, in general, if the results of the susceptibility test would result in a change in treatment that would avoid the use of azoles or that would provide reassurance regarding the usefulness of azoles against a given isolate, then testing is reasonable.

**SUMMARY**

On the basis of efficacy, safety, and cost considerations, fluconazole therapy is considered to be the preferred empirical therapy for disseminated candidiasis in nonneutropenic, hemodynamically stable patients. For hemodynamically unstable patients or patients who are suspected to be infected with C. glabrata or C. krusei, a broader-spectrum agent is preferred, including amphotericin in nonlipid or lipid formulations or an echinocandin. Voriconazole may also be used in these high-risk settings, although it should be used cautiously if C. glabrata is the likely pathogen, until further data are available. Modification of empirical therapy depends largely on response to therapy, as well as the subsequent microbiological identification of the offending pathogen. Central venous catheters should be removed from all patients, if feasible, and antifungal therapy should be administered to all patients. Treatment should be continued for 14 days beyond the resolution of signs and symptoms of infection.

**Acknowledgments**

**Financial support.** National Institute of Allergy and Infectious Diseases Public Health Service (grants K08 AI060661 to B.J.S., RO1 AI054928 to S.G.F., and RO1 AI119990 to J.E.E.), National Institute of Dental and Craniofacial Research Public Health Service (grant RO1 DE013974 to S.G.F.), and Bristol-Myers Squibb (unrestricted Freedom to Discover Grant for Infectious Disease to J.E.E.).

**Potential conflicts of interest.** B.J.S. has received speaking fees from Fujisawa, as well as consulting fees and research grant support from Gilead. J.E.E. is supported by an unrestricted Infectious Diseases Research Award from Bristol-Myers Squibb and has received grants from Pfizer, Merck, Gilead, and Elan for research on the pathogenesis and treatment of fungal infections. S.G.F. has received grant support from Pfizer for research.

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