# Guidelines

# for

# Anti-Fungal Therapy

**By**

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**Clinical Standards & Guidelines**


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**For Medical Specialties**

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Setting Clinical and Professional Excellence

The term candidemia describes the presence of Candida species in the blood. Candidemia is the most common manifestations of invasive candidiasis.
Candida in a blood culture should never be viewed as a contaminant and should always prompt a search for the source of the bloodstream infection. Candidemia could be originated in a variety of organs or from an infected indwelling intravenous catheter.
In all cases, candidemia requires treatment with an antifungal agent; it should never be assumed that removal of a catheter alone is adequate therapy for candidemia.
C. albicans is the most common cause of candidemia, but there has been increased isolation of non-albicans species of Candida in recently. Most prominent have been C. glabrata and C. parapsilosis, followed by C. tropicalis and C. krusei. This is important because some C. glabrata isolates and all C. krusei isolates are resistant to fluconazole

**ANTIFUNGAL AGENTS**
Antifungal classes for the treatment of candidiasis: polyenes, azoles, echinocandins.

**Azoles** *(fluconazole, voriconazole, posaconazole, and itraconazole)*
Azoles interact with multiple different cytochrome P450 enzymes necessary for the conversion of lanosterol to ergosterol, a vital component of the cellular membrane of fungi. Alternative antifungal agents, such as echinocandins, may be preferred if patients are taking other medications that utilize P450 pathways.
*Fluconazole* has been widely used for the treatment of candidiasis & has an excellent safety profile and is available in intravenous and oral formulations and is also inexpensive, since it is now generic. Fluconazole is highly bioavailable, making oral dosing appropriate.
The dose is: 800 mg (12 mg/kg) loading dose, then 400 mg (6 mg/kg) orally daily.
*Voriconazole* has activity against Candida species is superior to that of fluconazole, with minimal inhibitory concentrations. However, cross-resistance between fluconazole and voriconazole is seen frequently, especially with C. glabrata.
*Posaconazole* is available only as an oral suspension. It is approved for use as a prophylactic agent for fungal infections in allogeneic hematopoietic cell transplant recipients with graft-versus-host disease, in patients with prolonged neutropenia due to chemotherapy for hematologic malignancies & for oropharyngeal candidiasis, but not for systemic candidiasis.
*Itraconazole* is sometimes used for mucosal candidiasis, but is not used for systemic infections.

**Echinocandins** *(caspofungin, anidulafungin, and micafungin)*
They are non-competitive inhibitors of the synthesis of integral component of the fungal cell wall. They have excellent activity against most Candida species, have favorable toxicity profiles, and are approved for the treatment of candidemia and other forms of invasive candidiasis. The echinocandins are preferred over azoles for the initial treatment of candidemia if C. glabrata or C. krusei is identified or suspected.
The echinocandins are administered *intravenously* as follows:
*Caspofungin*: initial dose of 70 mg on the first day of treatment, followed by 50 mg daily; dose reduction is required with hepatic dysfunction.

*Anidulafungin*: initial dose of 200 mg on the first day, followed by 100 mg daily.
*Micafungin*: initial dose of 100 mg daily for candidemia; no loading dose is needed.

**Polyenes** *(Amphotericin B deoxycholate, liposomal amphotericin B , amphotericin B lipid complex {ABLC}, amphotericin B colloidal dispersion {ABCD})*

Amphotericin B is a polyene antifungal agent that disrupts fungal cell wall synthesis because of its ability to bind to sterols, primarily ergosterol, which leads to the formation of pores that allow leakage of cellular components.

Amphotericin B deoxycholate, which was the standard drug for the treatment of candidiasis for decades, demonstrates rapidly cidal activity against most species of candida but is associated with significant nephrotoxicity. This has led to the development of various lipid-based derivatives, including liposomal amphotericin B and amphotericin B lipid complex (ABLC). A third formulation, amphotericin B colloidal dispersion (ABCD) is used infrequently, in part because it causes more infusion-related reactions than amphotericin B deoxycholate. These lipid-based compounds have much less toxicity than amphotericin deoxycholate but are significantly more expensive.

The recommended doses for candidemia follow:
*Amphotericin B deoxycholate* : 0.5 - 1 mg/kg intravenously daily
*Lipid formulations of amphotericin B* : 3 - 5 mg/kg intravenously daily

**SUSCEPTIBILITY PATTERNS**

For most patients with invasive candidiasis; the most important issue is whether the isolate is susceptible to fluconazole. Increasingly, resistance among C. glabrata isolates has been noted to voriconazole, as well as fluconazole.

*C. albicans*: resistance to fluconazole is extremely low but may occur in immunosuppressed patients who are taking fluconazole chronically for prophylaxis.
Most C. albicans isolates are susceptible to the echinocandins & amphotericin B.

*C. krusei*: is intrinsically resistant to fluconazole due to an altered cytochrome P450 isoenzyme. This resistance cannot be overcome with use of higher drug doses. However; Voriconazole has higher rates of susceptibility.
C. krusei demonstrates decreased susceptibility to amphotericin B, requiring higher doses (1 mg/kg daily of amphotericin B deoxycholate or 5 mg/kg daily of lipid-based formulations) to be used for treatment.

*C. glabrata*: many isolates are resistant to the azoles which can sometimes be overcome by using higher doses of fluconazole. Isolates that are resistant to fluconazole are generally resistant to voriconazole as well.
The echinocandins have generally retained excellent activity against C. glabrata
Higher doses of amphotericin B are recommended when treating known C. glabrata infection (1 mg/kg daily of amphotericin B deoxycholate or 5 mg/kg daily of lipid-based formulations).

*C. parapsilosis*: should be treated with fluconazole rather than an echinocandin. However, for patients with C. parapsilosis who are already improving clinically on an echinocandin and whose follow-up blood cultures are negative, continuing with the echinocandin is reasonable.

**EVIDENCE**

Fluconazole is as effective as amphotericin B for the treatment of candidemia in immunocompetent patients. The echinocandins appear to be as effective as and better tolerated than amphotericin B formulations in not neutropenic.

Neutropenic patients with candidemia are treated with an echinocandin or an amphotericin B formulation**.**

**APPROACH TO ANTIFUNGAL THERAPY**

The most common antifungal agents used currently for the treatment of candidemia are fluconazole and the echinocandins (caspofungin, micafungin, anidulafungin). Formulations of amphotericin B are given less often due to the risk of toxicity.

Resistance should be suspected in patients who have received echinocandins in the recent past and in patients who develop candidemia while receiving an echinocandin for prophylaxis or empiric therapy (eg, for neutropenic fever); in these situations, an amphotericin B formulation should be used until antifungal susceptibility testing results are available.

When choosing an antifungal agent in patients with suspected candidemia, consider:

●Severity of illness

●Relevant comorbidities that increase the risk of fluconazole-resistant Candida species (e.g, neutropenia)

●Evidence of involvement of the central nervous system, cardiac valves, eyes, visceral organs

●History of recent azole exposure

●History of intolerance of to an antifungal agent

●Prevalence of different Candida species and current antifungal susceptibility data in the clinical unit and medical center

*Non-neutropenic patients*

In non-neutropenic patients with candidemia who are clinically stable, who have not been exposed to recent azole therapy, and who are in clinical units or medical centers in which C. glabrata or C. krusei are uncommonly isolated; initial therapy with fluconazole rather than an echinocandin is recommended

In non-neutropenic patients with moderately severe or severe infections and/or who are at increased risk of C. glabrata or C. krusei infection, echinocandin (caspofungin, micafungin, or anidulafungin) is recommended rather than fluconazole as initial therapy.

However, in patients who have documented C. glabrata infection, who are already improving clinically on fluconazole or voriconazole, and whose follow-up blood cultures are negative, continuing with the azole is reasonable.

*Neutropenic patients*

Most neutropenic patients with candidemia should be treated with an echinocandin or an amphotericin B (preferably lipid formulation ) especially who are heavily pre-treated with azole drugs as part of prophylactic regimens as they are at increased risk for fluconazole-resistant Candida spp, such as C. glabrata and C. krusei .

Fluconazole should be restricted to clinically stable patients who have not received recent azole prophylaxis.

**ORAL STEP- DOWN THERAPY**

Non-neutropenic patients with Candida isolates likely to be fluconazole-susceptible (eg, C. albicans) or proven to be fluconazole-susceptible by antifungal susceptibility testing who are clinically stable can be switched from an echinocandin to fluconazole

Voriconazole is recommended as oral step-down therapy only for patients with C. krusei or voriconazole-susceptible C. glabrata

**DURATION OF TREATMENT**

A minimum of two weeks of therapy after blood cultures become negative is recommended. Daily blood cultures should be performed after initiating therapy in order to determine the date of sterilization. If blood cultures remain positive, then search for a metastatic focus, such as an abscess or endocarditis. In addition, all patients should have resolution of symptoms attributable to candidemia and resolution of neutropenia ( absolute neutrophil count >500 cells/microL and showing a consistent increasing trend) before antifungal therapy is discontinued.

**COMBINATION THERAPY**

Whether more than one antifungal agent should be used together for the treatment of candidemia has not been established, although combination therapy is not generally given for the treatment of candidemia.

**OPHTHALMOLOGIC EVALUATION**

All patients who have candidemia should undergo an ophthalmologic examination by an ophthalmologist to look for evidence of endophthalmitis, whether or not they have ocular symptoms.

**CATHETER REMOVAL**

Central intravenous catheters should be removed in patients with candidemia as clearance of fungemia & decrease mortality occurs more quickly when catheters are removed. In addition, treatment with an antifungal agent is required; it should never be assumed that removal of a catheter alone is adequate therapy for candidemia.

However, some authorities have suggested that catheter removal may not be necessary in neutropenic patients with candidemia (eg, patients with hematologic malignancies undergoing cytotoxic chemotherapy, hematopoietic cell transplant recipients), in whom the source is often the gastrointestinal tract rather than the central venous catheter & some clinicians will attempt to retain the catheters in such patients.

## EMPIRIC ANTIFUNGAL THERAPY

Empiric antifungal therapy is given routinely to patients with neutropenic fever since they are at substantial risk for invasive candidiasis.

In addition, non-neutropenic patients who have persistent fever or unexplained hypotension despite broad-spectrum antibacterial agents may have candidemia or invasive candidiasis. These patients may benefit from early empiric or pre-emptive therapy with an antifungal agent. The choice of agent should be guided by the hemodynamic stability of the patient and with whether the patient has a history of prior exposure to antifungal agents.

In such patients; therapy with either an echinocandin or fluconazole, depending upon the risk of resistant Candida species is recommended.

## OUTCOMES

Untreated candidemia has a mortality rate of over 60%.

With treatment, the overall mortality of candidemia is approximately 30 - 40 %.

## SUMMARY AND RECOMMENDATIONS

●The choice of antifungal therapy for invasive candidiasis, including candidemia, depends upon a variety of factors including history of recent azole exposure; prevalence of different Candida species and current antifungal susceptibility data in the clinical unit and medical center; severity of illness; relevant comorbidities (eg, neutropenia, recent abdominal surgery); evidence of involvement of the central nervous system, cardiac valves, eyes, and/or visceral organs; and history of intolerance to an antifungal agent.

● For non-neutropenic patients with candidemia who are clinically stable, have not been exposed to recent azole therapy, and who are in clinical units or medical centers in which C. glabrata or C. krusei are uncommonly isolated (<15 % of all species causing candidemia); use fluconazole rather than an echinocandin, fluconazole can also be used for the uncommon neutropenic patients who meet these criteria.

● For non-neutropenic and neutropenic patients with candidemia who are clinically unstable, or in patients who have risks for infection with azole-resistant organisms, such as with prior drug exposure, use echinocandin rather than fluconazole for initial therapy.

For patients at risk for echinocandin resistance (eg, prior recent exposure to an echinocandin), an amphotericin B formulation should be used until antifungal susceptibility testing results are available. Treatment can be changed to fluconazole (or an echinocandin) if the isolate is found to be susceptible.

●Blood cultures should be checked daily after initiating antifungal therapy until they become negative.

●All patients who have candidemia should undergo an ophthalmologic examination by an ophthalmologist to look for evidence of endophthalmitis, whether or not they have ocular symptoms.

●In the patient with candidemia alone, treatment should be continued for 14 days after blood cultures have yielded no yeast. In addition, all patients should have resolution of symptoms attributable to candidemia and resolution of neutropenia before antifungal therapy is discontinued. Patients with candidemia and metastatic foci of infection (eg, eye, bone, heart, liver, spleen) require a longer duration of therapy.

●Central intravenous catheters should be removed in patients with candidemia when feasible. However, catheter removal is controversial in neutropenic patients, in whom the gastrointestinal tract is often the source. Some clinicians will attempt to retain the catheter in these patients.

●Empiric antifungal therapy using either an echinocandin or fluconazole, is reasonable in a subset of high-risk ICU patients who have all of the following characteristics:

* Persistent fever despite broad-spectrum antibiotics after 4-7 days of a broad-spectrum antibacterial regimen and no identified source of fever.
* Risk factors for invasive candidiasis
* Positive serologic markers for invasive candidiasis and/or isolation of Candida from multiple non-sterile sites**.**

## REFERENCES


1. Clancy CJ, Nguyen MH. The end of an era in defining the optimal treatment of invasive candidiasis. Clin Infect Dis 2012; 54:1123.
2. Pfaller MA, Castanheira M, Lockhart SR, et al. Frequency of decreased susceptibility and resistance to echinocandins among fluconazole-resistant bloodstream isolates of Candida glabrata. J Clin Microbiol 2012; 50:1199.
3. Carol Kaufman. Treatment of candidemia & invasive candidiasis in adults. Dec 2013. www.uptodate.com/contents/treatment-of-candidemia-and-invasive-candidiasis-in-adults
4. Alexander BD, Johnson MD, Pfeiffer CD, et al. Increasing echinocandin resistance in Candida glabrata: clinical failure correlates with presence of FKS mutations and elevated minimum inhibitory concentrations. Clin Infect Dis 2013; 56:1724.
5. Andes DR, Safdar N, Baddley JW, et al. Impact of treatment strategy on outcomes in patients with candidemia and other forms of invasive candidiasis: a patient-level quantitative review of randomized trials. Clin Infect Dis 2012; 54:1110.
6. Brass EP, Edwards JE. Should the guidelines for management of central venous catheters in patients with candidemia be changed now? Clin Infect Dis 2010; 51:304.
7. Pfeiffer CD, Garcia-Effron G, Zaas AK, et al. Breakthrough invasive candidiasis in patients on micafungin. J Clin Microbiol 2010; 48:2373.
8. Colombo AL, Ngai AL, Bourque M, 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.
9. Ells R, Kock JL. Candida albicans or Candida dubliniensis? Mycoses 2011; 54:1.
10. Pappas PG, Kauffman CA, Andes D, et al. Clinical practice guidelines for the management of candidiasis. Clin Infect Dis 2009; 48:503.
11. Bennett JE. Echinocandins for candidemia in adults without neutropenia. N Engl J Med 2006; 355:1154.
12. Oxman DA, Chow JK, Frendl G, et al. Candidaemia associated with decreased in vitro fluconazole susceptibility: is Candida speciation predictive of the susceptibility pattern? J Antimicrob Chemother 2010; 65:1460.
13. Kofteridis DP, Lewis RE, Kontoyiannis DP. Caspofungin-non-susceptible Candida isolates in cancer patients. J Antimicrob Chemother 2010; 65:293.
14. Pfaller MA, Messer SA, Boyken L, et al. Selection of a surrogate agent (fluconazole or voriconazole) for initial susceptibility testing of posaconazole against Candida spp: results from a global antifungal surveillance program. J Clin Microbiol 2008; 46:551