

Treatment Guidelines

from The Medical Letter®

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Antifungal Drugs

The drugs of choice for treatment of fungal infections are listed in the table that begins on page 62. Some of the indications and dosages recommended here have not been approved by the FDA. More detailed guidelines for some of these infections are available online from the Infectious Diseases Society of America (www.idsociety.org).

AZOLES

Azole antifungal agents inhibit synthesis of ergosterol, an essential component of the fungal cell membrane. They vary in their spectrum of activity, oral bioavailability, adverse effects and potential for drug-drug interactions.

FLUCONAZOLE — Fluconazole (*Diflucan*, and others) is active against most *Candida* species other than *C. krusei*, which is intrinsically resistant, and many strains of *C. glabrata*, which are variably resistant. It has good activity against *Coccidioides* spp. and *Cryptococcus neoformans* and some activity against *Histoplasma capsulatum*.¹ The drug has no clinically significant activity against most molds, including *Aspergillus* spp., *Fusarium* spp., and the Mucorales (formerly called Zygomycetes), such as *Mucor* spp. and *Rhizopus* spp..

Adverse Effects – Fluconazole is generally well tolerated. Headache, gastrointestinal distress, facial edema, rash and pruritus can occur. Stevens-Johnson syndrome, anaphylaxis, hepatic toxicity, leukopenia and hypokalemia have been reported. QT prolongation and torsades de pointes have also been reported.

Pregnancy – Fluconazole is teratogenic in animals. It is classified as pregnancy category C (risk cannot be ruled out) when used in a low dose (single dose of 150 mg) for vaginal candidiasis. It is classified as pregnancy category D (positive evidence of risk) when used for any other indication. Congenital abnormali-

ties, including brachycephaly, cleft palate and congenital heart disease, have been reported in infants exposed *in utero* to high doses (400-800 mg/day) of fluconazole during most or all of the first trimester.²

Drug Interactions – Fluconazole is a strong inhibitor of CYP2C9 and 2C19 and a moderate inhibitor of CYP3A4; it can increase serum concentrations of drugs metabolized by these pathways. Concurrent use of fluconazole with other drugs known to prolong the QT interval, particularly those metabolized by CYP2C9, 2C19 or 3A4, may increase the risk of QT prolongation and torsades de pointes.³ Taking fluconazole with the potent CYP enzyme inducer rifampin can reduce fluconazole serum concentrations, possibly to subtherapeutic levels.

ITRACONAZOLE — Itraconazole (*Sporanox*, and others) has a broader spectrum of activity than fluconazole. It is active against a wide variety of fungi including *C. neoformans*, *Aspergillus* spp., *Blastomyces dermatitidis*, *Coccidioides* spp., *H. capsulatum*, *Paracoccidioides brasiliensis*, *Sporothrix* spp., and dermatophytes. It is also active against most species of *Candida*. Itraconazole has no clinically significant activity against *Fusarium* spp. or the Mucorales and has variable activity against *Scedosporium* spp..

Itraconazole is available in capsules and as an oral solution; an IV formulation is no longer available in the US. The oral solution is more bioavailable than the capsules. The capsules should be taken with food, while the solution is absorbed best without food.

Adverse Effects – The most common adverse effects of oral itraconazole are nausea, diarrhea, vomiting and rash. Stevens-Johnson syndrome and serious hepatic toxicity can occur. Negative inotropic effects, peripheral and pulmonary edema, and congestive heart failure have been reported; itraconazole should not be used in

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Table 1. Treatment of Fungal Infections

Infection	Drug of Choice ¹	Some Alternatives ¹
Aspergillosis	Voriconazole 6 mg/kg IV q12h x 2 doses, then 4 mg/kg IV q12h ³ or 200 mg ⁴ PO bid until resolved	A lipid formulation of amphotericin B ² IV Posaconazole 200 mg PO qid, then 400 mg bid Caspofungin 70 mg IV x 1, then 50 mg IV 1x/d Micafungin 100-150 mg IV 1x/d
Blastomycosis⁵		
<i>Mild to moderate</i>	Itraconazole 200 mg PO tid x 3 d, then bid x 6-12 mo	Fluconazole 400-800 mg PO 1x/d ⁶⁻⁸
<i>Moderately severe to severe</i>	Amphotericin B ² 0.7-1 mg/kg/d IV x 1-2 wks, then itraconazole 200 mg PO tid x 3 d, then 200 mg bid x 6-12 mos ⁹	
Candidiasis		
Vulvovaginal ¹⁰	Intravaginal butoconazole, clotrimazole, miconazole, nystatin, tioconazole, terconazole 1x/d x 1-14 d ¹¹	
<i>Recurrent</i>	or Fluconazole 150 mg PO once ¹² Topical or oral azole x 10-14 d, then fluconazole 150 mg PO 1x/wk x 6 mos	Itraconazole 200 mg PO bid x 1d Clotrimazole 200 mg 2x/wk topically or 500 mg 1x/wk intravaginally
Urinary ¹³	Fluconazole 200 mg (3 mg/kg) ^{8,14} IV or PO 1x/d x 2 wks	Amphotericin B ² 0.3-0.6 mg/kg/d ¹⁴ IV x 1-7 d
Oropharyngeal ¹⁵⁻¹⁹	Fluconazole 100-200 mg (3 mg/kg) ⁸ PO x 7-14 d	Itraconazole ²⁰ 200 mg PO 1x/d Posaconazole 400 mg PO bid x 3 d, then 400 mg 1x/d Voriconazole 200 mg ^{3,4} PO bid Amphotericin B oral susp 100 mg/mL qid An echinocandin: Micafungin 150 mg IV 1x/d Caspofungin 50 mg IV 1x/d Anidulafungin 200 mg IV 1x/d Amphotericin B 0.3 mg/kg/d IV
Esophageal ^{17,18,21}	Fluconazole 200-400 mg (3-6 mg/kg) ⁸ PO or 400 mg IV 1x/d	Itraconazole ²⁰ 200 mg PO 1x/d Posaconazole 400 mg PO bid Voriconazole 200 mg ^{3,4} PO or IV bid Amphotericin B ² 0.3-0.7 mg/kg/d IV An echinocandin: Micafungin 150 mg IV 1x/d Caspofungin 50 mg IV 1x/d Anidulafungin 200 mg IV 1x/d
Candidemia and Invasive Candidiasis ^{17,22}	or Fluconazole ²³ 400 mg (6 mg/kg) ^{6,8} IV 1x/d An echinocandin ²⁴ Caspofungin 70 mg x 1, then 50 mg IV 1x/d Micafungin 100 mg IV 1x/d Anidulafungin 200 mg x 1, then 100 mg IV 1x/d	Amphotericin B ² 0.5-1 mg/kg/d IV

- Usual adult dosage. Some drugs may need dosage adjustment for renal or hepatic dysfunction or when used with interacting drugs. The optimal duration of treatment with antifungal drugs is often unclear. Depending on the disease and its severity, they may be continued for weeks or months or, particularly in immunocompromised patients, indefinitely. Some of these indications and dosages have not been approved by the FDA.
- Lipid-based formulations are often preferred, especially in patients at risk for nephrotoxicity or who are expected to receive a long course of therapy. Usual doses of lipid-based formulations for treatment of invasive fungal infection are: amphotericin B lipid complex (*Abelcet*) 5 mg/kg/d; liposomal amphotericin B (*AmBisome*) 3-5 mg/kg/d; amphotericin B cholesteryl sulfate (*Amphotec*) 3-4 mg/kg/d. For treatment of mucormycosis or fusariosis, the lipid formulation dosage is ≥ 5 mg/kg/d. For treatment of cryptococcal meningitis in HIV patients, the dosage of *AmBisome* is 4-6 mg/kg/d. The usual dosage of amphotericin B deoxycholate for treatment of systemic fungal infections is 0.7-1 mg/kg/d.
- Children may need higher doses. According to the manufacturer, serum concentrations in children with doses of 4 mg/kg are similar to those in adults given 3 mg/kg. In the European Union, where voriconazole is licensed for use in children 2-11 years old, the recommended maintenance dosage is 8 mg/kg IV bid or 200 mg PO bid (LE Friberg et al, *Antimicrob Agents Chemother* 2012; 56:3032).
- Some Medical Letter reviewers recommend a weight-based dose of oral voriconazole (4 mg/kg PO bid) rather than the FDA-approved dose of 200 mg PO bid because of the potential for subtherapeutic serum concentrations. According to the manufacturer, adults who weigh <40 kg should receive half the oral maintenance dose.
- Patients with severe illness or CNS involvement should receive a lipid formulation of amphotericin B for 4-6 weeks, followed by an azole for at least 1 year.
- In general, a loading dose of twice the daily dose is recommended on the first day of therapy.
- For use in patients who cannot tolerate itraconazole or amphotericin B.
- Children need higher doses of fluconazole than adults do. According to the manufacturer, an adult dose of 100 mg is equivalent to a pediatric dose of 3 mg/kg.
- For disseminated extrapulmonary or osteoarticular disease, treat for at least 12 months.
- Non-albicans species, such as *C. glabrata* and *C. krusei*, respond to boric acid 600 mg intravaginally daily x 14 days or to topical 17% flucytosine cream (JD Sobel et al, *Am J Obstet Gynecol* 2003; 189:1297).
- Duration of treatment varies with drug and formulation.
- May be repeated every 72 hours x 3 doses if patient remains symptomatic.
- Asymptomatic candiduria usually does not require treatment. Patients who are symptomatic, neutropenic, or are undergoing urologic manipulation and infants with low birth weight should be treated.
- Dose for cystitis. For pyelonephritis, increase the dose of fluconazole to 200-400 mg/d and of amphotericin B to 0.5-0.7 mg/kg for 2 weeks.

Table 1. Treatment of Fungal Infections (continued)

Infection	Drug of Choice ¹	Some Alternatives ¹
Coccidioidomycosis ²⁵	Fluconazole 400-800 mg ^{6,8} IV or PO 1x/d x >1 yr or Itraconazole 200 mg PO bid or tid x >1 yr	Amphotericin B ² 0.5-1.5 mg/kg/d or qod IV ²⁶
Cryptococcosis ²⁷	Amphotericin B ² 0.7-1.0 mg/kg/d IV plus flucytosine 25 mg/kg PO qid x 2 wks, ²⁸ then fluconazole 400 mg (6 mg/kg) ^{6,8} PO 1x/d x ≥8 wks	Amphotericin B ² 0.7-1.0 mg/kg/d IV x 4-6 wks Amphotericin B ² 0.7 mg/kg/d IV plus fluconazole 800 mg PO 1x/d x 2 wks, then fluconazole 800 mg PO 1x/d x ≥8 wks Fluconazole ≥800 mg PO 1x/d plus flucytosine 100 mg/kg/d PO x 6 wks Fluconazole 800-2000 mg PO 1x/d x 10-12 wks
<i>Chronic suppression</i> ²⁷	Fluconazole 200 mg PO 1x/d	Itraconazole 200 mg PO bid Amphotericin B ² 1 mg/kg IV 1x/wk
Fusariosis	A lipid formulation of amphotericin B ² IV and/or voriconazole 6 mg/kg IV q12h x 2 doses, then 4 mg/kg IV q12h ³ or 200 mg ⁴ PO bid until resolved ²⁹	
Histoplasmosis		
<i>Moderately severe to severe</i>	A lipid formulation of amphotericin B ² IV x 1-2 wks, ³⁰ then itraconazole 200 mg PO tid x 3 d, then bid x 12 wks	Fluconazole 800 mg ^{6,8} PO 1x/d
<i>Chronic suppression</i> ²⁷	Itraconazole 200 mg PO 1x/d	Amphotericin B ² 0.5-1 mg/kg IV wkly
Mucormycosis	A lipid formulation of amphotericin B ² IV until resolved	Posaconazole 200 mg PO qid
Paracoccidioidomycosis ⁵	Itraconazole 100-200 mg PO 1x/d x 6-12 mos or Amphotericin B ^{2,31} 0.7-1 mg/kg/d IV	
Scedosporiosis (asexual form of <i>Pseudallescheriasis</i>)	Voriconazole 6 mg/kg IV q12h x 2 doses, then 4 mg/kg IV q12h ³ or 200 mg ⁴ PO bid until resolved	Posaconazole 200 mg PO tid-qid
Sporotrichosis		
Cutaneous	Itraconazole 200 mg PO 1x/d or bid x 3-6 mos	Terbinafine 500 mg PO bid Saturated solution of potassium iodide 1-5 mL PO tid Fluconazole ³² 400-800 mg ^{6,8} PO 1x/d
Extracutaneous ⁵	Amphotericin B ² 0.7-1.0 mg/kg x 6-12 wks, then itraconazole 200 mg bid PO x ≥12 mos	Itraconazole 200 mg PO bid x ≥12 mos

15. For uncomplicated oropharyngeal thrush, clotrimazole troches (10 mg) 5x/d, miconazole buccal tablet (*Oravig*) 50 mg once daily, or nystatin suspension 400,000-600,000 units (4-6 mL) qid for 7-14 days can also be used. Azole-resistant oropharyngeal or esophageal candidiasis usually responds to amphotericin B or an echinocandin.
16. Duration of treatment is usually 7-14 days. Fluconazole-refractory disease should be treated for up to 28 days.
17. *Candida albicans* is generally highly susceptible to fluconazole. *C. krusei* infections are resistant to fluconazole. *C. glabrata* infections are often resistant to low doses, but may be susceptible to high doses of fluconazole. *C. lusitanae* may be resistant to amphotericin B.
18. HIV-infected patients with frequent or severe recurrences of oral or esophageal candidiasis may require prophylaxis. For patients with organisms that are still susceptible, the regimen of choice is fluconazole 100-200 mg PO once daily.
19. Amphotericin B 0.3 mg/kg/d or an echinocandin can be used for patients with refractory disease.
20. For patients with oropharyngeal or esophageal candidiasis, itraconazole oral solution 200 mg given once daily without food is more effective than itraconazole capsules.
21. Duration of treatment for esophageal candidiasis is 14 to 21 days after clinical improvement.
22. Until 2 weeks after afebrile and blood cultures negative.
23. Recommended for initial treatment of patients who are less critically ill without prior *C. glabrata* or *C. krusei* colonization or recent azole exposure.
24. Preferred over fluconazole for initial treatment in patients with moderately severe to severe illness or recent azole exposure. A recent study has demonstrated an increase in resistance to echinocandins among fluconazole-resistant *C. glabrata* isolates (MA Pfaller et al, J Clin Microbiol 2012. Jan 25 epub).
25. Itraconazole is the drug of choice for non-meningeal coccidioidomycosis. Fluconazole is preferred for coccidioid meningitis. Patients with meningitis who do not respond to fluconazole or itraconazole may require intrathecal amphotericin B 0.1-1.5 mg per dose at daily to weekly intervals.
26. Lipid-based formulations should be administered daily.
27. For patients with HIV infection.
28. Dosage must be decreased in patients with diminished renal function. When given with amphotericin B, some Medical Letter consultants recommend beginning flucytosine at 75 mg/kg/day divided q6h, until the degree of amphotericin nephrotoxicity becomes clear or flucytosine blood levels can be determined.
29. Susceptibility of *Fusarium* spp. varies. Combination therapy should be considered in immunosuppressed patients and in those with severe disease to ensure the patient is receiving at least one active drug.
30. Amphotericin B should be continued for 4-6 weeks in patients with CNS involvement. In one study, liposomal amphotericin B (*Ambisome*) was associated with greater improvement in survival compared to amphotericin B deoxycholate (PC Johnson et al, Ann Intern Med 2002;137:105).
31. Initial treatment of severely ill patients. To be followed by itraconazole.
32. Only if patient cannot tolerate other drugs.

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patients with a history of heart failure or ventricular dysfunction. Peripheral neuropathy, visual disturbances, hearing loss and tinnitus have also been reported.

Pregnancy – Itraconazole is teratogenic in rats; it is classified as category C (risk cannot be ruled out) for use during pregnancy.

Drug Interactions – The absorption of itraconazole is reduced by drugs that increase gastric pH, such as antacids, H₂-receptor blockers and proton pump inhibitors. Itraconazole is a substrate of CYP3A4; its metabolism may be affected if it is taken with an inducer or inhibitor of this pathway. It is also a strong inhibitor of CYP3A4 and may increase serum concentrations of other drugs metabolized by this enzyme.⁴ Taking itraconazole with a CYP3A4 substrate that prolongs the QT interval increases the risk of QT prolongation and torsades de pointes.³ Itraconazole is also a P-glycoprotein (P-gp) inhibitor and can increase serum concentrations of P-gp substrates.

VORICONAZOLE — Voriconazole (*Vfend*, and others) has a spectrum of activity similar to that of itraconazole, but is clinically considered to be more active against *Aspergillus* spp. and most species of *Candida*, including *C. glabrata* and *C. krusei*. Voriconazole is active against *Fusarium* spp. and *Scedosporium* spp.. It is not active against the Mucorales; infection with these organisms has developed during treatment with voriconazole. In a randomized trial of initial treatment of invasive aspergillosis, compared to amphotericin B, voriconazole improved survival and had fewer adverse effects.⁵

Voriconazole can be administered orally or by IV infusion. Taking the oral tablets or suspension with food can decrease absorption of the drug. Serum concentrations of voriconazole can vary widely from patient to patient; monitoring of voriconazole levels is recommended, particularly in patients with invasive fungal infections.⁶ Serum concentrations <1 mcg/mL have been associated with poor response, and levels >5.5 mcg/mL have been associated with neurologic toxicity.⁷

Adverse Effects – Transient visual disturbances including blurred vision, photophobia and altered perception of color or image have occurred in about 20% of patients treated with voriconazole. Fever, nausea, rash (including Stevens-Johnson syndrome), photosensitivity, increased transaminase levels, confusion, hallucinations and anaphylactoid infusion reactions have also occurred. Long-term administration of voriconazole may cause painful periostitis of long bones, premature aging, and an increased incidence of squamous cell carcinoma or melanoma in sun-exposed skin.⁸⁻¹¹ The IV formulation has only been recom-

mended for patients with a creatinine clearance (CrCl) ≥50 mL/min, because in patients with CrCl <50 mL/min, the vehicle of the IV formulation (sulfobutylether-beta-cyclodextrin) can accumulate. The vehicle, however, can be effectively removed by hemodialysis,¹² and in one recent study, use of IV voriconazole in patients with renal dysfunction did not result in further worsening of their renal function.¹³

Pregnancy – Voriconazole is teratogenic in animals. It is classified as pregnancy category D (positive evidence of risk) for use during pregnancy.

Drug Interactions – Voriconazole is a substrate of CYP2C19, 2C9 and 3A4. Drugs that inhibit or induce one or more of these pathways may significantly alter serum concentrations of voriconazole. Patients deficient in CYP2C19 (about 3-5% of Caucasians and African-Americans and about 15-20% of Asians do not express it) may have 2- to 4-fold higher serum concentrations of the drug.

Voriconazole is also an inhibitor of CYP2C9, 3A4, and 2C19; it may significantly increase serum concentrations of drugs metabolized by these pathways. Rifampin and phenytoin decrease voriconazole plasma levels by more than half. Concurrent use of voriconazole with other drugs that prolong the QT interval, particularly those metabolized by CYP2C9, 2C19 or 3A4, may increase the risk of QT prolongation and torsades de pointes.³

POSACONAZOLE — Posaconazole (*Noxafil*) has an antifungal spectrum similar to that of voriconazole, but is also active against many of the Mucorales. It has variable activity against *Fusarium* spp.. Posaconazole is only available for oral use and must be taken with a full meal, a liquid nutritional supplement, or an acidic carbonated beverage for optimal absorption.

HIV-infected patients with oropharyngeal or esophageal candidiasis refractory to treatment with fluconazole or itraconazole have responded to posaconazole; in one study, 75% of such patients achieved cure or improvement after 28 days of treatment.¹⁴ Posaconazole is not approved in the US for salvage therapy of invasive mycoses, but it has been used successfully for this indication in patients with invasive aspergillosis.¹⁵ It has also been used off-label to treat coccidioidomycosis and mucormycosis.¹⁶⁻¹⁹

Adverse Effects – Fever, diarrhea, nausea, rash, headache, fatigue, vomiting, QT prolongation and abnormal liver function have been reported with posaconazole. Arrhythmias, toxic epidermal necrolysis, angioedema and anaphylaxis have occurred rarely.

Pregnancy – Posaconazole causes skeletal malformations in rats. It is classified as pregnancy category C (risk cannot be ruled out) for use during pregnancy.

Drug Interactions – Posaconazole is primarily metabolized via UDP glucuronidation; it is also a substrate of P-gp. Any drug that inhibits or induces these clearance pathways may alter serum concentrations of posaconazole. Cimetidine and esomeprazole have been shown to decrease the absorption of posaconazole. Other H₂-receptor blockers and antacids did not have the same effect. Posaconazole is a strong inhibitor of CYP3A4 and an inhibitor of P-gp and may increase serum concentrations of drugs that are metabolized by these pathways.⁴ Taking posaconazole with other drugs that prolong the QT interval, especially those metabolized by CYP3A4, may increase the risk of QT prolongation.³

KETOCONAZOLE — Ketoconazole (*Nizoral*, and others) is seldom used now for treatment or prophylaxis of fungal infections. Other azoles are preferred.

Adverse Effects – Anorexia, nausea and vomiting are common with higher doses (>400 mg/day) of ketoconazole. Pruritus, rash, dizziness and photophobia may occur. Ketoconazole can decrease plasma testosterone concentrations and cause gynecomastia, decreased libido and erectile dysfunction in men and menstrual irregularities in women. High doses may inhibit adrenal steroidogenesis and decrease plasma cortisol concentrations. Hepatic toxicity, including fatal hepatic necrosis, can occur.

Pregnancy – Ketoconazole is teratogenic in animals. It is classified as pregnancy category C (risk cannot be ruled out) for use during pregnancy.

Drug Interactions – Ketoconazole is an inhibitor of multiple CYP isozymes and P-gp; it can significantly increase serum concentrations of many other drugs.⁴ The absorption of ketoconazole is significantly reduced by drugs that increase gastric pH, such as proton pump inhibitors, H₂-receptor blockers and antacids.

ECHINOCANDINS

Echinocandins inhibit synthesis of β (1, 3)-D-glucan, an essential component of the fungal cell wall. Their potential for adverse effects in humans is relatively low due to the absence of cell walls in mammalian cells. Caspofungin, micafungin and anidulafungin all have activity against most *Candida* species, including those resistant to azoles. They have some activity against *Aspergillus* spp., but are not clinically active against *Cryptococcus* spp., *Trichosporon* spp. or

dimorphic fungi. All 3 echinocandins are given intravenously once daily, do not require dosage adjustment for renal dysfunction, do not significantly interact with other drugs, and appear to be similar to each other in efficacy and safety.²⁰

CASPOFUNGIN — In a large controlled trial, caspofungin (*Cancidas*) was at least as effective as amphotericin B for treatment of invasive candidiasis and candidemia.²¹ It has shown some efficacy in treating aspergillosis that is refractory to other drugs,²² but data on its use for primary treatment of aspergillosis are limited.

Adverse Effects – Although generally well tolerated, caspofungin can cause diarrhea, rash, fever, nausea, vomiting, headache, hypokalemia and hepatic toxicity. Stevens-Johnson syndrome and exfoliative dermatitis have been reported. Anaphylaxis has occurred. Maintenance dosage should be reduced in patients with moderate hepatic impairment.

Pregnancy – Caspofungin is embryotoxic in animals. It is classified as pregnancy category C (risk cannot be ruled out) for use during pregnancy.

Drug Interactions – Rifampin, carbamazepine, dexamethasone, efavirenz, nevirapine and phenytoin may increase the clearance of caspofungin. Caspofungin can decrease serum concentrations of tacrolimus.

MICAFUNGIN — In 2 randomized clinical trials in patients with candidemia or invasive candidiasis, micafungin (*Mycamine*) was found to be as effective as liposomal amphotericin B and caspofungin.^{23,24}

Adverse Effects – Micafungin is well tolerated. Rash, pruritus and facial swelling can occur. Anaphylaxis has been rare. Fever, hepatic dysfunction, hemolytic anemia, hypokalemia, thrombocytopenia, renal dysfunction, headache, nausea, vomiting and diarrhea have been reported, but rarely limit therapy.

Pregnancy – Micafungin is teratogenic in animals. It is classified as pregnancy category C (risk cannot be ruled out) for use during pregnancy.

ANIDULAFUNGIN — In a randomized, double-blind trial, anidulafungin (*Eraxis*) was noninferior to fluconazole for treatment of invasive candidiasis.²⁵

Adverse Effects – Anidulafungin has a low incidence of adverse effects similar to those of caspofungin and micafungin. Unlike micafungin and caspofungin, hepatic failure does not appear to increase anidulafungin serum concentrations.

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Pregnancy – Anidulafungin causes skeletal malformations in rats. It is classified as pregnancy category C (risk cannot be ruled out) for use during pregnancy.

AMPHOTERICIN B

Amphotericin B binds to ergosterol in the fungal cell membrane, leading to loss of membrane integrity and leakage of cell contents. Conventional amphotericin B and the newer lipid-based formulations have the same spectrum of activity and are active against most pathogenic fungi and some protozoa. They have variable activity against *Fusarium* spp. and are not active against most strains of *Aspergillus terreus*, *Scedosporium apiospermum*, *Scedosporium prolificans*, *Trichosporon* spp., or *Candida lusitanae*. Amphotericin B is the preferred treatment for deep fungal infections during pregnancy because of long experience with such use and its apparent safety.

Conventional Amphotericin B – Amphotericin B deoxycholate is the least expensive formulation of amphotericin, but also the most toxic, particularly to the kidneys. The development of better tolerated lipid-based formulations has led to a decrease in its use. Intravenous infusion of amphotericin B deoxycholate frequently causes fever and chills, and sometimes headache, nausea, vomiting, hypotension and tachypnea, usually beginning 1-3 hours after starting the infusion and lasting about 1 hour. The intensity of these infusion-related acute reactions tends to decrease after the first few doses. Pretreatment with acetaminophen or a nonsteroidal anti-inflammatory drug (NSAID) such as ibuprofen, diphenhydramine, and/or hydrocortisone has been used to decrease the severity of the reaction. Meperidine is used to shorten the duration of rigors.

Nephrotoxicity is the major dose-limiting toxicity of amphotericin B deoxycholate; sodium loading with normal saline may prevent or ameliorate it and is generally recommended for patients who can tolerate a fluid load. The nephrotoxicity of amphotericin B may add to the nephrotoxicity of other drugs including cyclosporine, tacrolimus and aminoglycoside antibiotics such as gentamicin. Hypokalemia and hypomagnesemia are common and are usually due to a mild renal tubular acidosis. Weight loss, malaise, anemia, thrombocytopenia and mild leukopenia can occur. Cardiac toxicity and myopathy have been reported.

Lipid Formulations – The 3 lipid formulations of amphotericin B available in the US appear to be as effective as amphotericin B deoxycholate. Compared to conventional amphotericin B, acute infusion-related

Table 2. Amphotericin B Formulations

Drug	Usual Daily Dosage ¹	Cost ^{2,3}
Amphotericin B deoxycholate generic	0.7-1.0 mg/kg IV	\$76.00
Amphotericin B lipid complex (ABLC)		
<i>Abelcet</i> (Sigma Tau)	5 mg/kg IV	740.00
Liposomal amphotericin B (L-AmB)		
<i>AmBisome</i> (Astellas)	3-5 mg/kg IV	1099.00
Amphotericin B cholesteryl sulfate complex (ABCD)		
<i>Amphotec</i> (Kadmon)	3-4 mg/kg IV	360.00

1. For invasive fungal infection.
2. Wholesale acquisition cost (WAC) for one day's treatment of a 70-kg patient at the highest usual dosage. Source: PricePointRx™. Reprinted with permission by FDB. All rights reserved. ©2012. <http://www.firstdatabank.com/support/drug-pricing-policy.aspx>. Accessed July 10, 2012. Cost may vary from institution to institution based on purchasing contracts.
3. Cost comparisons with amphotericin B lipid formulations should take into account the fact that conventional amphotericin B deoxycholate may cause renal failure, which can increase the length of hospital stays, healthcare costs and mortality rates (AJ Ullman et al, Clin Infect Dis 2006; 43:e29).

reactions are more severe with *Amphotec*, less severe with *Abelcet*, and least severe with *AmBisome*. Acute, severe pain in the chest, back or abdomen has occurred rarely during the first infusion of *AmBisome*²⁶; the cause of the pain is unknown, but some patients have tolerated subsequent, slower infusions of the drug when pretreated with diphenhydramine. Nephrotoxicity is less common with lipid-based products than with amphotericin B deoxycholate and, when it occurs, less severe. Intravenous administration of a liter of saline each day for adults can decrease azotemia. Liver toxicity, which is generally not associated with amphotericin B deoxycholate, has occurred rarely with the lipid formulations.

OTHER DRUGS

FLUCYTOSINE — Flucytosine (*Ancobon*, and others) is a prodrug of fluorouacil. Colitis, hepatotoxicity, potentially lethal, dose-related bone marrow toxicity, and rapid development of resistance have occurred with flucytosine monotherapy; it is mainly used in combination with amphotericin B for treatment of cryptococcal meningitis or systemic candidiasis. Keeping serum concentrations below 100 mcg/mL decreases the toxicity of the drug, but delays in obtaining assay results often limit their utility. Flucytosine is only available for oral use in the US. The dosage must be adjusted for renal dysfunction. It is classified as category C (risk cannot be ruled out) for use during pregnancy.

Table 3. Treatment of Onychomycosis and Tinea Pedis

Infection	Drug of Choice ¹	Alternatives ¹
Onychomycosis^{2,3}	Terbinafine 250 mg PO once/d x 12 wks ⁴ or Itraconazole 200 mg PO once/d x 3 mos ⁴ or 200 mg PO bid 1 wk/mo x 3 mos ⁴	Fluconazole ⁵ 150-300 mg PO once/wk x 6-12 mos ⁴
Tinea Pedis⁶	Terbinafine cream ^{7,8} twice daily application x 1-2 wks or Topical azoles (i.e. clotrimazole, ⁸ miconazole, ⁸ econazole) once or twice daily application x 4 wks	Fluconazole ⁵ 150 mg PO once/wk x 1-4 wks

1. Usual adult dosage. Some drugs may need dosage adjustment for renal or hepatic dysfunction or when used with interacting drugs.
2. Nail specimens should be obtained prior to any drug therapy to confirm the diagnosis of onychomycosis.
3. Topical treatment with ciclopirox 8% nail laquer (*Penlac*, and others) is indicated for treatment of mild-to-moderate distal superficial onychomycosis. Ciclopirox is less effective than systemic therapy, but has no systemic side effects or drug interactions.
4. Duration for toenail infection. Duration of treatment for fingernail infection: 6 weeks with terbinafine, 2 months (1 week on, 3 weeks off x 2 treatment cycles) with itraconazole and 3-6 months with fluconazole.
5. Not FDA-approved for this indication.
6. Topical treatment of "athlete's foot" is adequate for mild cases. Relapse is common and requires prolonged treatment (>4 wks).
7. Other topical non-azoles, including butenafine and naftifine, may also be used. Butenafine should be applied twice daily for 1 week or once daily for 4 weeks. Naftifine should be used for 4 weeks.
8. Available without a prescription.

TERBINAFINE — Terbinafine (*Lamisil*, and others) is a synthetic allylamine approved by the FDA for treatment of onychomycosis of the toenail or fingernail due to dermatophytes. It inhibits squalene epoxidase which blocks ergosterol synthesis and results in fungal cell death.

The most common adverse effects of oral terbinafine have been headache, gastrointestinal symptoms including diarrhea, dyspepsia and abdominal pain, and occasionally a taste disturbance that may persist for weeks after the drug is stopped. Rash, pruritus and urticaria, usually mild and transient, have occurred. Serious skin reactions, including toxic epidermal necrolysis, have been reported. Increased aminotransferase levels and serious hepatic injury have occurred; liver function should be assessed before starting and periodically during treatment with terbinafine. Anaphylaxis, pancytopenia and severe neutropenia have also been reported. Terbinafine is classified as category B (no evidence of risk) for use during pregnancy.

Drug Interactions – Terbinafine is an inhibitor of CYP2D6 and may increase serum concentrations of drugs metabolized by this enzyme. Concurrent administration of fluconazole may increase serum concentrations of terbinafine. Cimetidine may reduce the clearance of terbinafine, and enzyme inducers such as rifampin may increase terbinafine clearance.

COMBINATION THERAPY

Attempts to improve outcomes in invasive mold infections using combinations of drugs have shown promise *in vitro* and in experimental murine infections, but most clinical data available to date have not shown an

improvement in efficacy. In a recent trial in 277 patients with proven or probable invasive aspergillosis, overall survival at 6 weeks was not significantly better in those treated with the combination of voriconazole and anidulafungin (80.7%) than in those who received voriconazole alone (72.5%).²⁷

NEUTROPENIA

PROPHYLAXIS — High-risk neutropenic patients, such as those undergoing allogeneic stem cell transplants and those with acute myelogenous leukemia, should receive prophylaxis against *Candida* spp.. Fluconazole has been the most commonly used antifungal for this indication, but itraconazole, voriconazole, posaconazole, micafungin and caspofungin are effective alternatives that are now used frequently because of their broader spectrum of activity. In one study, however, fluconazole was not inferior to voriconazole in preventing invasive fungal infections in hematopoietic stem cell transplant recipients.²⁸ Voriconazole or posaconazole should be considered for prophylaxis in neutropenic patients at high risk of invasive aspergillosis.²⁹

FEVER AND NEUTROPENIA — For neutropenic patients with fever that persists despite treatment with antibacterial drugs, empiric addition of an antifungal drug is common practice. Caspofungin and voriconazole are now widely used for this indication.

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The expected outcome of the CME Program is to increase the participant's ability to know, or apply knowledge into practice after assimilating, information presented in materials contained in *Treatment Guidelines*.

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Issue 120 Questions

<p>1. Azole antifungal drugs: a. inhibit the synthesis of cholesterol b. inhibit the synthesis of β (1,3)-D-glucan c. inhibit the synthesis of ergosterol d. all of the above</p> <p style="text-align: right;">Issue 120</p>	<p>8. Nephrotoxicity is more common with: a. <i>Abelcet</i> b. <i>AmBisome</i> c. amphotericin B deoxycholate d. <i>Amphotec</i></p> <p style="text-align: right;">Issue 120</p>
<p>2. Fluconazole has clinically significant activity against: a. <i>Candida krusei</i> b. <i>Aspergillus</i> spp. c. <i>Fusarium</i> spp. d. none of the above</p> <p style="text-align: right;">Issue 120</p>	<p>9. A 59-year-old woman with invasive aspergillosis is not responding to treatment with voriconazole. Which of the following drugs has been effective in treating refractory aspergillosis? a. caspofungin b. fluconazole c. flucytosine d. none of the above</p> <p style="text-align: right;">Issue 120</p>
<p>3. Painful periostitis of long bones has been reported with long-term administration of: a. fluconazole b. itraconazole c. voriconazole d. posaconazole</p> <p style="text-align: right;">Issue 120</p>	<p>10. Potentially lethal, dose-related bone marrow toxicity has occurred with: a. terbinafine b. flucytosine c. caspofungin d. anidulafungin</p> <p style="text-align: right;">Issue 120</p>
<p>4. Children may need higher doses when treated with: a. voriconazole b. anidulafungin c. amphotericin B deoxycholate d. itraconazole</p> <p style="text-align: right;">Issue 120</p>	<p>11. Headache, gastrointestinal symptoms, and occasionally a taste disturbance that can persist for weeks after the drug is stopped have been reported with: a. flucytosine b. terbinafine c. fluconazole d. miconazole</p> <p style="text-align: right;">Issue 120</p>
<p>5. Caspofungin, micafungin and anidulafungin: a. are administered intravenously once daily b. do not require dosage adjustment for renal dysfunction c. do not interact significantly with other drugs d. all of the above</p> <p style="text-align: right;">Issue 120</p>	<p>12. A 64 year-old-man is undergoing allogeneic stem cell transplantation and is expected to have prolonged profound neutropenia. Which of the following would you recommend for prophylaxis against invasive aspergillosis? a. amphotericin B deoxycholate b. voriconazole c. terbinafine d. fluconazole</p> <p style="text-align: right;">Issue 120</p>
<p>6. Gynecomastia, decreased libido and erectile dysfunction have been reported with: a. ketoconazole b. anidulafungin c. caspofungin d. posaconazole</p> <p style="text-align: right;">Issue 120</p>	
<p>7. In clinical trials, micafungin was found to be about as effective as liposomal amphotericin B for treatment of: a. oral candidiasis b. candidemia c. aspergillosis d. all of the above</p> <p style="text-align: right;">Issue 120</p>	

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