Antifungal Drugs

The drugs of choice for treatment of some fungal infections are listed in the table that begins on page 96. Some of the indications and dosages recommended here have not been approved by the FDA. More detailed guidelines are available online from the Infectious Diseases Society of America (www.idsociety.org).

AZOLES

Aazole antifungal agents inhibit synthesis of ergosterol, an essential component of the fungal cell membrane.

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 increasingly resistant. Fluconazole has good activity against Coccidioides and Cryptococcus spp.; higher doses may be needed against Histoplasma capsulatum. The drug has no clinically significant activity against most molds, including Aspergillus spp., Fusarium spp. and Zygomycetes, such as Mucor 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. Some post-marketing cases of QT prolongation and torsades de pointes have also been reported. Fluconazole is teratogenic in animals (pregnancy category C).

Drug Interactions – Fluconazole is a strong inhibitor of CYP2C9 and 2C19 (in vitro) and a moderate inhibitor of CYP3A4; it may increase serum concentrations of drugs metabolized by these enzymes.¹ Concomitant administration of rifampin can lower serum concentrations of fluconazole. 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.¹,²

ITRACONAZOLE — Itraconazole (Sporanox, and others) has a broader spectrum of activity than fluconazole. It is active against a wide variety of fungi including Cryptococcus 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 Scedosporium spp., Fusarium spp., Scopulariopsis spp. or Zygomycetes.

Itraconazole is available orally in both capsules and solution; an IV formulation is no longer being produced in the US. Absorption after oral dosing is variable. The 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 itraconazole are nausea, vomiting and rash. Stevens-Johnson syndrome and serious hepatic toxicity can occur. The drug can cause hypokalemia, edema and hypertension. Negative inotropic effects and congestive heart failure have been reported; itraconazole should not be used in patients with a history of heart failure or ventricular dysfunction. Peripheral neuropathy, visual disturbances, hearing loss and tinnitus have also been reported. Itraconazole is teratogenic in rats (pregnancy category C).

Drug Interactions – The absorption of itraconazole from capsules is reduced by drugs that decrease gastric acidity, such as antacids, H₂-receptor blockers or proton pump inhibitors.
### Table 1. Treatment of Fungal Infections

<table>
<thead>
<tr>
<th>Infection</th>
<th>Drug</th>
<th>Dosage/Duration</th>
<th>Alternatives</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Aspergillosis</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Voriconazole(^2)</td>
<td>6 mg/kg IV q12h x 1d, then 4 mg/kg IV q12h or 200-300 mg PO bid ≥10 wks(^3)</td>
<td>Posaconazole 200 mg PO tid-qid(^3)</td>
</tr>
<tr>
<td></td>
<td>or Amphotericin B</td>
<td>1-1.5 mg/kg/d IV(^5)</td>
<td>Itraconazole 200 mg tid x 3d, followed by 200 mg bid</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Caspofungin 70 mg IV x 1d, then 50 mg IV 1x/d</td>
</tr>
<tr>
<td><strong>Blastomycosis(^6)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Itraconazole</td>
<td>200 mg PO bid x 6-12 mos</td>
<td>Fluconazole 400 mg PO 1x/d(^5),(^7),(^8)</td>
</tr>
<tr>
<td></td>
<td>or Amphotericin B</td>
<td>0.5-1.0 mg/kg/d IV(^5)</td>
<td></td>
</tr>
<tr>
<td><strong>Candidiasis</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Vaginal</strong></td>
<td>Topical therapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Butoconazole, clotrimazole, miconazole, tioconazole, or terconazole</td>
<td>1x/d x 1-7d</td>
<td></td>
</tr>
<tr>
<td><strong>Systemic therapy</strong></td>
<td>Fluconazole</td>
<td>150 mg PO once(^10)</td>
<td>Itraconazole(^9) 200 mg PO bid x 1d</td>
</tr>
<tr>
<td><strong>Recurrent</strong></td>
<td>Fluconazole</td>
<td>150 mg PO 1x/wk</td>
<td>Ketoconazole(^3) 200 mg PO bid x 5d</td>
</tr>
<tr>
<td><strong>Urinary</strong></td>
<td>Fluconazole</td>
<td>200 mg IV or PO 1x/d x 7-14d</td>
<td>Amphotericin B 0.3-0.5 mg/kg/d IV(^5) x 1-7d</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Flucytosine 25 mg/kg PO qid x 5-7d(^13)</td>
</tr>
<tr>
<td><strong>Oropharyngeal</strong></td>
<td>Fluconazole</td>
<td>200 mg IV or PO once, then 100-200 mg 1x/d x 2-3 wks(^15),(^20)</td>
<td>Voriconazole(^17) 200 mg PO bid x 1-3 wks(^18)</td>
</tr>
<tr>
<td></td>
<td>or An echinocandin</td>
<td></td>
<td>Itraconazole(^19) 200 mg PO x 1d, then 100 mg/d(^20) x 1-3 wks(^18)</td>
</tr>
<tr>
<td></td>
<td>Caspofungin</td>
<td>70 mg IV x 1d, then 50 mg IV 1x/d x 1-3 wks(^18)</td>
<td>Posaconazole 100 mg bid x 1d then 100 mg 1x/d x 1-3 wks(^18),(^21)</td>
</tr>
<tr>
<td></td>
<td>Micafungin</td>
<td>150 mg IV 1x/d x 1-3 wks(^18)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Anidulafungin</td>
<td>100 mg IV x 1d, then 50 mg 1x/d x 1-3 wks(^18)</td>
<td></td>
</tr>
<tr>
<td><strong>Candidemia</strong></td>
<td>Fluconazole</td>
<td>400 mg IV 1x/d, then PO(^22)</td>
<td>Voriconazole 6 mg/kg IV q12h x 1d then 3-4 mg/kg IV bid or 200 mg PO bid(^4),(^22)</td>
</tr>
<tr>
<td></td>
<td>or An echinocandin</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Caspofungin(^23)</td>
<td>70 mg IV x 1d, then 50 mg IV 1x/d(^22)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Anidulafungin</td>
<td>200 mg IV x 1d, then 100 mg 1x/d(^22)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Micafungin</td>
<td>100 mg IV 1x/d(^22)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>or Amphotericin B</td>
<td>0.5-1.0 mg/kg/d IV(^5),(^22)</td>
<td></td>
</tr>
</tbody>
</table>

1. 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.
2. In one large controlled trial, voriconazole was more effective than amphotericin B for treatment of invasive aspergillosis (R Herbrecht et al, N Engl J Med 2002; 347:408).
3. Not FDA-approved for this indication.
4. Children may need higher maintenance 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 2-12 years old, the recommended maintenance dosages are 7 mg/kg IV bid or 200 mg PO bid, without loading doses (MO Karlsson et al, Antimicrob Agents Chemother 2009; 53:9351).
5. Dosage of amphotericin B deoxycholate given once daily. Lipid-based formulations may be preferred. 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 cholesterol sulfate (Amphotec) 3-4 mg/kg/d. For treatment of zygomycosis, the dosage of Ambisome is 5 mg/kg/d. For treatment of cryptococcal meningitis in HIV patients, the dosage of Ambisome is 4-6 mg/kg/d.
6. Patients with severe illness or CNS involvement should receive amphotericin B.
7. In general, a loading dose of twice the daily dose is recommended on the first day of therapy.
8. For use only in patients who cannot tolerate itraconazole or amphotericin B.
9. Non-albicans species, such as C. glabrata and C. krusei, respond to boric acid 600 mg intravaginally daily x 14d or to topical flucytosine cream (JD Sobel et al, Am J Obstet Gynecol 2003; 189:1297).
10. May be repeated in 72 hours if patient remains symptomatic.
### Table 1. Treatment of Fungal Infections (continued)

<table>
<thead>
<tr>
<th>Infection</th>
<th>Drug</th>
<th>Dosage/Duration</th>
<th>Alternatives</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Coccidioidomycosis</strong></td>
<td>Itraconazole³</td>
<td>200 mg PO bid x &gt;1 yr</td>
<td></td>
</tr>
<tr>
<td>or Fluconazole³</td>
<td>400 mg PO 1x/d x &gt;1 yr⁷</td>
<td></td>
<td></td>
</tr>
<tr>
<td>or Amphotericin B</td>
<td>0.5-1.5 mg/kg/d IV⁵ x &gt;1 yr</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Cryptococcosis</strong></td>
<td>Amphotericin B</td>
<td>0.5-1.0 mg/kg/d IV⁵ x 2 wks</td>
<td>Fluconazole³ 200 mg PO bid</td>
</tr>
<tr>
<td>+ Flucytosine⁴</td>
<td>25 mg/kg PO qid⁵</td>
<td></td>
<td>Itraconazole³ 200 mg PO bid⁵</td>
</tr>
<tr>
<td>then Flucytosine⁴</td>
<td>400 mg PO 1x/d x 10 wks⁷</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Chronic suppression</strong></td>
<td>Fluconazole</td>
<td>200 mg PO 1x/d</td>
<td></td>
</tr>
<tr>
<td><strong>Fusariosis</strong></td>
<td>Amphotericin B</td>
<td>1-1.5 mg/kg/d IV⁵</td>
<td></td>
</tr>
<tr>
<td>or Voriconazole</td>
<td>6 mg/kg IV q12h x 1d, then 4 mg/kg q12h or 200 mg PO bid⁴</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Histoplasmosis</strong></td>
<td>Amphotericin B²⁷</td>
<td>0.5-1.0 mg/kg/d IV⁵ x 2 wks</td>
<td>Fluconazole³ 400 mg PO 1x/q⁷,⁸</td>
</tr>
<tr>
<td>or Itraconazole³</td>
<td>200 mg tid x 3d then 200 mg PO bid x 6 wks-12 mos</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Chronic suppression</strong></td>
<td>Itraconazole³</td>
<td>200 mg PO 1x/d or bid</td>
<td>Amphotericin B 0.5-1 mg/kg IV wkly⁶</td>
</tr>
<tr>
<td><strong>Paracoccidioidomycosis</strong></td>
<td>Itraconazole³</td>
<td>100-200 mg PO 1x/d x 6-12 mos</td>
<td>Ketoconazole 200-400 mg PO 1x/d</td>
</tr>
<tr>
<td>or Amphotericin B²⁸</td>
<td>0.4-0.5 mg/kg/d IV⁵</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Scedosporiosis</strong> (asexual form of Pseudallescheria)</td>
<td>Voriconazole</td>
<td>6 mg/kg IV q12h x 1d, then 4 mg/kg IV bid, or 200 mg PO bid x 12 wks⁴</td>
<td>Posaconazole³ 200 mg PO tid-qid</td>
</tr>
<tr>
<td><strong>Sporotrichosis</strong></td>
<td>Itraconazole³</td>
<td>200 mg PO 1x/d x 3-6 mos</td>
<td>Terbinafine³ 500 mg PO bid</td>
</tr>
<tr>
<td><strong>Cutaneous</strong></td>
<td></td>
<td></td>
<td>Saturated solution of potassium iodide 1-5 mL PO tid</td>
</tr>
<tr>
<td>or Amphotericin B³⁹</td>
<td>0.7-1 mg/kg/d IV⁶ x 6-12 wks</td>
<td></td>
<td>Fluconazole³,⁷ 400-800 mg PO 1x/d</td>
</tr>
<tr>
<td><strong>Extracutaneous</strong></td>
<td>Itraconazole³</td>
<td>200 mg PO 1x/d x 12 mos</td>
<td></td>
</tr>
<tr>
<td><strong>Zygomycosis</strong></td>
<td>Amphotericin B</td>
<td>1-1.5 mg/kg/d IV⁵ x 6-10 wks</td>
<td>Posaconazole³,²⁹ 200 mg PO tid-qid</td>
</tr>
</tbody>
</table>

12. Asymptomatic candiduria usually does not require treatment. Patients who are symptomatic, neutropenic, have renal allografts or are undergoing urologic manipulation and infants with low birth weight should be treated.
13. Dosage must be decreased in patients with diminished renal function.
14. For uncomplicated oropharyngeal thrush, clotrimazole troches (10 mg) 5x/d or nystatin suspension 500,000 units (5 mL) qid can also be used. Azole-resistant oropharyngeal or esophageal candidiasis usually responds to amphotericin B or an echinocandin.
15. 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. lusitaniae may be resistant to amphotericin B.
16. 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.
18. Duration of treatment for esophageal candidiasis is 14 to 21 days after clinical improvement.
19. For patients with oropharyngeal disease, itraconazole oral solution 200 mg (20 mL) given once daily without food is more effective than itraconazole capsules.
20. Use up to 400 mg/d for esophageal candidiasis.
21. For refractory oropharyngeal candidiasis, use 400 mg once/d or bid.
22. Until 2 weeks after afebrile and blood cultures negative.
23. In a large controlled trial, caspofungin was at least as effective as amphotericin B for treatment of invasive candidiasis or candidemia (J Mora-Duarte et al, N Engl J Med 2002; 347:3090).
24. Itraconazole is the drug of choice for non-meningeal coccidioidomycosis. Fluconazole is preferred for coccidioidal 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.
25. Dosage must be decreased in patients with diminished renal function. When given with amphotericin B, some Medical Letter consultants recommend beginning fluconazole at 75 mg/kg/day divided q6h, until the degree of amphotericin nephrotoxicity becomes clear or fluconazole blood levels can be determined.
26. For patients with HIV infection.
27. For severe disease, before switching to itraconazole. 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).
28. Initial treatment of severely ill patients. To be followed by itraconazole.
29. Posaconazole has been used after mucormycosis was clinically improved and oral alimentation was sufficient to enhance absorption (AM Tobon et al, Clin Infect Dis 2003; 36:1488).
**VORICONAZOLE** — Voriconazole (Vfend) has a spectrum of activity similar to that of itraconazole but appears to be more active against Aspergillus spp. and most species of Candida, including C. glabrata and C. krusei. Unlike itraconazole, voriconazole is active against Fusarium spp. and Scedosporium spp. It is not active against Sporothrix spp. or Zygomycetes; infection with these organisms has developed during treatment with voriconazole. In a randomized trial of initial treatment of invasive aspergillosis, voriconazole improved survival compared to amphotericin B and caused fewer severe adverse effects.

Patients with mild to moderate hepatic insufficiency should receive a normal loading dose of voriconazole, but half the maintenance dose. Serum concentrations of voriconazole may need monitoring; they vary from patient to patient and with the formulation used (lower with capsules and higher with the solution). Children need a higher per-kg dose than adults because they clear the drug more rapidly.

**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. Rash (including Stevens-Johnson syndrome), photosensitivity, increased transaminase levels, confusion and hallucinations have also occurred. In patients with creatinine clearance <50 mL/min, the oral formulation is preferred because the solubilizing agent in the IV formulation (sulfobutyl ether beta-cyclodextrin) can accumulate and cause toxicity. Anaphylactoid infusion reactions have occurred. Voriconazole is teratogenic in animals (pregnancy category D).

**Drug Interactions** — Voriconazole is a substrate of CYP2C19, 2C9, 3A4 and P-gp. Drugs that inhibit or induce one or more of these clearance pathways may significantly alter serum concentrations of voriconazole. Patients deficient in CYP2C19 (about 3-5% of Caucasians and African-Americans and about 15% of Asians do not express it) may have 2- to 4-fold higher serum concentrations of voriconazole. Voriconazole is an inhibitor (*in vitro*) of CYP2C9, 3A4 and, to a lesser extent, 2C19; it may significantly increase serum concentrations of drugs metabolized by these enzymes. 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.

**POSACONAZOLE** — Posaconazole (Noxafil), the newest triazole, has an antifungal spectrum similar to that of itraconazole, but its *in vitro* activity is about twice as great; it can be used to treat *Fusarium* spp. and *Scedosporium* spp. and has up to 4-fold greater activity against many species of *Mucor*, such as *Absidia* spp. Posaconazole is only available for oral use and must be taken with meals for optimal absorption.

**Clinical Studies** — A randomized, open-label clinical trial of posaconazole for prophylaxis against fungal infections found that 602 adults who were neutropenic as a result of induction chemotherapy for acute myelogenous leukemia (AML) or myelodysplastic syndrome (MDS) had fewer invasive mycoses (including aspergillosis) and lower mortality rates when taking posaconazole (200 mg t.i.d.) compared to those taking fluconazole (400 mg once/day) or itraconazole (200 mg b.i.d.). A double-blind randomized trial in 600 adults with graft-versus-host disease following allogeneic hematopoietic stem cell transplantation (HSCT) found posaconazole similar to fluconazole in preventing invasive mycoses and superior in preventing invasive aspergillosis and death.

HIV-infected patients with oropharyngeal or esophageal candidiasis refractory to treatment with fluconazole or itraconazole have responded to posaconazole; in one study, 75% of these patients achieved cure or improvement after 28 days of treatment. 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. It has also been used off-label to treat coccidioidomycosis and zygomycosis.

**Adverse Effects** — Posaconazole has a safety profile comparable to that of fluconazole; dry mouth, rash, headache, diarrhea, fatigue, nausea, vomiting, QT prolongation and abnormal liver function have been reported, but infrequently lead to drug discontinuation. Arrhythmias, toxic epidermal necrolysis, angioedema and anaphylaxis have been rare. Posaconazole causes skeletal malformations in rats (pregnancy category C).
Table 2. Treatment of Onychomycosis and Tinea Pedis

<table>
<thead>
<tr>
<th>Infection</th>
<th>Drug</th>
<th>Dosage/Duration</th>
<th>Alternatives</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onychomycosis²,³</td>
<td>Terbinafine</td>
<td>250 mg PO once/d x 12 wks</td>
<td>Fluconazole⁴ 150-300 mg PO once/wk x 6-12 mos⁴</td>
</tr>
<tr>
<td>or Itraconazole</td>
<td>200 mg PO once/d x 3 mos⁴ or 200 mg PO bid 1 wk/mo x 3 mos⁴</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tinea Pedis⁴</td>
<td>Terbinafine cream² twice daily application x 1-2 wks</td>
<td>Fluconazole⁴ 150 mg PO once/wk x 1-4 wks</td>
<td></td>
</tr>
<tr>
<td>or topical azoles (i.e. clotrimazole, miconazole, econazole) once or twice daily application x 4 wks</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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 lacquer (Penlac, and others) is indicated for treatment of mild to moderate onychomycosis caused by T. rubrum that does not involve the lunula. 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 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, but the duration of treatment should then be increased to 2-4 weeks.

**Drug Interactions**

Posaconazole is primarily metabolized through UDP glucuronidation and is also a substrate of P-gp. Any drug that inhibits or induces these clearance pathways may alter serum concentrations of posaconazole. Drugs that increase gastric pH, such as proton pump inhibitors, H₂-receptor blockers or antacids, may decrease the absorption of posaconazole. Posaconazole is a strong inhibitor of CYP3A4 and may increase serum concentrations of drugs that are metabolized by this enzyme. Posaconazole is contraindicated for use with sirolimus, ergot alkaloids, and CYP3A4 substrates that also prolong the QT interval. It should be used with caution with other drugs known to prolong the QT interval.

**KETOCONAZOLE**

Ketoconazole (Nizoral, and others) is seldom used now. Other azoles are preferred because they have fewer adverse effects.

**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 hepatitis necrosis, can occur. Ketoconazole is teratogenic in animals (pregnancy category C).

**Drug Interactions**

Ketoconazole is a strong inhibitor of CYP3A4 and other metabolic pathways; it can significantly increase serum concentrations of many other drugs. 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 low due to the absence in mammalian cells of enzymes involved in glucan synthesis. Caspofungin, anidulafungin and micafungin all have activity against most Candida species, including those resistant to azoles. Their activity against molds appears to be confined to Aspergillus. All 3 echinocandins are given intravenously once daily, do not require dose adjustment for renal failure, do not significantly interact with other drugs, and appear to be similar to each other in efficacy and safety.

**CASPOFUNGIN**

Casopfungin (Cancidas) is FDA-approved for treatment of esophageal candidiasis, candidemia, intra-abdominal abscesses, peritonitis, and pleural space infections due to Candida. It is also approved for empiric treatment of presumed fungal infections in febrile, neutropenic patients and for treatment of invasive aspergillosis in patients who are refractory to or intolerant of other therapies. Data on its use for primary treatment of aspergillosis is lacking.

**Adverse Effects**

Although generally well tolerated, caspofungin occasionally causes rash, fever, nausea, vomiting, headache, hypokalemia and mild hepatic toxicity. Stevens-Johnson syndrome and exfoliative dermatitis have been reported. Anaphylaxis has occurred. Dosage should be reduced in patients with moderate hepatic dysfunction. Caspofungin is embryotoxic in animals (pregnancy category C).

**Drug Interactions**

Rifampin, carbamazepine, dexamethasone, efavirenz, nevirapine and phenytoin may increase the clearance of caspofungin. An increase in

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caspofungin dosage to 70 mg daily (70 mg/m²/day in children, max 70 mg) should be considered when it is co-administered with these drugs. Caspofungin can decrease serum concentrations of tacrolimus.

**MICAFUNGIN** — Micafungin (Mycamine) is FDA-approved for treatment of esophageal candidiasis and prevention of invasive candidiasis in autologous or allogeneic stem cell transplant recipients. It is also approved for treatment of candidemia and deeply invasive candidiasis. Approval was based on showing noninferiority in 2 large randomized clinical trials in patients with invasive candidiasis, one comparing micafungin to liposomal amphotericin B and the other comparing it to caspofungin. In an open-label, noncomparative trial, micafungin appeared to be efficacious in 12 patients with untreated and 24 patients with partially treated aspergillosis.

**Adverse Effects** — Micafungin is well tolerated. Adverse effects have included rash, pruritus and facial swelling. Anaphylaxis has been rare. Fever, hepatic function abnormalities, hypokalemia, thrombocytopenia, renal dysfunction, headache, nausea, vomiting and diarrhea have been reported, but rarely limit therapy. Micafungin is teratogenic in animals (pregnancy category C).

**ANIDULAFUNGIN** — Anidulafungin (Eraxis) is FDA-approved for treatment of esophageal candidiasis. It is also approved for treatment of candidemia and deeply invasive candidiasis based on a randomized, double-blind trial demonstrating noninferiority to fluconazole.

**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. Its safety in pregnancy has not been established (pregnancy category C).

**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 are not active against most strains of *Aspergillus terreus*, *Scedosporium apiospermum*, *Trichosporon* spp., *Fusarium* spp. and *Candida lusitaniae*. Amphotericin B is the preferred treatment for deep fungal infections during pregnancy because of experience with its use and apparent safety.

### Table 3. Amphotericin B Formulations

<table>
<thead>
<tr>
<th>Drug</th>
<th>Usual Daily Dosage</th>
<th>Cost²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amphotericin B deoxycholate generic (Abbott)</td>
<td>1-1.5 mg/kg IV</td>
<td>$34.92</td>
</tr>
<tr>
<td>Amphotericin B lipid complex (ABLC)</td>
<td>5 mg/kg IV</td>
<td>840.00</td>
</tr>
<tr>
<td>Abelcet (Enzon)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AmBisome (Astellas)</td>
<td>3-5 mg/kg IV</td>
<td>1318.80</td>
</tr>
<tr>
<td>Amphotericin B cholesteryl sulfate complex (ABCD)</td>
<td>3-4 mg/kg IV</td>
<td>733.33</td>
</tr>
<tr>
<td>Amphotel (Three Rivers)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1. For invasive fungal infection.
2. Cost for one day’s treatment of a 70-kg patient at the highest usual dosage according to AWP prices listed in Redbook 2009.

**Conventional Amphotericin B** — Amphotericin B deoxycholate, the non-lipid formulation of amphotericin, is the least expensive but also the most toxic, particularly to the kidney. 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 25 mg IV and/or hydrocortisone 25 mg IV can decrease the severity of the reaction. Treatment with meperidine 25-50 mg IV can 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 marketed in the US appear to be as effective as amphotericin B deoxycholate. Compared to conventional amphotericin B, acute infusion-relat-
ed 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 during the first infusion of liposomal amphotericin B. The cause of the pain is unknown. 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. Liver toxicity, which is generally not associated with amphotericin B deoxycholate, has occurred rarely with the lipid formulations.

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.

OTHER DRUGS

FLUCYTOSINE — Potentially lethal, dose-related bone marrow toxicity and rapid development of resistance have occurred with flucytosine (Ancobon) 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 toxicity, but delays in obtaining assay results often limit their utility. Flucytosine is only available for oral use in the US. Doses must be adjusted for renal dysfunction. It is classified as category C for use in pregnancy.

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 acts by inhibiting squa-lene epoxidase and blocking ergosterol synthesis.

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. Toxic epidermal necrolysis and erythema multiforme 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 for use in pregnancy.

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

COMBINATION THERAPY

Use of combination therapy for treatment of immunosuppressed patients with invasive aspergillosis, which has a high rate of morbidity and mortality despite current treatments, is controversial. In vitro studies and animal data suggest a potential benefit of combining an echinocandin with either an azole or amphotericin B, but clinical studies are lacking.

NEUTROPENIA

PROPHYLAXIS — High-risk neutropenic patients, such as those undergoing allogeneic and certain autologous stem cell transplants, and those with hematologic malignancy who are expected to have prolonged profound neutropenia, may require prophylactic treatment with antifungal drugs. Fluconazole (400 mg PO or IV once daily) has been used, but because of the high risk of invasive aspergillosis in these patients, some clinicians now use voriconazole (6 mg/kg every 12 hours x 2 doses, then 4-5 mg/kg every 12 hours) or posaconazole (200 mg t.i.d.) instead. Itraconazole solution, 200 mg twice daily, is an alternative but may not be well tolerated. In a prospective, randomized trial for prevention of invasive fungal infections in neutropenic patients with acute myelogenous leukemia or myelodysplastic syndrome undergoing chemotherapy, posaconazole was superior to fluconazole or itraconazole and improved survival. Micafungin 50 mg/day has been recommended for prophylactic use in patients with neutropenia.

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 appear to be as effective as liposomal amphotericin B. Fluconazole and itraconazole have also been used for this indication.

Antifungal Drugs


Coming Soon in Treatment Guidelines:
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The mission of The Medical Letter’s Continuing Medical Education Program is to support the professional development of health care professionals including physicians, nurse practitioners, pharmacists and physician assistants by providing independent, unbiased drug information and prescribing recommendations that are free of industry influence. The program content includes current information and unbiased reviews of FDA-approved and off-label uses of drugs, their mechanisms of action, clinical trials, dosage and administration, adverse effects and drug interactions. The Medical Letter delivers educational content in the form of self-study material.

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The Medical Letter will strive to continually improve the CME program through periodic assessment of the program and activities. The Medical Letter aims to be a leader in supporting the professional development of health care professionals by providing continuing medical education that is unbiased and free of industry influence.

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The objective is to meet the need of health care professionals for unbiased, reliable and timely information on treatment of major diseases.

Activity participants will read and assimilate unbiased reviews of FDA-approved and off-label uses of drugs and drug classes. Participants will be able to select and prescribe, or confirm the appropriateness of the prescribed usage of the drugs and other therapeutic modalities discussed in Treatment Guidelines with specific attention to clinical evidence of effectiveness, adverse effects and patient management. Through this program, The Medical Letter expects to provide the prescribing health care community with educational content that they will use to make independent and informed therapeutic choices in their practice.

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**Have any questions?** Call us at 800-211-2769 or 914-235-0500 or e-mail us at: custserv@medicalletter.org

Questions start on next page
1. **Azole antifungal drugs:**
   a. inhibit the synthesis of ergosterol
   b. inhibit the synthesis of β-(1, 3)-D-glucan
   c. inhibit the synthesis of cholesterol
   d. all of the above  
   Pg. 95

2. Fluconazole has clinically significant activity against:
   b. *Candida krusei*
   c. *Aspergillus* spp.
   Pg. 95

3. Itraconazole has clinically significant activity against:
   b. *Fusarium* spp.
   c. *Zygomycetes*
   d. *Aspergillus* spp.
   Pg. 95

4. Negative inotropic effects and congestive heart failure have been reported with:
   a. anidulafungin
   b. itraconazole
   c. amphotericin B deoxycholate
   d. voriconazole
   Pg. 95

5. Children may need higher doses when treated with:
   a. voriconazole
   b. posaconazole
   c. ketoconazole
   d. anidulafungin
   Pg. 98

6. Transient visual disturbances, including blurred vision, photophobia and altered perception of color or image have occurred with:
   a. anidulafungin
   b. voriconazole
   c. mycamine
   d. posaconazole
   Pg. 98

7. Caspofungin, micafungin, and anidulafungin:
   a. have activity against most *Candida* species
   b. are given intravenously once daily
   c. do not require dose adjustment for renal failure
   d. all of the above
   Pg. 99

8. Caspofungin is not FDA-approved for the primary treatment of:
   a. esophageal candidiasis
   b. candidemia
   c. peritonitis
   d. aspergillosis
   Pg. 99

9. Nephrotoxicity is more common with:
   a. amphotericin B deoxycholate
   b. *Amphotec*
   c. *AmBisome*
   d. *Abelcet*
   Pg. 101

10. Potentially lethal, dose-related bone marrow toxicity and rapid development of resistance with monotherapy has the limited use of:
    a. terbinafine
    b. fluconazole
    c. micafungin
    d. anidulafungin
    Pg. 101

11. Use of combination therapy for treatment of immunosuppressed patients with invasive aspergillosis:
    a. is recommended
    b. is controversial
    c. is supported by clinical evidence
    d. none of the above
    Pg. 101

12. High-risk neutropenic patients requiring antifungal therapy may be treated prophylactically with:
    a. posaconazole
    b. voriconazole
    c. micafungin
    d. all of the above
    Pg. 101