Antifungal Agents
Spectrum of Activity, Pharmacology, and Clinical Indications

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KEYWORDS

- Antifungal • Spectrum of activity • Azole • Echinocandins • Amphotericin B
- Pharmacokinetics • Indications • Toxicity

KEY POINTS

- The currently available antifungal agents vary significantly in terms of spectrum of activity. The echinocandins exhibit potent activity against *Candida*, whereas the newer triazoles offer an extended spectrum of activity that includes *Aspergillus* and emerging filamentous pathogens.
- The pharmacokinetic properties differ among the antifungal drugs. Important considerations include absorption, tissue site penetration, impact of organ dysfunction on dosing, routes of metabolism, and the need for therapeutic drug monitoring.
- Many triazoles are metabolized via hepatic CYP450 enzymes. Drug–drug interactions are frequent and common enzyme polymorphisms may lead to unpredictable drug levels.
- Drug dosing and Food and Drug Administration–approved clinical indications for individual antifungal drugs are reviewed.

INTRODUCTION: THE EVOLUTION OF ANTIFUNGAL DRUG THERAPY

Continued advancement of medical science offers life-saving treatment options for a variety of hematologic, oncologic, and rheumatologic conditions. Immunosuppression, a common therapeutic side-effect, predisposes patients to invasive fungal infections, which are escalating in prevalence.[1,2] The development of effective, well-tolerated antifungals has lagged behind the advances of antibacterial therapy. Amphotericin B deoxycholate, an antifungal developed in the 1950s, marked a major therapeutic advance (**Box 1**). Although very effective for the treatment of numerous

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> **Box 1**
> **History of antifungal therapy**
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> - The first antifungal, amphotericin B deoxycholate, was introduced in 1958. It offers potent, broad-spectrum antifungal activity but is associated with significant renal toxicity and infusion reactions.
> - Flucytosine, a pyrimidine analogue introduced in 1973, is active against *Candida* and *Cryptococcus*. Its use is limited by emergence of drug resistance and toxicity.
> - The first-generation azole drugs, including fluconazole and itraconazole, became available in the 1990s. These agents offer the advantage of oral administration and have good activity against yeast pathogens. Due to CYP450 interactions, there are many drug–drug interactions.
> - Lipid-based amphotericin B formulations were introduced in the 1990s and maintain the potent, broad-spectrum activity of the deoxycholate formulation with less toxicity.
> - The echinocandin drugs became available in the 2000s and offer excellent activity against *Candida* with few drug–drug interactions; however, they are available in parenteral form only.
> - The second-generation of azole drugs, including voriconazole, posaconazole, and isavuconazole, were brought to market beginning in the 2000s. The major advantage of these agents is the extended spectrum of activity against filamentous fungi.

invasive fungal infections, it is not without cost. Side-effects, including renal failure, electrolyte abnormalities, and infusion reactions, often limit its use.[3] However, for many years, amphotericin B remained the sole option for the treatment of invasive mycosis. In the 1970s, flucytosine, a pyrimidine analogue, was introduced. Its use has been limited by rapid emergence of resistance when used alone, as well as associated toxicities, including bone marrow suppression. In the mid-1990s, new lipid-based amphotericin B formulations were brought to market. Compared with the initial deoxycholate formulation, these have improved side-effect profiles with reduced nephrotoxicity and remain the mainstay for treatment of many life-threatening fungal infections.

In addition to the advent of the lipid-based amphotericin B formulations, another major advance of the 1990s was the addition of the triazole drug class (see **Box 1**). Compared with the amphotericin B formulations, the azole drugs are significantly better tolerated. The first-generation azole drugs (fluconazole-1990, itraconazole-1992) demonstrate excellent activity against *Candida* spp. The spectrum of itraconazole activity also includes endemic fungi, such as histoplasmosis. However, the original triazoles agents are inferior to amphotericin B for treatment of invasive filamentous fungal infections, such as aspergillosis and mucormycosis. The second-generation azole drugs (voriconazole-2002, posaconazole-2006) are broad-spectrum agents, with additional activity against filamentous fungi while retaining anti-*Candida* activity.[4,5] The newest azole released in 2015 (isavuconazole) has similarly broad activity with more favorable pharmacologic properties, allowing for improved bioavailability, more predictable drug levels, and fewer drug interactions.

The newest antifungal class, the echinocandins, was introduced in 2001 with caspofungin. Micafungin and anidulafungin were soon to follow. These agents exhibit potent activity against *Candida* spp, including many azole-resistant organisms and *C glabrata*. In addition, they demonstrate modest activity against *Aspergillus* spp. Favorable attributes of the echinocandin drugs include their excellent side-effect profiles and few drug–drug interactions. However, only parental formulations are available for this drug class.

PHARMACOLOGIC CONSIDERATIONS

Numerous obstacles are encountered on delivery of an antimicrobial compound to the site of fungal infection. Important pharmacokinetic factors include absorption in the gastrointestinal tract (for oral formulations), anatomic distribution, metabolism, and elimination. For example, amphotericin B and the echinocandin drugs have minimal gastrointestinal absorption and are solely available as parenteral formulations. Conversely, the azole drugs are able to be absorbed through the gastrointestinal mucosa, although the extent varies by individual antifungal. For example, fluconazole and isavuconazole are readily absorbed with high bioavailability, whereas absorption of posaconazole is limited and saturable.[6,7] The newer posaconazole capsule formulation circumvents this limitation by delayed release of the compound, resulting in higher bioavailability with more predictable drug levels.[8] Another important variable to consider is drug metabolism. For example, polymorphisms are common in the CYP2C19 enzyme that metabolizes voriconazole. Variable metabolism leads to unpredictable drug levels, which may place patients at risk for toxicity or therapeutic failure.[9] The anatomic distribution also varies among the antifungals. An example of an important clinical consideration is the limited penetration of the echinocandins into the cerebrospinal fluid, eye, and urine.[10,11]

POLYENES

Polyenes are natural products of *Streptomyces nodosus*, a soil actinomycete (Fig. 1).[12] A single agent, amphotericin B, is available for treatment of systemic fungal infections; however, there are multiple formulations. The deoxycholate formulation was initially developed and 3 lipid-based formulations have been designed and developed to limit toxicity and improve tolerability. Amphotericin B exerts its activity through hydrophobic interactions with cell membrane ergosterol, subsequently disrupting membrane function. Pores formation allows the efflux of potassium, leading to cell death.[13]

Spectrum of Activity and Resistance

Amphotericin B is one of the most potent antifungals, demonstrating activity against an array of yeast and filamentous fungal pathogens (Table 1).

Amphotericin B exhibits activity against *Cryptococcus* spp and most *Candida* spp, with the exception of *Candida lusitaniae*, which routinely is found to have higher minimal inhibitory concentrations (MICs).[14–16] It also demonstrates activity against *Aspergillus* spp, with the major exception of *Aspergillus terreus*, which is often resistant.[17] In addition, the amphotericin B formulations are active against the dimorphic fungi, including *Histoplasma capsulatum*, *Blastomyces dermatitidis*, *Coccidioides immitis* and *posadasii*, and *Paracoccidioides* spp.[17–19] Amphotericin B is active against many pathogenic organisms of the Mucorales group. However, *Scedosporium* spp and *Fusarium* spp, often have higher MICs.[15,17,20,21] In general, acquired resistance to amphotericin B is exceedingly uncommon despite its multiple decades of clinical use.

Pharmacology

Amphotericin B is available as the original deoxycholate formulation and as 2 lipid-based formulations: liposomal amphotericin B (L-AmB) and amphotericin B lipid complex (ABLC). A fourth formulation, amphotericin B colloidal dispersion (ABCD), is not currently being manufactured. Given the limited solubility of amphotericin B and its poor oral bioavailability, all formulations are parenteral. The drug can be dosed daily
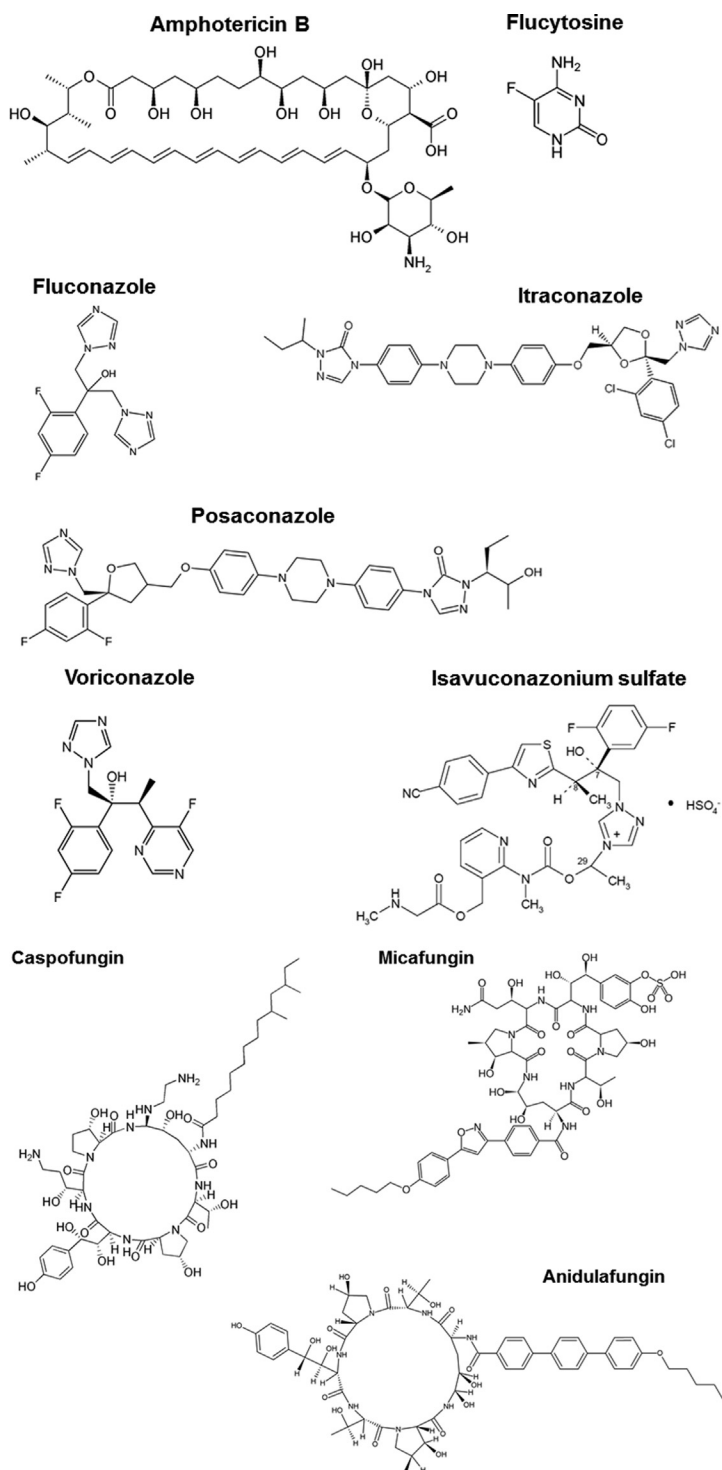
Fig. 1. Structures of commonly used systemic antifungal agents.

Table 1
Spectrum of activity for systemic antifungal agents

	AMB	5FC	FLU	ITR	VOR	POS	ISA	CAS	MICA	ANI
Candida albicans	++	++	++	++	++	++	++	++	++	++
Candida glabrata	++	++	+	+	++	++	++	+	+	+
Candida parapsilosis	++	++	++	++	++	++	++	++	++	++
Candida tropicalis	++	++	++	++	++	++	++	++	++	++
Candida krusei	++	+	−	+	++	++	++	++	++	++
Candida lusitaniae	−	++	++	++	++	++	++	++	++	++
Aspergillus fumigatus	++	−	−	+	++	++	++	+	+	+
Cryptococcus neoformans	++	++	++	++	++	++	++	−	−	−
Mucorales	++	−	−	−	−	++	++	−	−	−
Fusarium spp	+	−	−	+	++	++	++	−	−	−
Scedosporium spp	+	−	−	+	+	+	+	−	−	−
Blastomyces dermatitidis	++	−	+	++	++	++	++	−	−	−
Coccidioides immitis	++	−	++	++	++	++	++	−	−	−
Histoplasma capsulatum	++	−	+	++	++	++	++	−	−	−

Abbreviations: 5FC, flucytosine; AMB, amphotericin B; ANI, anidulafungin; CAS, caspofungin; FLU, fluconazole; ISA, isavuconazole; ITR, itraconazole; MICA, micafungin; POS, posaconazole; VOR, voriconazole.

given its long half-life.[22,23] Animal studies have shown the lipid formulations of amphotericin B to be less potent than amphotericin B deoxycholate on a weight (mg/kg) basis.[24] Approximately 4-fold to 5-fold higher concentrations of the lipid-based formulations are required to achieve efficacy similar to the deoxycholate formulation. This is consistent with the higher clinical dosing of these formulations (L-AmB 3–6 mg/kg/d, ABLC 3–6 mg/kg/d, and ABCD 3–4 mg/kg/d) compared with the conventional deoxycholate formulation (0.7–1 mg/kg/d) (**Table 2**).

Amphotericin B is widely distributed throughout the host. Although drug levels in the cerebrospinal fluid are nearly undetectable, it remains the drug of choice for the treatment of cryptococcal meningitis.[25,26] Given the high protein binding of amphotericin B, it is assumed that the drug accumulates in the brain parenchyma, with the relatively low cerebral spinal fluid levels not predicting the drug's activity at this site. The pharmacokinetic properties vary among the individual amphotericin B formulations. For example, L-AmB demonstrates enhanced central nervous system penetration, achieving 4-fold to 7-fold higher brain parenchyma concentrations compared with the other formulations. In an animal model of meningitis, this characteristic was found to correlate with greater efficacy.[13,27] One similarity among the lipid-based amphotericin B formulations is the ability of the carrier molecules to decrease renal tubular cell binding, significantly reducing (10-fold–20-fold) the propensity for renal toxicity.

Amphotericin B exhibits a long elimination half-life (>15 days). The drug accumulates most highly in the liver and spleen and to a lesser extent in the kidney, lung, myocardium, and brain. In addition, it has not been shown to be metabolized.[28,29] Amphotericin B deoxycholate is excreted as unchanged drug into the feces (43%) and urine (21%).[29] The liposomal formulation is also excreted as unchanged drug. However, only 10% of the L-AmB formulation was found to be excreted in the urine or feces. It is suspected that the liposome carrier enhances tissue sequestration, decreasing the rate of elimination.

Table 2
Dosing regimens and clinical indications for frequently used systemic antifungal agents

	Clinical Indications	Dosing: Adult			Dosing: Pediatric
		IV	Oral	Notes	
Amphotericin B	Aspergillosis Candidiasis, invasive Candidiasis, mucosal Cryptococcosis Coccidioidomycosis Blastomycosis Histoplasmosis Mucormycosis Penicilliosis Phaeohyphomycosis Sporotrichosis	0.7–1 mg/kg/d[a]	NA	—	0.7–1 mg/kg/d[a]
Flucytosine	Cryptococcosis (in combination therapy) Second-line: Candidiasis	NA	25 mg/kg 4×/d	GFR <50: Decrease dosing interval to q 12–48 h	25 mg/kg 4×/d
Fluconazole	Candidiasis, invasive Candidiasis, mucosal[c] Cryptococcosis Prophylaxis, candidiasis	400–800 mg/d 100–200 mg/d[c]	400–800 mg/d 100–200 mg/d[c]	CrCl <50:Decrease dose by 50%	3–12 mg/kg/d
Itraconazole	Blastomycosis Candidiasis, mucosal Coccidioidomycosis Histoplasmosis Onychomycosis Paracoccidioidomycosis Sporotrichosis Second-line: Aspergillosis	NA	200 mg 1-3×/d	NA	2.5–5 mg/kg 2–3×/d

Voriconazole	Aspergillosis Candidiasis, invasive Candidiasis, mucosal Fusariosis Scedosporiosis	6 mg/kg for 2 doses, then 4 mg/kg q 12 h	400 mg bid for 2 doses, then 200 mg q 12 h	CrCl <50: Avoid IV formulation Hepatic impairment: Consider 50% reduction	4–7 mg/kg q 12 h
Posaconazole	Candidiasis, mucosal Prophylaxis, invasive fungal infection	300 mg/d	Suspension: 800 mg/d divided Tablet: 300 mg bid for 2 doses, then 300 mg/d	GFR <50: Avoid IV formulation	Age ≥13: Suspension: 200 mg tid Tablet: 300 mg bid for 2 doses, then 300 mg/d
Isavuconazole	Aspergillosis Mucormycosis	372 mg q 8 h for 6 doses, then 372 mg/d	372 mg IV q 8 h for 6 doses, then 372 mg/d	Severe hepatic impairment: caution	NA
Caspofungin	Candidiasis, invasive Candidiasis, mucosal Empiric therapy[b] Second-line: Aspergillosis	70 mg for 1 dose, then 50 mg/d	NA	Moderate hepatic impairment: 35 mg/d	50 mg/m^2/d
Micafungin	Candidiasis, invasive Candidiasis, mucosal Prophylaxis, invasive[c] fungal infection	100–150 mg/d 50 mg/d[c]	NA	NA	1–3 mg/kg/d
Anidulafungin	Candidiasis, invasive Candidiasis, mucosal	100–200 mg for 1 dose, then 50–200 mg/d	NA	NA	Age >16: 100–200 mg for 1 dose, then 50–100 mg/d

Abbreviations: CrCl, creatinine clearance; GFR, glomerular filtration rate; IV, intravenous.

[a] Dosing is listed for the amphotericin B deoxycholate formulation. Dosages for the lipid formulations are higher, L-AmB 3 to 6 mg/kg/d, ABLC 3 to 6 mg/kg/d, and ABCD 3 to 4 mg/kg/d.

[b] For patients with febrile neutropenia.

[c] Lower doses can be administered for the specified indication.

Clinical Indications

Amphotericin B was the first antifungal drug developed and is approved for the treatment of many invasive fungal infections including candidiasis, aspergillosis, cryptococcosis, blastomycosis, histoplasmosis, mucormycosis, and sporotrichosis (see **Table 2**). It is associated with significant renal toxicity, particularly the deoxycholate formulation, which may its limit use or result in dose reduction, ultimately leading to treatment failure.[30] The lipid-based preparations of amphotericin B have an improved toxicity profile and are commonly used as first-line agents for many of the approved indications.[30,31]

Amphotericin B is approved for the treatment of candidemia and invasive candidiasis based on multiple trials demonstrating effectiveness.[12,32–34] The current Infectious Diseases Society of America (IDSA) guidelines list the lipid-based amphotericin B formulations as second-line therapies with the deoxycholate formulation as a third-line alternative in resource limited areas.[2] However, given the efficacy and safety of alternative agents, such as the echinocandins, amphotericin B is not commonly used for this indication. Of note, the deoxycholate formulation is well-tolerated in neonates and remains first-line for the treatment of disseminated candidiasis in this patient population.[2,35] Given its enhanced ability to penetrate the central nervous system, L-AmB is the preferred formulation for the treatment of *Candida* meningitis or endophthalmitis.[2,36]

The amphotericin B formulations are recommended for initial treatment of many endemic fungal infections, particularly for patients with severe, life-threatening infections.[25,37–39] Amphotericin B is first-line therapy for the treatment of cryptococcal meningitis and is administered in combination with flucytosine during the induction period.[39–41] The lipid-based formulations are preferred for organ transplant recipients. Amphotericin B is approved for the treatment of coccidioidomycosis, histoplasmosis, and blastomycosis. It is recommended as initial therapy for the treatment of severe infections.[25,37,38] The liposomal formulation of amphotericin B is recommended as first-line for the treatment of mucormycosis.[42] L-AmB is also an option for treatment of sporotrichosis, particularly patients with disseminated or severe disease.[43] Amphotericin B has an indication for the treatment of aspergillosis. However, voriconazole is the preferred therapy for aspergillosis based on efficacy in a multicenter trial.[44,45] An important role for amphotericin B is the treatment of mycoses in pregnant patients because the triazole class is contraindicated due to established teratogenicity.[46]

Toxicities

Although amphotericin B demonstrates potent antifungal activity, its use is often limited by significant toxicities. Common adverse effects include renal toxicity, infusion reactions, electrolyte abnormalities, and hepatotoxicity.[3,47] Renal toxicity is mediated by both direct tubular damage and rapid vasoconstriction via tubuloglomerular feedback from osmotic changes.[48] Intravenous fluid is commonly administered to help reduce renal damage. The risk of renal toxicity is dose-dependent, increasing with the total cumulative dose. Acute renal failure occurs in approximately 30% of patients and is associated with a mortality rate of more than 50% in this setting.[3] Surprisingly, the rate of nephrotoxicity is significantly lower in children and neonates.[2,35] The deoxycholate formulation of amphotericin B is commonly used in these patient populations with minimal toxicity. The lipid-based formulations are associated with significantly less nephrotoxicity.[13,49] However, infusion-related reactions often occur. These reactions seem to be induced by toll-like receptor (TLR)-2 activation, resulting in a proinflammatory cytokine response.[31] Pretreatment with nonsteroidal

anti-inflammatory agents, antihistamines, and corticosteroids may be helpful. The hepatotoxicity associated with amphotericin B is uncommon and generally mild.[50]

Drug–Drug Interactions

Amphotericin B is not metabolized by hepatic CYP450 enzymes and has very few drug–drug interactions (Box 2). The pertinent drug–drug interactions for amphotericin B are related to the nephrotoxicity and electrolyte disturbance that may be augmented by other drugs with similar renal side effects. One common example is the coadministration of amphotericin B with immunosuppressants, such as tacrolimus or cyclosporine, in transplant recipients. This combination is associated with increased risk of kidney injury and electrolyte disturbances.[51]

FLUCYTOSINE

Flucytosine is a fluorinated pyrimidine (5-fluorocytosine) (see Fig. 1). As a pyrimidine analogue, it is imported by fungal cytosine permease and converted to fluorouracil by cytosine deaminase. Fluorouracil impairs nucleic acid synthesis, ultimately interfering with protein synthesis as well.[52]

Spectrum of Activity and Resistance

The activity of flucytosine is limited to the common pathogenic yeasts (see Table 1). Its spectrum includes many *Candida* spp, including *C albicans*, *C glabrata*, *C parapsilosis*, and *C tropicalis*. *C krusei* and *C lusitaniae* are also included in the spectrum but MICs are higher. Despite this activity, flucytosine is rarely used for the treatment of candidiasis alone because resistance rapidly develops with monotherapy.[2,53] Flucytosine demonstrates activity against *Cryptococcus* spp and is commonly administered in conjunction with amphotericin B.[16] It is not active against the dimorphic fungi or filamentous fungal pathogens.[21,54] Resistance to *Candida albicans* is reported to be near 10%, often related to decreased drug

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Box 2
Summary of drug–drug interactions for systemic antifungal agents

- Amphotericin B has few significant drug–drug interactions. The main concerns arise from drugs with the potential for additive nephrotoxicity.

- Absorption of 2 triazole formulations—the itraconazole oral capsules and the posaconazole oral solution—is affected by gastric acidity. Medications that alter gastric pH, such as proton pump inhibitors and histamine-2 blockers, should be avoided.

- The azole drugs act as substrates and inhibitors of the CYP450 enzymes (CYP3A4, CYP2C19, CYP 2C9) and the affinities for each enzyme vary significantly by individual drug.

- Given the hundreds of potential drug–drug interactions for azoles, a patient's medication list should be carefully examined with initiation and discontinuation of azoles.

- Some of the common drug–drug interactions for azoles include antiarrhythmics, antipsychotics, immunosuppressants, migraine medications, antibiotics, anticoagulants, antidepressants, antiepileptics, antiretrovirals, chemotherapeutics, antihypertensives, lipid-lowering agents, narcotics, sedatives, hormonal therapies, and medications for diabetes.

- The echinocandin drugs have relatively few drug–drug interactions. A unique aspect for caspofungin is that it uses the OATP-1B1 transporter and may interact with immunosuppressants, antiepileptics, antiretrovirals, and rifampin.

uptake by the cytosine permease.[55,56] During therapy, mutations in enzymes converting flucytosine to the toxic metabolites 5-fluorouracil and 5-fluorouridine monophosphate may also lead to resistance.

Pharmacology

Flucytosine is highly bioavailable (80%–90%) and the only formulation available in the United States is an oral capsule.[57] It is dosed frequently, 4 times daily, due to its short half-life and pharmacodynamic characteristics.[58,59]

Flucytosine accumulates ubiquitously throughout host compartments. Specifically, high cerebrospinal fluid and vitreal fluid levels are achievable.[58,59] The drug is not significantly metabolized. The drug is primarily excreted renally and the unchanged drug exhibits excellent antifungal activity in the urine.[10,57] Patients with renal insufficiency have impaired drug clearance. Therefore, a 2-fold to 4-fold longer dosing interval is recommended for patients with a glomerular filtration rate (GFR) less than 50 (see Table 2). These dosing changes are guided by therapeutic drug monitoring with peak concentration targets ranging from 30 to 100 mg/L.

Clinical Indications

Flucytosine is a first-line therapy for the treatment of cryptococcal meningitis. It is administered with amphotericin B during the induction period.[39–41] Although flucytosine exhibits activity against most *Candida* spp, resistance develops quickly during use, limiting its treatment potential as a single agent.[2,53] To prevent emergence of resistance, flucytosine can be coadministered with an additional antifungal drug, such as amphotericin B, in select situations. Of note, flucytosine monotherapy may be an option for treatment of *Candida* cystitis given the high urinary concentrations of flucytosine and the relatively short course of therapy.[17,49,58]

Toxicities

Flucytosine is associated with 2 main toxicities: bone marrow suppression and liver toxicity. Bone marrow toxicity, in particular, can be limiting, leading to the lowering of the drug dose or drug discontinuation.[58] Cytopenias, including anemia, leukopenia, and thrombocytopenia, are dose-dependent, occurring more frequently with serum flucytosine concentrations of 125 μg/mL or greater.[60] Considering the renal clearance of flucytosine, patients with renal insufficiency are at high risk for toxicity. Both peak drug levels and cell counts should be monitored during therapy. Dose reductions are often needed. Flucytosine administration can also be associated with gastrointestinal upset and rash. Animal studies demonstrate teratogenic effects and flucytosine is contraindicated in pregnancy.[61]

Drug–Drug Interactions

Flucytosine is not a substrate or inhibitor of the CYP450 enzymes (see Box 2). There are very few drug–drug interactions. Because flucytosine is renally cleared, medications altering renal function may affect drug levels and the risk of toxicity.

AZOLES

The antifungal azole drug class is composed of imidazoles (clotrimazole, ketoconazole, miconazole) and triazoles (fluconazole, itraconazole, voriconazole, posaconazole, isavuconazole) that are named according to the number of nitrogen atoms in the azole ring.[62] These agents impair ergosterol synthesis by inhibiting C14-α sterol demethylase. Cell membrane integrity is disrupted by the accumulation of sterol

precursors and the reduction of ergosterol.[63–68] The original azole drugs (ketoconazole, miconazole) exhibit significant toxicity during systemic administration. However, the newer triazoles (fluconazole, itraconazole, posaconazole, voriconazole, isavuconazole) have an improved safety panel (see **Fig. 1**).[63] Many azole drugs (ketoconazole, miconazole, clotrimazole, butoconazole, tioconazole, terconazole) are also available as topical preparations for the treatment of vaginal candidiasis or cutaneous fungal infection.[2]

Spectrum of Activity and Resistance

Fluconazole
Fluconazole is active against many medically important *Candida* spp, including *C albicans*, *C parapsilosis*, *C tropicalis*, *C lusitaniae*, and *C dubliniensis* (see **Table 1**).[69] MICs are higher for *Candida* spp, including *C glabrata*, *C guilliermondii*, and *C rugosa*.[14] Of note, fluconazole is not active against *Candida krusei*. Fluconazole displays excellent activity against *Cryptococcus neoformans*.[16,70] Although the spectrum of activity includes dimorphic pathogens *B dermatitidis*, *Coccidioides immitis*, and *H capsulatum*, MICs are significantly higher for fluconazole compared with other available azoles (itraconazole, posaconazole, voriconazole, isavuconazole) and fluconazole is less commonly used for the treatment of these infections, with the exception of coccidioidomycosis.[71] Fluconazole is not active against *Aspergillus* spp, *Fusarium* spp, *Scedosporium* spp, or the Mucorales.[17,21,71–74]

Itraconazole
Like fluconazole, itraconazole demonstrates activity against most *Candida* spp, with higher MICs for *C glabrata* and *C krusei* (see **Table 1**).[70,75,76] The spectrum of activity also includes the dimorphic fungal pathogens *B dermatitidis*, *H capsulatum*, *Coccidioides* spp, *Paracoccidioides* spp, and *Sporothrix schenckii* (see **Table 1**).[18,19,71,77] Itraconazole is also active against many *Aspergillus* spp, including *A fumigatus*, *A flavus*, *A nidulans*, and *A terreus*.[15] Itraconazole exhibits minimal activity against *Fusarium* spp and the Mucorales.

Voriconazole
Voriconazole offers anti-*Candida* activity in many ways similar to fluconazole and itraconazole (see **Table 1**).[76,78] In addition, voriconazole displays activity against a subset of fluconazole-resistant *C glabrata* strains.[79,80] Voriconazole is also active *Cryptococcus* spp and the dimorphic fungal pathogens *B dermatitidis*, *Coccidioides immitis*, and *H capsulatum* (see **Table 1**).[4,16,18,69] It exhibits potent activity against most *Aspergillus* spp, including amphotericin B–resistant *A terreus*.[15,71] The spectrum of activity of voriconazole also includes *Fusarium* spp *and Scedosporium* spp; however, activity against the Mucorales is minimal.[15,20,71,81]

Posaconazole
Posaconazole is active against most *Candida* spp, including *C albicans*, *C parapsilosis*, *C tropicalis*, and *C lusitaniae*, with higher MICs for *C krusei*, *C glabrata*, and *C guilliermondii* (see **Table 1**).[17,70,82] Like voriconazole, posaconazole also displays activity against a subset of fluconazole-resistant isolates but higher MICs are observed for these organisms.[14] The spectrum of activity of posaconazole includes *Cryptococcus* spp, *Coccidioides immitis*, *B dermatitidis*, and *H capsulatum*[70,71,83] (see **Table 1**). Posaconazole demonstrates potent activity against *Aspergillus* spp, including *A fumigatus*, *A flavus*, *A niger*, and *A terreus*.[15,17] Posaconazole also exhibits activity against several of the Mucorales.[15,81]

Isavuconazole

The spectrum of activity of isavuconazole includes most *Candida* spp, including *C glabrata* and *C krusei* (see **Table 1**).[84,85] Isavuconazole is active against most common *Aspergillus* spp, including *A fumigatus*, *A flavus*, and *A terreus*. MICs are similar to those observed for voriconazole and are higher than those observed for posaconazole.[86,87] Isavuconazole exhibits potent activity against *Cryptococcus* spp, as well as the dimorphic fungal pathogens *B dermatitidis*, *Coccidioides immitis*, and *H capsulatum*.[85,88,89] Isavuconazole further demonstrates activity against a subset of *Scedosporium* spp and organisms in the Mucorales group.[89,90]

Resistance

The term resistance includes both intrinsic resistance, as discussed in the spectrum of activity, and extrinsic resistance, which is acquired. The rate of extrinsic triazole resistance has been increasing, particularly for *C glabrata*. During the past decade, the frequency of fluconazole-resistant *C glabrata* has increased from 9% to 14%.[91,92] Azole cross-resistance is common, with most fluconazole-resistant isolates exhibiting resistance to voriconazole as well. In recent years, the rate of azole-resistant *A fumigatus* has also been rising significantly, particularly in Europe, where rates are reported as high as 20%, although they vary by geographic region.[93,94] The higher resistance rates in certain areas have been linked to antifungal use in agriculture. Azole-resistant invasive aspergillosis has a very poor prognosis, with mortality rates above 80%.[94] The main mechanism of azole resistance for *Aspergillus*, *Candida*, and *Cryptococcus* spp involves the mutation of the azole drug target, lanosterol 14α-demethylase.[93] For *Aspergillus* spp, this commonly leads to resistance to all azole drugs. However, for *Candida* spp, the modification of this drug target may lead to resistance to fluconazole alone, azole pan-resistance, or resistance to a subset of azoles. A second mechanism of resistance, the upregulation of efflux pumps, has also been shown to promote drug resistance via a decrease in intracellular drug levels.

Pharmacology

Fluconazole

The pharmacokinetic characteristics of the individual azole drugs are distinct due to their variation in molecular weight, solubility, and protein binding. Fluconazole is unique due to its low molecular weight and high aqueous solubility. It demonstrates high bioavailability, approximately 90%, and its absorption is not affected by gastric acidity or food.[6,95,96] Currently, there are 2 oral formulations, a tablet and a powder for suspension, and an intravenous solution. The recommended dosages are not affected by the route of administration (see **Table 2**). Due to its relatively long half-life and pharmacodynamic pattern of activity, fluconazole is dosed daily.

Fluconazole effectively penetrates most host body tissues, including the central nervous system. Therapeutic concentrations can be achieved in the cerebrospinal fluid and ocular compartments.[97] Fluconazole achieves high urinary concentrations because it is primarily renally cleared with approximately 66% to 76% of unchanged fluconazole secreted into the urine.[98,99] Dose reductions are thus recommended for patients with advanced renal insufficiency.[100] Fluconazole is removed by hemodialysis and should be administered following hemodialysis.[101,102] Unlike other triazole drugs, fluconazole is not extensively metabolized in the liver. Dose adjustments are not necessary for patients with hepatic impairment.

Itraconazole

Itraconazole is currently available in 2 oral preparations: a capsule and an oral solution complexed with hydroxypropyl-β-cyclodextrin. It has also been formulated with

cyclodextrin for intravenous use but this preparation is not currently available. The absorption and bioavailability of the 2 itraconazole oral formulations vary. Absorption of the capsule formulation is approximately 55% but it is improved with gastric acidity and food intake.[6,103,104] Therefore, it is recommended to be administered with an acidic beverage and food. Medications that reduce gastric acidity, such as proton pump inhibitors and histamine-2 blockers, should be avoided. The oral solution exhibits superior bioavailability, near 80%, and the absorption of itraconazole is not affected by gastric acidity or food intake.[105] Interpatient variability is less with this formulation and serum concentrations are typically 30% higher than for the tablet formulation.

Several clinical studies have examined the relationship between itraconazole serum levels and therapeutic response for a variety of fungal infections.[106–109] Itraconazole levels can be measured by either high-performance liquid chromatography (HPLC) or bioassay. The former measures the concentrations of 2 active compounds, the parent drug and the active hydroxyitraconazole metabolite.[110] Based on available data, an itraconazole level greater than 0.5 μg/mL is suggested for treatment of oral candidiasis or prophylaxis for fungal infections.[111] However, for treatment of invasive fungal infection, an itraconazole concentration of 1 to 2 μg/ml has been linked to treatment success.[108]

Itraconazole is highly protein bound (99%).[112] Unlike fluconazole and voriconazole, only low levels of the drug are found in the cerebrospinal fluid and fluid compartments of the eye.[112,113] Thus, the use of itraconazole for the treatment of infections involving the central nervous system or the eye is not commonly recommended. A unique pharmacokinetic observation is the accumulation of itraconazole in the skin and nail tissues. With levels reaching nearly 20-fold higher concentrations than those measured in the plasma, it is an ideal agent for the treatment of cutaneous and nail mycoses.[114–116] Itraconazole is metabolized, primarily by the CYP450 isoenzyme 3A4, to the active metabolite hydroxyitraconazole and several inactive metabolites.[114] Although metabolites can be found in both the urine and feces, the urinary metabolites are inactive and itraconazole is not useful for the treatment of infections involving the lower urinary tract.[114,117] Dose reductions are not required for renal failure or dialysis.[118,119] However, itraconazole is hepatically metabolized and dose reduction is recommended for patients with hepatic impairment (see **Table 2**).[114,120]

Voriconazole

Voriconazole is formulated as an oral tablet, an oral suspension, and an intravenous solution (complexed with sulfobutylether β-cyclodextrin). The bioavailability for both oral formulations is quite high, greater than 90%.[10,121] Absorption is not affected by gastric acidity and is optimal in the fasted state. Loading doses for the first 24 hours are recommended to more rapidly achieve therapeutic levels (see **Table 2**).[4,63] Given its shorter half-life (6 hours), voriconazole is dosed twice daily.

Serum levels of voriconazole may vary widely among patients, primarily due to differences in metabolism. Voriconazole is extensively metabolized by the CYP450 enzymes and polymorphisms are common in the primary enzyme CYP2C19.[122,123] Patients can possess polymorphisms that lead to either slow or rapid metabolism, placing them at risk for toxicity or therapeutic failure, respectively.[124–127] Clinical studies show therapeutic success is associated with voriconazole serum trough concentrations ranging from 1 to 2 μg/mL.[128,129] However, higher voriconazole concentrations, those exceeding 6 μg/mL, have been linked to adverse drug events, including hepatitis and delirium. Given the variability in metabolism of voriconazole among

patients, therapeutic drug monitoring is recommended during treatment of invasive fungal infections.[9]

Voriconazole is 58% protein bound.[4] Similar to fluconazole, levels in the cerebrospinal fluid and ocular compartments reach greater than 50% of serum concentrations, allowing for the treatment of infections of the central nervous system and eye.[130–132] Voriconazole is metabolized via the hepatic CYP450 isoenzymes CYP2C9, CYP2C19, and CYP3A4; dose reduction is recommend for patients with impaired liver function.[133] Because minimal active drug is secreted into the urine, voriconazole is not useful for the treatment of fungal urinary tract infections.[122,133] Although voriconazole is not significantly renally cleared, the cyclodextrin component of the intravenous formulation may accumulate in patients with renal insufficiency. Although studies have not identified cyclodextrin toxicity, the intravenous formulation is not commonly recommended for patients with a GFR less than 50 if other treatment options are available.[134]

Posaconazole

Posaconazole is currently available as an oral suspension, a delayed release tablet, and an intravenous solution that is complexed with sulfobutylether β-cyclodextrin (see Table 2). Absorption and bioavailability differ between the 2 oral formulations. For the oral solution, absorption highly depends on food intake with high-fat meals best promoting absorption.[135] Like itraconazole, the absorption depends on gastric acidity and is reduced by proton pump inhibitors and histamine-2 blockers.[136–138] Posaconazole exhibits saturable absorption, requiring the oral suspension to be dosed multiple times daily, despite its relative long half-life (>24 hours).[10,139] The newer tablet formulation incorporates a pH-dependent polymer matrix that allows for delayed drug release. This circumvents the saturable absorption limitation of the oral solution and allows for once-daily dosing. Absorption of the tablet formulation is not significantly influenced by food intake or gastric acidity, allowing for improved bioavailability (54%) and more reliable serum concentrations.[82]

Similar to studies with itraconazole and voriconazole, clinical studies suggest therapeutic drug monitoring is of benefit for posaconazole, particularly for the oral suspension formulation.[140–144] For patients receiving posaconazole for treatment of refractory aspergillosis, the greatest efficacy was observed in those with steady state concentrations greater than 1.25 μg/mL, whereas those with levels less than 0.5 μg/mL had the lowest success rate. In studies examining the efficacy for prophylaxis, posaconazole concentrations greater than 0.5 μg/mL or greater than 0.7 μg/mL were associated with fewer breakthrough fungal infections.

Posaconazole is highly protein bound (98%). Available data from clinical investigations and animal studies show poor penetration of posaconazole into the cerebrospinal fluid and ocular compartments; posaconazole is not recommended for treatment of endophthalmitis or infections of the central nervous system.[10,83,145–147] Posaconazole undergoes metabolism by uridine diphosphate (UDP)-glucuronidation and is excreted via the bile and feces.[148] Dose adjustments are not necessary for patients with renal insufficiency. However, similar to voriconazole, the intravenous formulation is complexed with a cyclodextrin that may accumulate with renal impairment.[149] Therefore, the intravenous formulation is not recommended for patients with a GFR less than 50.

Isavuconazole

Isavuconazonium, the water-soluble prodrug of isavuconazole, is available as an oral capsule and an intravenous solution. In contrast to the intravenous formulations for

voriconazole and posaconazole, the isavuconazonium intravenous formulation does not contain the sulfobutylether β-cyclodextrin vehicle that may accumulate with renal insufficiency. Isavuconazole exhibits a prolonged half-life (>75 hours) and is dosed daily following a 2-day loading period (see **Table 2**).[150] The oral formulation is highly bioavailable and the absorption is not significantly affected by food intake or gastric acidity.[85,150] Preliminary patient pharmacokinetic data have thus far not demonstrated utility for therapeutic drug monitoring for isavuconazole. Given the high bioavailability and relatively consistent metabolism, the interpatient variability in drug levels is expected to be lower than that observed for posaconazole, itraconazole, and voriconazole.

Isavuconazole is highly protein bound (>99%). The distribution of isavuconazole has not been extensively studied but drug levels in the cerebral spinal fluid and eye compartments are predicted to be low.[85] However, brain parenchymal concentrations in animal studies are higher than those observed in serum. Isavuconazole is metabolized by hepatic CYP450 enzymes and metabolites are excreted in the feces.[150] Because minimal active drug is excreted in the urine, treatment of fungal urinary tract infections is not recommended. Because hepatic metabolism and drug clearance have shown to be slowed in patients with liver impairment, a 50% dose reduction is recommended.[151] Dose reductions are not required for patients with renal insufficiency or dialysis.

Clinical Indications

Fluconazole

Fluconazole has indications for the treatment of both mucosal and systemic candidiasis, the treatment of cryptococcosis, and prophylaxis for candidiasis (see **Table 2**). Clinical trials have shown fluconazole to be effective for the treatment of invasive candidiasis in non-neutropenic patients.[152–155] However, recent meta-analysis suggests the triazoles are inferior to echinocandins as initial therapy for invasive disease.[156] The current IDSA guidelines recommend fluconazole as a first-line therapy for treatment of mucosal candidiasis and as a first-line option for step-down therapy for invasive candidiasis due to susceptible *Candida* isolates.[2] Multiple trials have confirmed the efficacy and tolerability of fluconazole for the treatment of oropharyngeal and esophageal candidiasis.[157–165] Fluconazole remains a first-line therapy for the treatment of patients with mucosal candidiasis, including those with human immunodeficiency virus (HIV). Fluconazole is also indicated for the treatment of vulvovaginal candidiasis in nonpregnant women.[2] Clinical trials have found a single dose of oral fluconazole to be as effective as topical therapy for uncomplicated vaginal candidiasis treatment.[166–168] In addition, weekly therapy has proven useful for disease prevention in patients with recurrent vulvovaginal candidiasis.[169]

Fluconazole is approved for the treatment of cryptococcosis.[41,170,171] Currently, it is recommended for initial treatment of mild-to-moderate pulmonary disease.[39] It is also first-line for consolidation therapy in patients with severe cryptococcosis or cryptococcal meningitis following successful induction therapy with an amphotericin B–containing regimen. At a lower dose, fluconazole is used for maintenance or suppressive therapy to prevent relapse. Fluconazole is approved for prophylaxis against fungal infections in neutropenic patients.[2,172,173] Compared with the azoles with activity against mold pathogens and amphotericin B, fluconazole is solely effective at preventing candidiasis.[144,174,175] When compared with posaconazole, clinical trials found fluconazole to be less effective for prevention of invasive aspergillosis.[144,175]

Itraconazole

Itraconazole is approved for the treatment of numerous mycoses, including blastomycosis, mucosal candidiasis, coccidioidomycosis, cryptococcosis, histoplasmosis,

onychomycosis, and sporotrichosis (see Table 2). It is also approved for empiric treatment of fungal infection in neutropenic patients and as second-line treatment of aspergillosis. For treatment of endemic fungal pathogens, it is primarily used as initial therapy for mild-to-moderate disease. For severe blastomycosis, histoplasmosis, coccidioidomycosis, paracoccidioidomycosis, and sporotrichosis, amphotericin B is recommended for initial therapy. Itraconazole can be administered for step-down therapy but it is not ideal for the treatment of mycoses involving the central nervous system due to its poor central nervous system penetration.[25,37,38,176–179] Although it has an indication for the treatment of cryptococcosis, it is not a preferred agent for consolidation or maintenance therapy given its poor cerebrospinal fluid penetration and higher reported failure rate.[39]

Itraconazole has been shown to be effective for the treatment of oropharyngeal, esophageal, and vaginal candidiasis but it is not currently recommended as first-line therapy for these infections.[2,180] It does not offer clear benefit compared with fluconazole treatment of mucosal candidiasis and is associated with more side-effects, variable gastric absorption, and less predictable drug levels.[157–159,181] Itraconazole does remain a treatment option for patients with these infections who are not responding to fluconazole. It is not approved for treatment of candidemia or invasive candidiasis.

Itraconazole effectively prevents invasive fungal infection in patients with hematologic malignancy or autologous bone marrow transplantation.[182–184] However, it is not as well tolerated as fluconazole, often leading to discontinuation due to gastrointestinal side effects, and it is not commonly used for this indication.[174] Although it likely offers protection against filamentous fungal infections, the activity spectrum for itraconazole does not include the Mucorales organisms.[21] Itraconazole is also approved as salvage therapy for the treatment of invasive aspergillosis. However, it has not been compared with voriconazole or amphotericin B. It is only recommended for patients who are unable to tolerate these preferred agents.[45,185] Conversely, itraconazole is commonly used for chronic pulmonary aspergillosis and allergic bronchopulmonary aspergillosis treatment.[186,187]

Voriconazole

Voriconazole is approved for the treatment of invasive aspergillosis, esophageal candidiasis, invasive candidiasis, scedosporiosis, and fusariosis (see Table 2). In a large randomized trial, voriconazole was found to be superior to amphotericin B for the treatment of invasive pulmonary aspergillosis and is currently recommended as first-line therapy.[44,45] It is also the drug of choice for most invasive forms of aspergillosis, including sinusitis, brain abscess, endocarditis, osteomyelitis, and septic arthritis. Additionally, it is also recommended for the treatment of fungal infections caused by *Scedosporium* spp or *Fusarium* spp based on salvage therapy trials and retrospective analysis.[4,188,189]

Voriconazole is approved for the treatment of both mucosal and invasive candidiasis. It was found to be as effective as a regimen of amphotericin B followed by fluconazole for treatment of candidemia in a randomized clinical trial.[154] However, voriconazole is not recommended as first-line therapy for the treatment of invasive candidiasis for most patient groups because there is little advantage when compared with fluconazole. The circumstances in which voriconazole should be considered in place of fluconazole include infection with *Candida krusei*, infection with fluconazole-resistant *Candida glabrata* (susceptible to fluconazole), intolerance to fluconazole, or if antifungal coverage for mold infection is warranted.[2] Likewise, voriconazole is approved for the treatment of esophageal candidiasis but is not commonly

used for this indication with the exception of candidiasis due to fluconazole-resistant organisms.[160]

Posaconazole

Posaconazole is approved for the treatment of oropharyngeal candidiasis and prophylaxis for invasive fungal infection (see **Table 2**). Clinical trials have shown posaconazole to be as effective or more effective for prevention of invasive fungal infection, when compared with fluconazole or itraconazole.[144,175] Studies have included stem cell transplant recipients with graft-versus-host disease and neutropenic patients. Given its extended spectrum of activity, posaconazole protects against many filamentous fungal pathogens in addition to invasive candidiasis. Posaconazole is also approved for treatment of oropharyngeal candidiasis based on noninferiority to fluconazole and effectiveness for azole-refractory cases.[164,190,191] It is not recommended as first-line therapy but may be an alternative for patients intolerant of other medications or with infection caused by resistant organisms. A randomized trial examining the utility of posaconazole for treatment of invasive aspergillosis is ongoing.

Isavuconazole

Isavuconazole is approved for the treatment of invasive aspergillosis and invasive mucormycosis (see **Table 2**). The indication for treatment of aspergillosis is based on results of a large randomized, controlled trial comparing isavuconazole and voriconazole for treatment of invasive aspergillosis and other mold infections (www.fda.gov). For all subjects and the subset with aspergillosis, both all-cause mortality and treatment success were similar and isavuconazole met noninferiority criteria. Isavuconazole is also approved for treatment of mucormycosis based on an open-label noncomparative trial which included subjects with refractory mucormycosis and subjects who had not received prior therapy (www.fda.gov). When examining overall response and all-cause mortality, results for isavuconazole-treated subjects (31% and 38%, respectively) were similar to those reported in prior investigations for amphotericin B and posaconazole.

Toxicities

In general, the triazole drugs are fairly well-tolerated. As a drug class, the most common side-effects include rash, headache, or gastrointestinal upset.[172,192,193] Hepatotoxicity, marked by elevation of liver chemistry tests and, less commonly, liver failure, is the most common and serious class effect. Voriconazole poses the highest risk (31%), whereas itraconazole, posaconazole, and isavuconazole present lower risks (10%–20%). Monitoring of liver chemistry tests during azole use is recommended but infrequently results in drug discontinuation.[50] Voriconazole has several unique side-effects, including a photosensitive skin rash, reversible visual changes (photopsia), and fluoride-associated bone toxicity.[44] The former has also been linked to skin malignancy in the setting of prolonged use. With the exception of isavuconazole, the azole drugs cause QT prolongation, presenting a risk for arrhythmia, especially in the setting of drug–drug interactions.[51] In contrast, isavuconazole is associated with QT shortening and is contraindicated for patients with familial short QT syndrome.[85] The azole drugs are contraindicated in pregnancy due to an established link to birth defects.[46,61]

Drug–drug interactions

Of the antifungal drug classes, the triazole drugs have the highest potential for serious drug–drug reactions. They are substrates and inhibitors of various hepatic CYP450 metabolic enzymes and have the potential for hundreds of drug–drug interactions.

The possible drug–drug interactions vary by individual drug because each has a variable affinity for the isoenzymes (CYP2C19, CYP3A4, CYP2C9).[194] As inhibitors of CYP450 enzymes, triazoles can impair metabolism of a coadministered drug, increasing the risk of toxicity. As substrates of the pathway, the concentrations of the triazoles can be substantially affected by concomitant use of medications that inhibit or induce the enzymes, as has been observed for itraconazole and voriconazole.[195,196] **Box 2** lists commonly used classes of medications that have the potential for serious interactions if administered with azoles. Closely examining a patient's medication list is recommended before starting and stopping medications given the high potential for drug–drug interactions. Absorption of the itraconazole oral capsules and the posaconazole oral solution is optimized by gastric acidity (see previous discussion), so proton pump inhibitors and histamine-2 blockers should be avoided.[136–138] Because the triazoles can cause QT prolongation, drug–drug interactions may be encountered by the additive effect of additional QT prolonging agents. Of note, isavuconazole is the only triazole that is not associated with QT prolongation.[85]

ECHINOCANDINS

The echinocandins are a class of semisynthetic lipopeptides composed of cyclic hexapeptides N-linked to a fatty acyl side chain (see **Fig. 1**). The compounds disrupt the fungal cell wall by inhibiting the synthesis of β-1,3 glucan, a fungal cell wall polysaccharide essential for many fungi.[197] For *Candida* spp, this results in fungicidal activity. For *Aspergillus* spp, the echinocandins inhibit cell wall growth primarily at the hyphal tip, producing a fungistatic effect.[198] The 3 echinocandins currently available include caspofungin, micafungin, and anidulafungin.

Spectrum of Activity and Resistance

Caspofungin, micafungin, and anidulafungin demonstrate very similar activities (see **Table 1**). The agents display potent activity against many *Candida* spp, including *C albicans*, *C glabrata*, *C dubliniensis*, *C tropicalis*, and *C krusei*.[91,199,200] For *C parapsilosis* and *C guilliermondii*, MICs are often higher but the echinocandins are often still useful agents for the treatment of these infections clinically.[201] The echinocandins are active against many *Aspergillus* spp, although the activity is fungistatic.[202–204] Additionally, the echinocandins seem to potentiate the activity of triazoles against *Aspergillus* spp in preclinical models.[205,206] The spectrum of activity for the echinocandins does not include *Cryptococcus* spp, endemic dimorphic fungi, Mucorales, *Fusarium* spp, or *Scedosporium* spp.[15,21,74] Resistance to *Candida* spp is relatively low, less than 3%, and is primarily mediated by mutations in 2 conserved regions of the gene-encoding glucan synthase, the echinocandin drug target.[93] Of note, resistance rates for *Candida glabrata* have been increasing and are now reported at rates ranging from 3% to 15%.[207]

Pharmacology

The pharmacokinetic and pharmacodynamic profiles of the echinocandin drugs are quite similar.[10,208–210] The agents are poorly absorbed through the gastrointestinal system and are thus only available in parenteral formulations (see **Table 2**). They can be dosed once daily given their long half-lives (10–26 h).[10,11] Animal studies show the echinocandins demonstrate optimal efficacy following administration of large doses given infrequently.[211–214]

The echinocandins have limited distribution to the central nervous system. Low concentrations are found in the cerebrospinal fluid and eye.[10,11] Therefore, the

echinocandins are not ideal agents for infections involving these compartments, such as meningitis or endophthalmitis. The echinocandins are primarily eliminated through nonenzymatic degradation to inactive products.[209] Excretion of the breakdown products is predominantly via the fecal route. Only low concentrations of active drugs are excreted in the urine and caution should be used with treatment of urinary tract infections. Although the echinocandins are not significantly metabolized by the CYP450 enzymes, caspofungin and micafungin undergo hepatic metabolism and dose reduction is recommended for patients with hepatic dysfunction receiving caspofungin.[215]

Clinical Indications

Drugs of the echinocandin class are effective for prevention of invasive fungal infection, empiric treatment of fungal infection, and treatment of candidiasis[155,161–163,165,216–222] (see Table 2). Due to their similar activities, caspofungin, micafungin, and anidulafungin are generally used interchangeably.[2] The echinocandins are recommended as first-line agents for the treatment of candidemia and invasive candidiasis based on a meta-analysis of randomized trials showing improved survival with this drug class compared with amphotericin B or triazoles.[155,156,223] The echinocandins also have indications for mucosal (oropharyngeal or esophageal) candidiasis based on trials demonstrating efficacy similar to amphotericin B and fluconazole.[161,162,165,219] However, as parenteral agents, they are not commonly used for this indication.

Although the echinocandins have not been shown to be effective for primary treatment of aspergillosis in a randomized trial, caspofungin has an indication for the treatment of refractory aspergillosis based on salvage therapy investigations.[224,225] Guidelines currently recommend caspofungin or micafungin only as second-line agents.[45] There has been interest in using the echinocandins as adjuvant antifungals for treatment of aspergillosis.[206,226,227] A randomized, controlled trial comparing voriconazole monotherapy and combination therapy with anidulafungin found a trend toward improved outcome in the combination therapy group in a post hoc subgroup analysis. However, this difference did not meet statistical significance to establish superiority.[228] Therefore, there are still only limited data to support the use of combination therapy for the treatment of aspergillosis. Micafungin has approval for prophylaxis of invasive fungal infection based on a randomized trial comparing it to fluconazole in hematopoietic stem cell transplant recipients.[222] It was found to prevent candidiasis and aspergillosis. For patients with neutropenic fever and suspected fungal infection, caspofungin demonstrated therapeutic efficacy with fewer side-effects than amphotericin B.[223] Caspofungin has approval for empiric treatment of fungal infection for this population.

Toxicities

Echinocandins are generally well-tolerated and patients experience very few side effects. The most commonly experienced adverse reactions include gastrointestinal upset, headache, elevation of liver (aminotransferase) tests, or mild infusion reaction.[10,199,200]

Drug–Drug Interactions

Echinocandins demonstrate very few drug–drug interactions because they are not metabolized through the CYP450 enzymatic pathways (see Box 2).[10,199,200] Caspofungin has been shown to use the OATP-1B1 transporter, which is also used by other drugs, such as rifampin.[229] Therefore, reduction of caspofungin is recommended in the setting of inducers of this enzyme, including rifampin, phenytoin, or dexamethasone.[210] Mild interactions with the immunosuppressants tacrolimus and cyclosporine

are predicted and monitoring of these drug levels is recommendation with coadministration.

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