Overview of treatment options for invasive fungal infections

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The introduction of several new antifungals has significantly expanded both prophylaxis and treatment options for invasive fungal infections (IFIs). Relative to amphotericin B deoxycholate, lipid-based formulations of amphotericin B have significantly reduced the incidence of nephrotoxicity, but at a significant increase in drug acquisition cost. Newer, broad-spectrum triazoles (notably voriconazole and posaconazole) have added significantly to both the prevention and treatment of IFIs, most notably Aspergillus spp. (with voriconazole) and the treatment of some emerging fungal pathogens. Finally, a new class of parenteral antifungals, the echinocandins, is employed most frequently against invasive candidal infections. While the role of these newer agents continues to evolve, this review summarizes the activity, safety and clinical applications of agents most commonly employed in the treatment of IFIs.

Keywords echinocandins, azole antifungals, amphotericin

Introduction

Despite recent advances in both the diagnosis and prevention of invasive fungal infections (IFIs), the incidence of disease, treatment failure and attributable mortality remains unacceptably high in patients at highest risk of infections. For example, increasing rates of candidemia have been reported [1]. Crude mortality in patients with candidemia is as high as 35% at 12 weeks [2]. Infection rates and treatment failure rates are even higher in select groups, such as those with prolonged and persistent neutropenia and graft-vers-host disease.

While amphotericin B deoxycholate has been the mainstay of treatment for IFIs since the early 1950s, treatment options have expanded considerably in the last 15 years. The addition of lipid-based formulations of amphotericin B, expanded-spectrum triazoles (i.e., voriconazole and posaconazole) as well as the echinocandins has increased options for both prevention and treatment. The objective of this review is to provide a concise review on the pharmacology, spectrum, adverse effects, and clinical applications of antifungal agents used in the treatment of IFIs. A summary of the agents as recommended by the Infectious Diseases Society of America (IDSA) guidelines is described in Table 1.

**Flucytosine**

Flucytosine (5-flucytosine, 5-FC, Ancobon®; Valeant pharmaceuticals Intl. Costa Mesa, CA, USA) was first discovered in 1957 and originally investigated as a potential antitumor therapy. Flucytosine’s antifungal properties were later recognized in 1961 [3]. Currently, flucytosine is rarely used as monotherapy due to resistance issues, but more commonly in combination with other antifungals (notably amphotericin B) to treat cryptococcal infections, select infections caused by Candida spp., and chromoblastomycosis [4–6].

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Table 1  First-Line Therapy Recommendations Per the Infectious Diseases Society of America Guidelines

<table>
<thead>
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<th>Drug Class</th>
<th>Individual Agent</th>
<th>Invasive Fungal Infections</th>
<th>Reference</th>
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<tbody>
<tr>
<td>---</td>
<td>5-FC</td>
<td>Induction therapy for cryptococcal meningitis: in combination with AmBd or LfAmB</td>
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<td></td>
<td></td>
<td><em>Candida</em> endocarditis: optional in combination with AmBd or LfAmB</td>
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<td><em>Candida</em> endocarditis: with or without 5-FC</td>
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<td>Diffuse <em>Coccidioides</em> spp. pneumonia</td>
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<td><em>Coccidioides</em> spp. meningitis: as intrathecal administration</td>
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<td>Induction therapy for cryptococcal meningitis: in combination with 5-FC</td>
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<td>Severe pulmonary <em>Cryptococcus</em> spp. infection; in combination with 5-FC</td>
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<td></td>
<td><em>Cryptococcus</em> meningitis; in combination with 5-FC</td>
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<td></td>
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<td>Acute <em>Histoplasma capsulatum</em> pulmonary infection-moderately severe to severe with methylprednisolone; followed by itraconazole</td>
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<tr>
<td></td>
<td>AmBd</td>
<td>Chronic disseminated candidiasis</td>
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<td><em>Candida</em> endocarditis: with or without 5-FC</td>
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<td>Diffuse <em>Coccidioides</em> spp. pneumonia</td>
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<td><em>Coccidioides</em> spp. meningitis: as intrathecal administration</td>
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<td>Induction therapy for cryptococcal meningitis: in combination with 5-FC</td>
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<td>Severe pulmonary <em>Cryptococcus</em> spp. infection; in combination with 5-FC</td>
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<td><em>Cryptococcus</em> meningitis; in combination with 5-FC</td>
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<td>Acute <em>Histoplasma capsulatum</em> pulmonary infection-moderately severe to severe with methylprednisolone; followed by itraconazole</td>
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<td>LfAmB</td>
<td>Disseminated-moderately severe to severe <em>Blastomyces dermatitidis</em> infection</td>
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<td>or pulmonary infection-moderately severe to severe; followed by itraconazole</td>
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<td>CNS <em>Blastomyces dermatitidis</em> infection; followed by itraconazole</td>
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<td><em>Candida</em> spp. CNS infection; with or without 5-FC</td>
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<td><em>Candida</em> endocarditis: with or without 5-FC</td>
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<td><em>Candida</em> osteomyelitis or septic arthritis</td>
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<td>Induction therapy for cryptococcal meningitis: in combination with 5-FC</td>
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<td>Acute <em>Histoplasma capsulatum</em> pulmonary infection-moderately severe to severe with methylprednisolone; followed by itraconazole</td>
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<td>Progressive disseminated histoplasmosis-moderately severe to severe</td>
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<td></td>
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<td>or CNS histoplasmosis; followed by itraconazole</td>
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<td><em>Sporothrix schenckii</em> infection-disseminated, meningitis or pulmonary;</td>
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<td>followed by itraconazole</td>
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<td>Triazoles</td>
<td>Fluconazole</td>
<td><em>Blastomyces dermatitidis</em> CNS infection after initial treatment with LfAmB</td>
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<td><em>Candida</em>emia-neutropenic</td>
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<td>Chronic disseminated candidiasis</td>
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<td><em>Candida</em> spp. CNS infection; after initial treatment with LfAmB with or without 5-FC</td>
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<td><em>Candida</em> osteomyelitis or septic arthritis</td>
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<td>Esophageal candidiasis</td>
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<td>Diffuse <em>Coccidioides</em> spp. pneumonia, disseminated infection or meningitis</td>
<td>[102]</td>
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<td><em>Cryptococcus</em> meningitis, severe cryptococcal pulmonary infection</td>
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<td>or cryptococcosia; as consolidation and maintenance therapy</td>
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<td></td>
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<td>Mild to moderate cryptococcal pulmonary infection</td>
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<td></td>
<td>Itraconazole</td>
<td><em>Blastomyces dermatitidis</em> disseminated infection-moderately severe to severe</td>
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<td></td>
<td></td>
<td>or CNS <em>Blastomyces dermatitidis</em> infection or pulmonary infection-moderately severe to severe; after initial therapy with LfAmB</td>
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<td><em>Blastomyces dermatitidis</em> disseminated infection-mild to moderate</td>
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<td>Disseminated <em>Coccidioides</em> spp. infection</td>
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<td></td>
<td></td>
<td>Acute <em>Histoplasma capsulatum</em> pulmonary infection-moderately severe to severe after treatment with AmBd or LfAmB</td>
<td>[103]</td>
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Pharmacology. 5-FC is a fluorinated pyrimidine analog that must be metabolized into its active form in order to exert its antifungal properties \[7,8\]. Flucytosine is taken up into the cell via a transport protein called cytosine permease. Once inside, 5-FC is deaminated by cytosine deaminase to produce 5-fluorouracil, then converted to 5-fluorouracil-ribose monophosphate (5-FUMP). It can then follow two different metabolic pathways. In the first pathway, 5-FUMP is converted to 5-fluorouridine triphosphate (5-FUTP), which can be incorporated into RNA and inhibit protein synthesis. In the alternative pathway, 5-FUMP is reduced to form 5-fluoro-2'-deoxyuridine-5'-monophosphate (5-FdUMP). 5-FdUMP is a powerful inhibitor of thymidate synthetase, an important enzyme in DNA synthesis. Through both of these mechanisms, 5-FC demonstrates its primarily fungistatic activity. While mammalian cells can also metabolize 5-FC, effects are minimized due to the lack of cytosine deaminase \[3,7,8\].

Flucytosine alone is considered to have fungistatic activity against most fungal isolates, with the exception of certain dermataceous molds \[9\]. When used with amphotericin B, the combination of these agents is fungicidal against most species and requires lower dosing of both agents. Flucytosine has primarily been used in combination with amphotericin B (AMB) for the treatment of invasive cryptococcal infections and some Candida spp. infections \[10 – 15\]. While mammalian cells can also metabolize 5-FC, effects are minimized due to the lack of cytosine deaminase \[16-21\]. The pharmacodynamic property that best correlates with efficacy appears to be the time above the minimum inhibitory concentration (T>MIC) \[22,23\]. Flucytosine does exhibit a post-antifungal effect (PAFE) against Candida spp. and \textit{C. neoformans}, which can persist for up to 7.4 or 5.4 h, respectively \[24\].

Mechanisms of resistance to 5-FC have been reported to include decreases in transport into the cell via cytosine permease, alterations in the activity of metabolic enzymes (cytosine deaminase, uridine monophosphate dehydrogenase), and increases in the production of competitive pyrimidines \[25\]. The most common mechanism appears to be the mutation in the cytosine deaminase gene \[27\].

Acute \textit{Histoplasma capsulatum} pulmonary infection-mild to moderate with symptoms for 4 weeks or chronic cavitary pulmonary histoplasmosis \[103\].

Histoplasma capsulatum pericarditis-moderate to severe; with prednisone \[103\].

Progressive disseminated histoplasmosis-moderate to severe or CNS histoplasmosis; after treatment with LfAmB or AmBd \[103\].

\textit{Sporothrix schenckii} infection-disseminated, meningitis or pulmonary; after treatment with LfAmB \[100\].
shown resistance rates from 1–2.5% among Candida species [31,32]. This however, is highly variable and species dependent. For example C. albicans species remain very susceptible (resistance < 1%) to 5-FC, while species such as C. krusei can exhibit almost complete resistance [31,32].

**Pharmacokinetics.** Flucytosine has an oral bioavailability of 78–89%, with peak serum concentrations occurring 2 h after an oral dose in patients with normal renal function [33,34]. The volume of distribution is 0.6–0.9 l/kg, which is similar to total body water [35]. Protein binding is nominal (2.9–4%) and tissue concentrations were equivalent to serum levels in the spleen, heart, liver, kidney, and lung, but lower in cerebrospinal fluid (80%) [11,36]. The majority of 5-FC (90%) is renally excreted as active drug, with a trivial amount being hepatically metabolized [33,34]. The half-life in healthy patients can range from 2.4–4.8 h, but is prolonged up to 85 h (range 29.9–250 h) in patients with renal insufficiency [33,34,37]. The dose should be adjusted depending on the degree of renal function. For example, a 50% dose reduction has been recommended for patients with a creatinine clearance of 20–40 ml/min, and a 75% reduction for a creatinine clearance of <20 ml/min [33,38,39]. Flucytosine is highly removed during hemodialysis, with a clearance resembling that of creatinine. Therefore, administration after dialysis sessions is recommended, with spot serum concentrations to maintain flucytosine levels below 100 μg/ml [39].

**Spectrum of activity.** Flucytosine has demonstrated favorable activity in vitro against several Candida spp. (except C. krusei), Cryptococcus spp., Rhodotorula spp., Saccharomyces cerevisiae, and certain causative pathogens of chromoblastomycosis (ex. Fonsecaea spp., Phialophora spp., Cladosporium spp.) [32,40,41]. The current Clinical Laboratory Standards Institute (CLSI) guidelines for antifungal susceptibility testing have established MIC breakpoints for Candida species against flucytosine as MIC ≤4 mg/l and resistant if ≥32 mg/l [42]. However, there is a lack of data correlating this breakpoint with clinical outcomes [42].

There are several decades of in vitro epidemiological data demonstrating the efficacy of flucytosine against Candida species. The SENTRY program included 1,448 Candida spp. from 2006–2007 [32]. The majority were C. albicans (n = 771), followed by C. parapsilosis (n = 238), C. glabrata (n = 202), C. tropicalis (n = 157), and C. krusei (n = 29). Utilizing CLSI methods (micro-broth dilution assay) and interpretive criteria, the overall susceptibility of Candida spp. was 95.9%. However, only 3.4% of C. krusei were considered susceptible [32,42].

Similar to Candida spp. and despite the lack of correlations between in vitro findings and clinical outcomes, MIC breakpoints for Cryptococcus spp. susceptible to flucytosine are an MIC ≤4 mg/l [42,43]. A global evaluation of 1,811 clinical isolates of Cryptococcus neoformans was performed between 1990 and 2004 utilizing the CLSI broth dilution methods [41]. Among the isolates tested, resistance to flucytosine ranged from 35% in the US to 68% in Latin America.

**Safety/tolerability.** The most common adverse effects reported with 5-FC therapy are gastrointestinal (6%) and can include nausea, vomiting, diarrhea, and abdominal discomfort [34,44,45]. Hepatotoxicity (reported with a range of 0–41%) has also been associated with flucytosine use, and typically presents with elevated transaminases and alkaline phosphatase [13,34,45,46]. The transaminitis is generally considered reversible once the drug is discontinued or the dose is reduced. Myelosuppression (especially at serum concentrations >100 μg/ml) can also occur, with one study demonstrating an incidence of 27% [46]. The most common manifestations of myelosuppression are either leukopenia or thrombocytopenia, but there also have been documented cases of pancytopenia [45,47]. Myelosuppression typically occurs after 2–4 weeks of therapy and can be irreversible [45,48]. Recovery time may be delayed depending on the intensity of treatment.

Risks of myelosuppression and hepatotoxicity can be reduced through monitoring peak serum concentrations, serum creatinine, liver function tests, and complete blood counts at regularly scheduled intervals during therapy. In addition, dosing adjustments in patients with renal impairment will help avoid excessive serum concentrations [34].

Steady-state peak levels are reached after 3–5 days of therapy, and should be measured 2 h post dose with a target concentration of 30–80 μg/ml [4]. Values of greater than 100 μg/ml have been associated with increased risk of toxicity and should be avoided [49].

**Current role in the treatment of invasive fungal infections.** Flucytosine is used primarily in combination with amphotericin B (AMB) for the treatment of invasive cryptococcal infections and some Candida spp. infections [10–15].

Monotherapy with either fluconazole or amphotericin B deoxycholate (AmB-d) to treat cryptococcal meningitis has resulted in poor clinical success rates, ranging from 34% with fluconazole to 40% with AmB-d [50]. Combination therapy of 5-FC with amphotericin B has been shown to sterilize the cerebral spinal fluid (CSF) at a more rapid rate in comparison to monotherapy with AmB-d [11]. Furthermore, clinical rates have been shown to improve
with combination therapy. For example, in a study of cryptococcal infections in HIV patients, individuals were randomized to receive amphotericin B (0.7 mg/kg daily) as monotherapy, in combination with either flucytosine (100 mg/kg daily) or fluconazole (400 mg daily), or triple drug therapy [11]. Cryptococcal eradication from the CSF was considerably more rapid with AmB-d and flucytosine than with AmB-d alone (P = 0.0006). Current treatment guidelines published by the IDSA recommend the combination of AMB-d + 5FC therapy as first-line treatment for the initial management of invasive cryptococcal infections [4,10–12].

Flucytosine may also be used in combination with amphotericin B for select candidal infections (such as endocarditis, meningitis, and endophthalmitis) [5]. However, experience with such combinations is primarily based on dated clinical studies, case reports and clinical expertise [14,15,51,52]. Furthermore, the role of 5-FC is somewhat limited with the advent of antifungals such as echinocandins and azoles. While flucytosine has also been used in the treatment of chromoblastomycosis, efficacy data for such infections are based primarily on case reports [6].

Polyenes

While both nystatin and amphotericin B are members of the polyene class, only amphotericin B is considered a treatment option for invasive fungal infections. Amphotericin B deoxycholate (Fungizone®, X-Gen pharmaceuticals. Big Flats, NY, USA), discovered in 1954, is used to treat many types of fungal, mold, and protozoa infections. Although it has the broadest spectrum of any antifungal, amphotericin B (including lipid based formulations such as a lipid complex, a colloidal dispersion and a liposomal preparation) use has been limited in recent years due to concerns regarding toxicity and in light of newer and safer alternatives for many IFIs [53].

Pharmacology. Amphotericin B binds to ergosterol (a cholesterol-like derivative of fungal cell membranes) forming micelles in the fungal cell membrane. The punctured cell membrane allows ions and other cellular constituents to escape [54,55]. Because of the structural similarities of ergosterol and cholesterol, there is a potential for toxicity of mammalian cells. However, the binding affinity of amphotericin B greatly favors ergosterol over cholesterol [56,57]. Amphotericin B also causes incorporation of lipid peroxidases and membrane proton pump inhibition [58,59].

Amphotericin B exhibits concentration dependant fungistatic activity against susceptible pathogens at lower concentrations and tends to be fungicidal at higher concentrations [11,60]. Based on pharmacokinetic-pharmacodynamic models, amphotericin B has a concentration-dependent kill with peak serum to MIC ratio (Cmax:MIC) correlating best with efficacy (R² = 0.9–0.93) [61,62]. Additionally, amphotericin B has a post antifungal effect (PAFE) ranging from 3–14 h depending on the species [60,63].

MIC breakpoints to determine resistance with amphotericin B against Cryptococcus and Candida spp. infections are not well established due to the lack of standardized in vitro testing methods and a lack of correlation between MIC breakpoints and clinical outcomes [42]. Resistance to amphotericin B is often linked to target site alterations such as a decrease or lack of ergosterol content in the cell wall, which is mediated through alterations in enzymes responsible for ergosterol production (i.e., lack of Δ(8,7) isomerase) [30]. Additionally, an increase in catalase activity may also be responsible for some resistance leading to a decrease in oxidative stress [64]. Resistance to amphotericin B is rare among Candida spp., but higher MICs have been reported with C. krusei and C. glabrata and intrinsic resistance has been reported with C. lusitaniae [65–67].

Pharmacokinetics. The pharmacokinetic profile for amphotericin remains ill-defined despite years of clinical experience. Amphotericin B is combined with the bile salt deoxycholate, thus increasing the water solubility for intravenous administration [57]. Amphotericin B is only available in an intravenous formulation due to its limited oral bioavailability (5–9%) [68]. The volume of distribution is approximately 4 l/kg and it follows a three-compartment model [61]. Amphotericin B distributes into many tissues including the liver, spleen, lung, kidney, and nominally into the cerebrospinal fluid (concentrations <2.5%) and is extensively protein bound (90%) [57,69]. Peak concentrations range from 0.5–2 mg/l with a 30–50 mg dose [38]. The distribution half-life can range from 24–48 h and is followed by a terminal elimination half-life of 15 days on average [38]. The metabolic pathway of amphotericin B is still uncertain, with only 2.5–5% of active drug being excreted in urine and a trivial amount in bile. Elimination can persist for weeks to months after therapy and is not efficiently removed through hemodialysis [38].

Comparisons between lipid formulations have been summarized here and elsewhere (see Table 2) [53,70,71]. Currently, there are three commercially available lipid formulations of amphotericin B and include AmBisome® (AmBi, liposomal amphotericin B. Gilead Sciences Inc., Foster City, CA, USA), Abelcet® (ABLC, amphotericin B lipid complex. Enzon Pharmaceuticals Inc., Bridgewater, NJ, USA; Cephalon Ltd, Welwin Garden City, UK), and Amphocil/Amphotec® (ABCD, amphotericin B colloidal dispersion. Three River Pharmaceuticals Inc., Cranberry Township, PA, USA). Tissue distribution of the
lipid formulations are higher than AmB-d in the liver and spleen [72]. ABLC distributes rapidly in lung tissue and poorly into kidneys, while ABCD distributes poorly into the kidneys, lungs, and brain [73,74].

**Spectrum of activity.** Amphotericin is considered to be the broadest-spectrum antifungal agent currently available. Amphotericin has demonstrated activity against the following organisms: *Leishmania*, *Candida* spp., *Aspergillus* spp., *Histoplasma capsulatum*, *Coccidioides immitis*, * Blastomyces dermatitidis*, *Rhodotorula* spp., *Cryptococcus neoformans*, *Sporothrix schenckii*, *Saccharomyces cerevisiae*, *Fusarium* spp., *Cladosporium* spp., *Scytalidium* spp., *Scedosporium* spp., and *Zygomycetes* [75–80]. Certain species, including *Candida lusitaniae*, *Trichosporon* spp., *Geotrichum* spp., *Scedosporium* spp., *Fusarium* spp., and *Aspergillus terrus* are intrinsically resistant to amphotericin B [81–83].

Developing in vitro interpretative susceptibility breakpoints such as the minimum inhibitory concentration (MIC) for yeast and molds with amphotericin B is problematic due to a lack of establishing a correlation between treatment failure or success and these breakpoints [30,84]. In 2006 and 2007, the SENTRY program evaluated amphotericin activity against *Candida* spp. (n = 1448), including *C. albicans* (n = 771), *C. parapsilosis* (n = 238), *C. glabrata* (n = 202), *C. tropicalis* (n = 157), *C. krusei* (n = 29), and *C. lusitaniae* (n = 14) [32]. *Aspergillus fumigatus* (n = 49) isolates were also tested. Using the CLSI broth dilution method and an interpretative breakpoint of ≤ 1 ng/ml, susceptibility rates for all of these species ranged from 93.1–100%. Only 71.4% of the *A. fumigatus* isolates tested were susceptible. While cryptococcal isolates were also included in the SENTRY program, they were not evaluated (due to the lack of defined in vitro susceptibility criteria for any antifungal agent against cryptococcal isolates) [32].

**Safety/tolerability.** Infusion-related reactions, nephrotoxicity, anemia, and anaphylaxis have been significant limitations in the ability of patients to tolerate therapy with amphotericin B [85].

Infusion-related reactions have been reported to occur in approximately 70–90% of patients initiating treatment with amphotericin B [85,86]. Such reactions include pain at the injection site, chills, rigors, fever, phlebitis, headache, bronchospasm, hypotension, cardiac arrhythmia, nausea and vomiting [70,86]. Such reactions may diminish with continued administration. Administration of premedications in an attempt to reduce the severity of the reactions may include corticosteroids to prevent phlebitis, antihistamines to diminish allergic response, and analgesics (acetaminophen or ibuprofen) to prevent fever and chills [86,87]. A test dose of 1 mg has been recommended in order to ensure that the patient does not have an acute hypersensitivity or anaphylaxis reaction [85]. Extended infusion times (over the recommended infusion time of 4–6 h) of up to 24 h may decrease some of the infusion related reactions [56,85,88–90]. However, such extended durations are not routinely recommended due to the lack of clinical response data in patients with documented IFIs. While infusion-related reactions were equivalent between ABCD and AmB-d, they have been shown to be reduced in patients treated with AMBi and ABLC [91–94]. The incidence of infusion-related reactions may be reduced with Ambisome® relative to the other formulations [74,95].

Common manifestations of nephrotoxicity include azotemia, hypokalemia, hypomagnesemia, hyperchloremia, renal tubular acidosis, or nephrocalcinosis. Such reactions have been documented in 24–80% of patients treated with amphotericin B [86,90]. The likelihood of nephrotoxicity is increased with the use of the deoxycholate formulation (relative to the lipid-based formulations), concomitant nephrotoxic medications, cumulative dose, and in patients with baseline renal insufficiency [62]. Administration of 500–1000 ml of normal saline prior to the administration of amphotericin B (sodium loading) is thought to decrease the incidence of nephrotoxicity, but has not been well-studied in controlled clinical trials [70,89]. Routine monitoring should include renal function studies, liver function tests, serum electrolytes, and complete blood counts [56,57,89]. Nephrotoxicity was significantly decreased in clinical studies that compared AMBi, ABLC, and ABCD to AmB-d [53,93,96,97].

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<th>Table 2 Pharmacokinetic properties of Amphotericin B Deoxycholate and lipid-based formulations [53,70,71].</th>
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<td><strong>Formulation</strong></td>
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<td>Amphotericin</td>
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<td>Abelcet® (Amphotericin lipid complex)</td>
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<td>Amphotec® (amphotericin B colloidal dispersion)</td>
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<td>Ambisome® (Liposomal amphotericin B)</td>
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</table>

*Amphotericin B clearance unit is ml/min.  
*Cmax = maximum plasma concentration; *AUC = area under the plasma concentration-time curve; *Vd = volume of distribution.
**Current role in the treatment of fungal infections.** Amphotericin B is used for the treatment of various invasive fungal, mold, and protozoa infections including candidiasis, cryptococcosis, aspergillosis, coccidioidomycosis, mucormycosis, sporotrichosis, blastomycosis, histoplasmosis, and leishmaniasis [4,5,11,98–103]. While still recommended first-line for the treatment of cryptococcal disease, its present place in therapy of other IFIs is likely to be reserved largely for life-threatening fungal infections and infections where other therapeutic options have been exhausted [4].

The combination of amphotericin B and flucytosine is considered first-line therapy for severe cryptococcal disease such as infections involving the CNS based on years of clinical experience and clinical studies [11,13,104,105]. A recent study evaluated the efficacy rates of amphotericin B plus flucytosine versus other combination therapies including amphotericin B plus fluconazole and triple drug therapy (AMB/flucytosine/fluconazole) and reported lower treatment failure rates and faster clearance of fungal burden with AmB-d plus flucytosine [11]. Additionally, high-dose AmB-d (1 mg/kg/day) was evaluated and compared against low-dose AmB-d (0.7 mg/kg/day) both in combination with flucytosine (100 mg/kg/day) for the treatment of HIV associated cryptococcal meningitis [10]. Treatment failure at the end of two weeks were lower in the high-dose AmB-d + 5-FC group in comparison to the low dose treatment group (26% AMB + 5-FC versus 56% all other treatment groups) \( (P = 0.001) \). Liposomal (AmBi) and lipid complex (ABLC) formulations have demonstrated similar efficacy in cryptococcal disease and can be utilized in place of conventional amphotericin B for patients at risk for nephrotoxicity [4,106–110].

Numerous studies have evaluated the efficacy of amphotericin B in the treatment of candidal infections [111–113]. In a recent meta-analysis of invasive candidiasis (15 studies), mortality rates were compared in patients receiving azole- (fluconazole), echinocandin- (caspofungin and micafungin) or amphotericin B-based therapy and found no significant differences in mortality rates between AMB-d and the other drugs (amphotericin B vs. fluconazole \( RR, 0.92; 95\% CI: 0.72–1.17 \); caspofungin vs. amphotericin B \( RR, 1.08; 95\% CI, 0.75–1.55 \); micafungin vs. liposomal amphotericin B \( RR, 1.04; 95\% CI, 0.75–1.43 \)) [114]. In terms of adverse effects, echinocandins were shown to have a lower incidence in comparison to amphotericin B \( RR, 0.11; 95\% CI, 0.04–0.36 \) and nephrotoxicity was significantly less with fluconazole when compared to amphotericin B \( RR, 0.11; 95\% CI, 0.03–0.48 \). Additionally, while newer azole antifungals (such as voriconazole) were not included in this meta-analysis, voriconazole has been compared to amphotericin B in a candidemia study and was found to be non-inferior [83]. Overall, the use of amphotericin B in the treatment of candidal infections is still highly supported and recommended in treatment guidelines [5]. However, its role is likely to be more of an alternative to other antifungals (such as azoles and echinocandins) in cases of refractory infection or in infections involving Candida spp. with limited data supporting the use of other agents such as in endophthalmitis, endocarditis, and CNS infections [5].

For treatment of invasive aspergillosis, amphotericin B is currently recommended as an alternative to voriconazole therapy [98]. Alternatively, it may be used first-line for empirical or preemptive therapy in high-risk patients (i.e., prolonged neutropenic patients) with a suspected invasive aspergillosis infection [98]. The largest clinical study evaluating the efficacy of amphotericin B in the setting of invasive aspergillosis randomized patients \( (n = 277) \) to receive either voriconazole (two doses of 6 mg per kilogram of body weight on day 1, then 4 mg per kilogram twice daily for at least seven days followed by 200 mg orally twice daily) or amphotericin B deoxycholate (1–1.5 mg/kg/day) [115]. After 12 weeks of therapy, 52.8% of patients had a response to voriconazole compared to 31.6% in the amphotericin group (absolute difference 21.2%; 95% CI, 10.4–32.9). Survival between groups favored voriconazole (70.8%) over amphotericin B (57.9%) \( (HR, 0.59; 95\% CI, 0.40–0.88) \).

Additionally, amphotericin B has been studied for its use as empiric therapy in febrile neutropenic patients [116,117]. One of the largest randomized controlled studies in febrile neutropenic patients \( (n = 1095) \) evaluated the efficacy of liposomal amphotericin B (3 mg/kg/day) vs. caspofungin (50 mg/day) over 14 days [116]. Survival rates were 92.6% vs. 89.2% for caspofungin and amphotericin B, respectively \( (P = 0.05) \). Overall, caspofungin was better tolerated than amphotericin B with a decreased incidence of nephrotoxicity (2.6% vs. 11.5%, respectively, \( P < 0.001) \). Therefore, amphotericin B remains a viable option for febrile neutropenic patients needing empiric antifungal therapy due to its broad-spectrum of activity. However, newer studies with broader spectrum azoles (such as voriconazole), as well as the newer classes of drugs (such as echinocandins), have largely replaced its use for such an indication.

Other additional uses for amphotericin B include the treatment of visceral leishmaniasis, histoplasmosis, and blastomycosis [118–122]. A randomized controlled study evaluated the safety and efficacy of amphotericin B against AIDS-associated histoplasmosis [118]. Patients \( (n = 81) \) were assigned to receive either conventional amphotericin B (0.7 mg/kg) or liposomal amphotericin (3.0 mg/kg) for two weeks, followed by itraconazole (dose not stated in the study) consolidation for 10 weeks. Clinical success was obtained in 64% and 88% of patients, respectively.
(P = 0.014). Additionally, amphotericin B is still considered first-line treatment for moderate to severe cases of blastomycosis, with a clinical cure rate without relapse of 70–91% [99,122].

Other non-conventional routes of administration of amphotericin B (either conventional or liposomal formulations) include aerosolized inhalation and bladder irrigation. Although there are several case reports utilizing aerosolized amphotericin B in combination with other systemic antifungal agents for the treatment of invasive fungal infections, it has primarily been studied as prophylactic therapy against these infections in immunocompromised patients (i.e. transplant recipients and patients with prolonged neutropenia) [123–131]. In a recent study, 271 patients with expected neutropenia of greater than 10 days received either 12.5 mg of aerosolized liposomal amphotericin B twice weekly or placebo [124]. Patients receiving aerosolized liposomal amphotericin B had a significant decreased in the incidence of invasive pulmonary aspergillosis when compared with placebo (4% vs. 14%, P = 0.005) [124]. However, discrepancies in duration of therapy, dosing regimens (5–20 mg once to three-times per day for prophylaxis and 7.5–50 mg/day for treatment), methods and equipment used for administration between clinical studies/case reports evaluating aerosolized amphotericin B make it difficult to determine an optimal regimen for prophylaxis or treatment [124,125,131–135]. Adverse effects associated with the aerosolized administration of amphotericin B include nausea, bad taste, coughing, bronchospasm, and increased dyspnea and sputum production [131]. Currently, despite some evidence, it is not recommended in the guidelines as prophylaxis or for treatment against invasive aspergillosis or candida infections [5,98,131].

The use of amphotericin B for bladder irrigations in the treatment of funguria has also been evaluated in multiple studies [131,136–138]. Doses of 5–50 mg per day given intermittently or continuously have demonstrated efficacy rates ranging from 43–100% [131,136,138–142]. However, optimal dosing and administration methods have not been fully elucidated. The overall utility of this practice is not currently recommended as first line treatment for urinary candidiasis and should generally not be considered except in cases of symptomatic candiduria caused by fluconazole resistant organisms or as adjunct treatment of urinary fungus balls [5].

As for costs per day, the lipid-based amphotericin products are generally 4- to 11-fold the cost (average-wholesale price [AWP]) of the generic amphotericin B products [143]. However, based on individual institution’s contract pricing, the actual price is variable which applies to all the mediation costs described in this paper.

**Triazoles**

The triazoles are essential for both prevention and treatment of invasive fungal diseases. Fluconazole was the first triazole approved for clinical use in the United States in 1990 [99]. While providing an invaluable oral option for treatment of invasive fungal diseases (particularly candidiasis and cryptococcosis), fluconazole use was limited by its lack of activity against molds [144]. Two years later, itraconazole (Sporanox®) was approved and provided a broader spectrum of activity, most notably *Aspergillus* spp. [145]. The use of itraconazole has been limited by erratic oral absorption, gastrointestinal adverse effects of the oral solution, and recent withdrawal of the intravenous formulation [146]. Within the past 10 years, two other triazole compounds have been approved for clinical use: voriconazole (Vfend®) and posaconazole (Noxafil®) [145]. These second-generation triazoles have activity against a wide range of fungal pathogens, including *Aspergillus* spp. and Zygomycetes (posaconazole only) as well as enhanced activity against *Candida* spp. However, these newer agents do not come without their own limitations, including the adverse effect profile of voriconazole and variable serum concentrations. Three triazoles (albaconazole, isavuconazole and ravuconazole) are currently being investigated in clinical trials, and will not be included in this review.

**Pharmacology.** Similar to the polyenes, the triazoles inhibit the synthesis of ergosterol, an essential component of the fungal cell membrane, through the inhibition of CYP-450-dependent lanosterol 14α-demethylase [147]. Inhibition of this enzyme leads to the accumulation of the methylsterols resulting in fungal cell death. Because the affinity to the various cytochrome P450 isoenzymes varies among the triazoles, each triazole differs in their *in vitro* potency and spectrum of activity [144]. In addition, the majority of the adverse effects and drug interactions observed with the triazoles are due to the cross-inhibition of human CYP450-dependent enzymes [148].

**Pharmacokinetics.** Triazoles have differing pharmacokinetic properties. While all triazoles are available as oral formulations, conditions for optimal absorption vary considerably for each agent [149]. For example, the absolute bioavailability of fluconazole exceeds 90%, and absorption is not affected by food or gastric pH [150]. In contrast, itraconazole formulations are significantly affected by both coadministration of food and gastric pH. The absolute bioavailability of itraconazole is > 55% [151]. For itraconazole capsules, absorption is optimized in the presence of food and gastric acid [151]. Gastric suppressive agents
(i.e., H2-antagonists and proton pump inhibitors) may decrease the absorption of itraconazole capsules by 30–60% and should be avoided if possible [152]. While itraconazole oral solution is not affected by gastric pH, food can decrease serum concentrations [153]. Therefore, it should be administered on an empty stomach [153]. Similar to fluconazole, voriconazole exhibits excellent bioavailability (>90%) [154]. However, administration of voriconazole with fatty foods decreases its bioavailability to 80% [155]. Absorption issues are a significant barrier to posaconazole’s clinical use. The bioavailability of posaconazole ranges from 8–47% when administered on an empty stomach [156]. When administered with a high-fat meal (~50 g fat) or nutritional supplement, the bioavailability increases by 400% [156]. Data have also shown increased posaconazole absorption when administered with an acidic carbonated beverage (i.e., ginger ale) [157]. Therefore, it is recommended to administer posaconazole with a high-fat meal, nutritional supplements, or an acidic carbonated beverage [156,157]. To further optimize absorption, it is recommended to divide the daily dose of posaconazole into 2–4 doses (preferably four doses when using for salvage therapy) [158]. Recent data suggest that proton pump inhibitors can decrease the absorption of posaconazole [157]. Therefore, concomitant use should be avoided [157].

Itraconazole and posaconazole are highly protein bound (>99%) primarily to albumin [159]. Protein binding for fluconazole and voriconazole are 11% and 58%, respectively [159]. Of the triazoles, fluconazole and voriconazole have the highest central nervous system (CNS) penetration, while fluconazole is the only triazole that achieves reliable concentrations as active drug in the urine [149].

With the exception of fluconazole, all of the triazoles are highly-dependent on metabolism for elimination. Fluconazole is primarily eliminated by renal excretion, with approximately 80% of unchanged drug appearing in the urine [150]. Thus, dosage adjustments are warranted in patients with a creatinine clearance <50 ml/min [150]. Itraconazole is metabolized by the liver (predominantly by the CYP3A4 isoenzymes system) and is the only triazole with an active metabolite (hydroxylitraconazole) which exerts similar antifungal efficacy as the parent compound [159]. Voriconazole is extensively metabolized by the hepatic cytochrome P450 enzymes CYP2C19, CYP2C9, and CYP3A4 [154]. CYP2C19 exhibits significant genetic polymorphism [159]. For example, 15–20% of Asians and 3–5% of Caucasians and African-Americans are poor metabolizers of voriconazole, resulting in significantly higher concentrations of the drug [154]. Even though voriconazole is not extensively renally eliminated, the intravenous preparation of voriconazole is not recommended for use in patients with a CrCl <50 ml/min due to concerns regarding potential accumulation of the sulfobutyl ether B-cyclodextrin sodium vehicle [154]. Posaconazole is hepatically metabolized and undergoes minimal glucuronidation, with the majority of the drug being eliminated in the feces (71%) [160]. With the exception of fluconazole, triazoles are not significantly removed by dialysis [159].

**Spectrum of activity.** As a class, the triazoles collectively have a broad spectrum of activity against a variety of yeasts and molds in vitro. However the spectrum of activity varies with each agent. Fluconazole has the most narrow spectrum of activity of all of the triazoles and is essentially limited to Candida spp., Cryptococcus neoformans, and dimorphic fungi [150]. Results from the most recent ARTEMIS DISK Global Antifungal Surveillance Study showed that fluconazole was most active against some of the more common Candida spp. (C. albicans, C. tropicalis, and C. parapsilosis) with susceptibility rates of >90% for these species [161]. However, C. glabrata often demonstrates dose-dependent susceptibility to fluconazole, while C. krusei is inherently resistant [161]. Itraconazole has a spectrum of in vitro activity similar to fluconazole with the addition of Aspergillus spp. [151,153]. Voriconazole and posaconazole are considered the expanded-spectrum triazoles. Voriconazole demonstrates activity against most Candida spp. (including C. krusei), Aspergillus spp., Scedosporium apiospermum, Fusarium spp., Cryptococcus spp., and dimorphic fungi [154]. While voriconazole has demonstrated activity in vitro against fluconazole-resistant Candida spp., cross-resistance can occur. For example, the ARTEMIS DISK study demonstrated only about 30% of these pathogens remained susceptible to voriconazole [161]. Posaconazole has the broadest spectrum of activity of all the triazoles. Its spectrum is very similar to voriconazole with the addition of Zygomycetes [146].

**Safety/tolerability.** As a class, the triazoles have been associated with nausea, vomiting, diarrhea, hepatic toxicity and QTc prolongation [162]. Relative to fluconazole and posaconazole, the incidence of adverse effects is generally higher with voriconazole and itraconazole. In addition to an increased incidence of hepatotoxicity, voriconazole has been associated with transient visual disturbances (including abnormal vision, photophobia, color vision changes, or hallucinations), skin reactions, and mental confusion [154]. Many of the adverse effects may be concentration-related [163]. Itraconazole is contraindicated in patients with congestive heart failure or a history of congestive heart failure due to its negative inotropic effects [151,153]. In addition, itraconazole oral solution has been associated with significant nausea and diarrhea [149].

In comparison to other antifungal classes, the triazoles appear to have the greatest potential for drug-drug interactions.
due to the cross-inhibition of human CYP-450-dependent enzymes, most notably 2C19, 2C9, and 3A4. Of the available triazoles, voriconazole is associated with the most drug-drug interactions, as it is both an inhibitor and substrate for all three CYP enzymes (2C19, 2C9, and 3A4) [148]. Because of their potential to inhibit CYP-450-dependent enzymes, the triazoles have the potential to interact with several classes of drugs. These include select antiretrovirals, anticonvulsants, chemotherapeutic agents, HMG-CoA reductase inhibitors, immunosuppressants and amiodarone. A complete review of CYP450-mediated drug interactions is reviewed elsewhere [164].

**Current role in the treatment of invasive fungal infections.** Triazoles have been extensively studied in the prevention and treatment of invasive fungal diseases. The majority of studies with fluconazole have focused on the treatment of oropharyngeal and esophageal candidiasis [165–170], invasive candidiasis [111,112,171], prophylaxis against invasive fungal diseases in patients with malignancies (including allogeneic stem cell transplants [172–174]), and treatment of cryptococcosis [50,175,176]. Due to its long track record, fluconazole is endorsed by several published guidelines, notably the IDSA clinical practice guidelines for the management of cryptococcal disease and candidiasis, along with the National Comprehensive Cancer Network (NCCN) clinical practice guidelines for the prevention and treatment of cancer related infections [4,5,177]. Fluconazole is often used as preferred therapy for the treatment of oropharyngeal and esophageal candidiasis. Urinary concentrations of fluconazole are 10–20 times the concentrations in the serum, thus fluconazole is also considered preferred therapy for urinary tract infections caused by susceptible Candida spp. [5]. Fluconazole can be used as initial therapy for candidemia in nonneutropenic patients who do not have moderately severe to severe illness or recent azole exposure [5]. Fluconazole has long been used as consolidation therapy for cryptococcal meningitis due to its ability to penetrate the CNS [4]. Finally, fluconazole has been recommended as primary antifungal prophylaxis in hematopoietic stem cell transplant recipients and patients with hematologic malignancy who are not at a substantial risk for invasive aspergillosis [177].

Similar to fluconazole, itraconazole has been studied and has demonstrated efficacy for the treatment of oropharyngeal and esophageal candidiasis [165,170], cryptococcosis [178], and as primary prophylaxis against invasive fungal diseases in patients with hematologic malignancies [179,180]. In addition, itraconazole has been evaluated for the treatment of invasive aspergillosis [98,178], as well as histoplasmosis [103] and blastomycosis [99]. Due primarily to concerns with erratic absorption (with the capsule formulation), high incidence of gastrointestinal intolerance (with the oral solution), availability of alternate azoles (such as posaconazole and voriconazole), and withdrawal of the intravenous preparation, its use clinically has declined over the years. With the exception of treatment of mild to moderate histoplasmosis and blastomycosis (where it remains the drug of choice) [99,103], most of the current IFI treatment guidelines endorse itraconazole as alternative therapy [5,98,177]. In the case of primary therapy for patients with cryptococcal meningoencephalitis, the current guidelines discourage the use of itraconazole due to its potential absorption issues and minimal concentrations of active drug in the CSF [4].

Voriconazole has demonstrated efficacy for the treatment of esophageal candidiasis [181], candidemia in non-neutropenic patients [182], refractory infections caused by Scedosporium apiospermum and Fusarium spp. [183,184], prophylaxis of invasive fungal diseases in allogeneic stem cell transplant recipients [185], and (most notably) treatment of invasive aspergillosis [115]. In the landmark study by Herbrecht et al., patients with invasive aspergillosis treated with voriconazole compared to those treated with amphotericin B had significantly better outcomes at week 12 (success rates of 53% vs. 32%; P < 0.0001) as well as better survival (70.8% vs. 57.9%, P = 0.02) [115]. Largely due to the results of this trial, the current guidelines recommend voriconazole as the drug of choice for primary treatment of invasive aspergillosis [98]. In addition to treatment of invasive aspergillosis, voriconazole is also commonly used in allogeneic stem cell transplant prophylaxis due to its excellent activity against both Aspergillus spp. and most Candida spp. [177]. Voriconazole is not commonly used for the treatment of candidemia in non-neutropenic patients since fluconazole provides a cheaper option in most cases. In cases where resistance to fluconazole is a concern, voriconazole is not used due to the likelihood of cross-resistance and an echinocandin is typically preferred [148,186].

The majority of studies with posaconazole thus far have been for the prevention of invasive fungal disease in high-risk patients, most notably allogeneic stem cell transplant recipients and neutropenic patients with acute myelogenous leukemia (AML) or myelodysplastic syndrome (MDS) [187,188] and as salvage therapy of invasive fungal diseases caused by Aspergillus spp. [189] and Zygomycetes [190]. In two studies evaluating posaconazole prophylactic therapy in patients with neutropenia (AML or MDS) and allogeneic stem cell transplant recipients with graft-versus-host disease (GVHD), posaconazole significantly reduced the number of proven or probable cases of invasive aspergillosis and improved survival [187,188]. An open-label, multicenter study reported patients with invasive aspergillosis who were refractory or intolerant of conventional
therapy had an overall success rate of 42% (45/107) with posaconazole monotherapy [189]. From the available data, it appears that posaconazole is not only an effective prophylactic agent in high-risk patients, but also a promising alternative agent for the treatment of zygomycosis and other refractory invasive fungal diseases. For example, in a retrospective study, 60% (54/91) of patients with zygomycosis refractory to prior antifungal therapy experienced a complete or partial response with posaconazole monotherapy [190].

**Key differences among agents in this class.** While fluconazole was the first triazole approved for use, it is still used extensively in clinical practice. This is due largely to its low cost, excellent bioavailability, and tolerable adverse effect profile. While maintaining high activity against select Candida spp. (notably C. albicans), its widespread use as empiric therapy for severe forms of invasive candidiasis (i.e., prior to species identification) has been impacted by its limited activity against some non-albican species (notably C. glabrata and C. krusei) [161]. Fluconazole continues to be used in select patient populations at high risk of candidiasis, as well as a treatment option for invasive cryptococcal infections [4,5]. Itraconazole is generally considered the drug of choice for mild to moderate histoplasmosis and blastomycosis [99,103]. However, due (in part) to erratic oral absorption, drug-drug interactions and recent withdrawal of the intravenous preparation, the clinical use of itraconazole has declined over the years for the treatment of other invasive fungal diseases. Voriconazole surpassed amphotericin B as the drug of choice for invasive aspergillosis [115]. It also appears to be an effective therapy for refractory infections caused by Scedosporium apiospermum and Fusarium spp. [183,184]. As previously mentioned, voriconazole appears to have the highest potential for drug-drug interactions and the most significant adverse effect profile. Posaconazole has emerged as a novel triazole being the first to expand activity against Zygomycetes [190]. Similar to fluconazole, it appears to be well-tolerated. Posaconazole is primarily used as prophylactic therapy of invasive fungal disease in high-risk patients. Currently, posaconazole is only available as an oral solution which could limit its use for treatment of serious, invasive fungal diseases.

Therapeutic drug monitoring may be warranted in select cases for patients receiving itraconazole, voriconazole and posaconazole, most notably those receiving treatment for serious, invasive fungal infections [163]. Due to both inter- and intrapatient variability in serum concentrations, therapeutic drug monitoring for posaconazole and itraconazole may be utilized in select settings to ensure adequate concentrations of the drug. In addition, due to the genetic polymorphisms of CYP2C19, non-linear kinetics, and the high potential for drug-drug interactions, voriconazole serum concentrations can be highly variable, and serum concentration monitoring may be clinically useful to ensure safety and efficacy. A detailed discussion of antifungal serum concentration monitoring is beyond the scope of this review [163].

The costs per day of the differentazole products vary with the most economical being fluconazole and itraconazole because of the availability of generic formulations. Voriconazole is generally 2–4 times the AWP cost of fluconazole while posaconazole can be as high as three times fluconazole’s AWP [143].

**Echinocandins**

The echinocandin antifungal class of drugs consists of three USA FDA-approved agents: caspofungin (MK-0991, Cancidas®, Merck & Co., Inc., Whitehouse Station, NJ, USA), micafungin (FK-463, Mycamine®; Astellas Pharma US, Inc., Deerfield, IL, USA) and anidulafungin (VER-003, LY303366, EraxisTM; Pfizer, Inc., New York, NY, USA).

**Pharmacology.** The echinocandins non-competitively inhibit the enzyme UDP-glucose β-(1,3)-D-glucan- β-(3)-D-glucosyltransferase which is responsible for the construction of 1,3- β-D glucan, a component of the fungal cell wall of select fungi (including Candida spp. and Aspergillus spp.). [191–193]. The echinocandins display concentration-dependent, fungicidal activity against most Candida spp and are fungistatic against most Aspergillus spp. [194–196].

**Pharmacokinetics.** The agents in the echinocandin class share some similar pharmacokinetic properties. Absorption after oral administration is limited, and thus all the echinocandins are only approved for intravenous use [191–193,197–199]. All of the agents are highly protein-bound (97% [for caspofungin] to greater than 99% [for micafungin and anidulafungin]), primarily to albumin [191–193]. Both caspofungin and anidulafungin exhibit extensive tissue distribution [192,193]. For example, caspofungin has 16-fold higher concentrations in the liver, 3-fold higher concentrations in the kidneys, and 2-fold higher concentrations in the large intestines when compared with that of simultaneous plasma concentrations. While the small intestines, lung and spleen have concentrations similar to the plasma, other organs, such as the heart and brain have much lower concentrations compared with plasma (0.3 and 0.06-fold, respectively) [192].

One notable pharmacokinetic difference among the drugs in this class is the metabolism. Caspofungin is...
metabolized via N-acetylation and hydrolysis, while micafungin is metabolized to three metabolites (M1, M2 and M5) [191,192,197,198]. In contrast, anidulafungin does not undergo hepatic metabolism, but rather is degraded by a slow chemical breakdown of the drug at physiologic pH and temperature [193,199]. Neither caspofungin nor anidulafungin are inhibitors, inducers or substrates of the CYP-450 isoenzyme system [192,193,197,199]. While micafungin is a substrate and weak inhibitor of CYP3A enzyme system in vitro, it does not appear to have clinical significance [191,197]. Neither caspofungin nor anidulafungin are substrates for p-glycoprotein [191–193,197], enzyme system anidulafungin are inhibitors, inducers or substrates of pH and temperature [193,199]. Neither caspofungin nor amphotericin B deoxycholate) for salvage therapy in invasive candidiasis [216–220], esophageal candidiasis [168,221–223], febrile neutropenia [116], and invasive aspergillosis [224–227]. For invasive candidiasis, specifically candidemia, caspofungin was found to be at least as effective as amphotericin B [216]. In addition, a head-to-head trial demonstrated non-inferiority of micafungin (100 mg/day or 150 mg/day) versus caspofungin (70 mg on day 1 followed by 50 mg/day thereafter) for invasive candidiasis including candidemia [217]. As for esophageal candidiasis, caspofungin has been compared to both fluconazole [168] and amphotericin B [221,223]. In these studies, caspofungin was as effective as the comparators and better tolerated than amphotericin B. Caspofungin has been compared with itraconazole for antifungal prophylaxis in patients diagnosed with Acute Myelogenous Leukemia or Myelodysplastic Syndrome who had induction chemotherapy [228]. Results of this study showed similar efficacy and safety for both agents [228]. In a febrile neutropenia study, patients were randomized to receive liposomal amphotericin B or caspofungin for empiric treatment [116]. Caspofungin was found to have a similar efficacy for successful outcomes (33.9% caspofungin vs. 33.7% liposomal amphotericin B (absolute difference, 0.2%; 95% CI: −5.6–6.6%)) and had fewer side-effects including nephrotoxicity (2.6% caspofungin vs. 11.5% liposomal amphotericin B, \( P < 0.001 \)) and infusion-related events (35.1% caspofungin vs. 51.6% liposomal amphotericin B, \( P < 0.001 \)) [116]. Finally, caspofungin has been studied both alone and in combination with other agents (voriconazole, itraconazole, ABLC, liposomal amphotericin B and amphotericin B deoxycholate) for salvage therapy in invasive aspergillosis [224–227].

Micafungin has been studied for the treatment of invasive candidiasis [217,229,230], esophageal candidiasis [166,231,232] as well as antifungal prophylaxis in neutropenic patients undergoing stem cell transplantations [174,233]. For invasive candidiasis including candidemia, micafungin has been compared to caspofungin (see above) and liposomal amphotericin B [217,229]. Micafungin had similar efficacy defined as treatment success compared with liposomal amphotericin B (89.6% vs. 89.5%,...
respectively [absolute difference after stratification, 0.7%; 95% CI: −5.7–6.7%]) with fewer side-effects [229]. For esophageal candidiasis, micafungin was studied both in open-label (no comparator) and double-blind fashion (with fluconazole comparison) [166,231,232]. Micafungin doses of 100 mg/day and 150 mg/day appear to be comparable in efficacy to fluconazole 200 mg/day based on these studies [166,231]. In the stem-cell transplant neutropenic population, micafungin (50 mg/day or 150 mg/day) was compared to fluconazole (400 mg/day) for the prophylaxis of invasive fungal infections [174,233]. In the first of these studies, micafungin was found to be significantly better than fluconazole with the success rate (defined as the absence of an IFI through the therapy duration and four weeks after treatment) of 80.0% in the micafungin group and 73.5% in the fluconazole group (absolute difference 6.5%; 95% CI: 0.9–12%) [174]. Interestingly, the higher dose micafungin study yielded a non-significant difference between micafungin and fluconazole for success (94% vs. 88%, respectively [absolute difference 6%; 95% CI: −5.4–17.4%]) [233].

Anidulafungin has been evaluated in the treatment of invasive candidiasis [171,234] and esophageal candidiasis [169]. Anidulafungin was compared with fluconazole in both of these treatment settings. In the invasive candidiasis non-inferiority study, anidulafungin had similar success rates to fluconazole (73.2% vs. 61.1%, respectively [difference 12.1%; 95% CI: −1.1–25.3%]) [135]. In the esophageal candidiasis study, anidulafungin was again non-inferior to fluconazole with treatment success rates of 97.2% vs. 98.8%, respectively (difference −1.6%; 95% CI: −4.1–0.8%) [169].

Key differences among agents in this class. All agents within the echinocandin class are comparable with regards to spectrum of activity, pharmacokinetics and adverse effect. All are approved for the treatment of candidemia and Candida spp. infections as well as Candida esophagitis. Because caspofungin is the oldest echinocandin, it has the most clinical data supporting its use [116,216–222, 226–228]. One disadvantage of caspofungin is its drug interaction with cyclosporine and its need for adjustment with liver dysfunction [198].

In the pediatric population, caspofungin is the only echinocandin to be approved for use in this age group (age >3 months old) and has clinical data evaluating Candida spp. and Aspergillus spp. infections to support its use among children [198,235]. Micafungin has data evaluating the safety and pharmacokinetics in pediatric patients as well as a substudy evaluating invasive candidiasis in pediatric patients [236–238]. At this time, anidulafungin only has data evaluating the safety and pharmacokinetics in pediatrics, but no published trials assessing efficacy [239]. Historically, one concern for anidulafungin’s use in the pediatric population was the alcohol content of the formulation. Anidulafungin was formerly reconstituted with ethanol which provided 12 g of ethanol in a 200 mg loading dose and 6 g of ethanol in a 100 mg maintenance dose [240]. Fortunately, this is no longer a concern because anidulafungin is now reconstituted with sterile water for injection [199].

The AWP costs (per day) of the echinocandins vary widely with micafungin being priced the lowest. Anidulafungin is approximately 1.5-fold the price of micafungin while caspofungin has the highest AWP pricing at up to four times micafungin’s AWP [143]. Unfortunately, at this time no generic formulation is available.

Conclusion
IfIs continue to occur at increasing rates with suboptimal treatment response rates. The introduction of several new antifungals has significantly expanded both prophylaxis and treatment options for IfIs. While lipid-based formulations of amphotericin B have significantly reduced the incidence of nephrotoxicity (relative to amphotericin B deoxycholate), they do so at a significantly increased drug acquisition cost. Expansion of the triazole class of compounds to most recently include voriconazole and posaconazole has added significantly to both the prevention and treatment of IfIs, most notably Aspergillus spp. (with voriconazole) and the treatment of some emerging fungal pathogens. Echinocandins are a new class of parenteral antifungals used most frequently against invasive candidal infections, but have also been used in the setting of invasive aspergillosis refractory to alternate therapies. While the role of these newer agents continues to evolve, each has made a significant impact for the prevention and/or treatment of IfIs.

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