Overview of Antifungal Agents

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The number of agents available to treat fungal infections has increased by 30% since the year 2000, yet still only 15 agents are currently approved for clinical use. The greater number of medications now available allows for therapeutic choices; however, differences in antifungal spectrum of activity, bioavailability, formulation, drug interactions, and side effects necessitates a detailed knowledge of each drug class.

POLYENES

Amphotericin B (AMB) and nystatin are the currently available polyenes, although differing safety profiles have limited nystatin to topical use.[1] The polyenes bind to ergosterol present within the fungal cell wall membrane. This process disrupts cell wall permeability by forming oligodendromes functioning as pores with the subsequent efflux of potassium and intracellular molecules causing fungal death.[2] There is also evidence that AMB acts as a proinflammatory agent and further serves to stimulate innate host immunity. This process involves the interaction of AMB with toll-like receptor 2 (TLR-2), the CD14 receptor, and by stimulating the release of cytokines, chemokines, and other immunologic mediators. It has been suggested that AMB may interact with host humoral immunity after the observation of synergistic activity of AMB and antibodies directed at heat shock protein 90 (hsp90), although further confirmatory data are needed.[2]

When AMB resistance occurs, it is generally attributed to reductions in ergosterol biosynthesis or the synthesis of alternative sterols with a reduced affinity for AMB. Resistance to AMB is common in *Aspergillus terreus*, *Scedosporium apiospermum*, *Scedosporium prolificans*, *Trichosporon* spp, and *Candida lusitaniae* (**Table 1**). Resistance has been reported with several other species, however.[3]

The peak serum level to mean inhibitory concentration (MIC) ratio is the best pharmacologic predictor of outcomes with polyene therapy. Drug levels are infrequently measured, nor are they necessary, and they are typically available only in the research setting.[4]

AMB is primarily used intravenously (IV) or through the inhalational route. In attempts to avoid the nephrotoxicity seen with amphotericin B deoxycholate (AmBd; Fungizone) several other formulations have been developed. The lipid preparations include: liposomal amphotericin B (L-AMB; Ambisome), amphotericin B lipid complex, (ABLC; Abelcet), and amphotericin B colloidal dispersion (ABCD; Amphotec, Amphocil). All currently available formulations are highly protein bound (>95%, primarily to albumin) and have long half-lives.

AMB exhibits poor cerebrospinal fluid levels (<5% of concurrent serum concentration); however, this agent remains the treatment of choice for cryptococcal meningitis.[5] Previous reports have described the use of intrathecal

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Table 1
Antifungal spectrum of activity against common molds and yeast

Organism	AMB	FLU	ITR	POS	VOR	ANI	MFG	CAS	5FC
Aspergillus fumigatus	+	−	+	+	+	+	+	+	−
A flavus	+/−	−	+	+	+	+	+	+	−
A terreus	−	−	+	+	+	+	+	+	−
A niger	+	−	+/−	+	+	+	+	+	−
A nidulans	+	−	+/−	+	+	+	+	+	−
Candida albicans	+	+	+	+	+	+	+	+	+
C glabrata	+	+/−	+/−	+	+	+	+	+	+
C krusei	+	−	+/−	+	+	+	+	+	+/−
C tropicalis	+	+	+	+	+	+	+	+	+
C parapsilosis	+	+	+	+	+/−	+/−	+/−	+	+
C guilliermondii	+	+	+	+	−	−	−	+	+
C lusitaniae	−	+	+	+	+	+	+	+	+
Cryptococcus spp	+	+	+	+	−	−	−	+	+
Blastomycoses	+	+	+	+	+	+/−	+/−	+/−	−
Histoplasmosis	+/−	+	+	+	+/−	+/−	+/−	−	−
Coccidioidomycosis	+	+	+	+	−	−	−	−	−
Fusarium spp	+/−	−	−	+	+	−	−	−	−
Phaeohyphomycoses[a]	−	+	+	+	+	+	+	−	−
Pichia spp	+	+	+/−	+	+	+	+	+	+
Saccharomyces spp	+	+	+	+	+	+	+	+	+
Scedosporium apiospermum	+/−	+	+	−	−	−	−	−	−
Scedosporium prolificans	−	+/−	+/−	−	−	−	−	−	−
Trichosporon spp	+/−	+	+	+	−	−	−	+	+
Zygomycetes	+/−	−	−	+	−	−	−	−	−

(+) implies antifungal activity against isolates, (−) implies no or limited activity against isolate, (+/−) implies variable activity against isolates.

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

[a] Infection requires debridement in almost all circumstances.

Data from Refs.[6] and [95–97].

AMB in an attempt to circumvent the poor cerebrospinal fluid (CSF) penetration; however, this practice is seldom used because of the difficulty of administration, poor patient tolerability, and availability of alternative agents for use in the salvage setting of invasive mycoses. AMB also has low vitreous penetration (0%–38%) and intraocular injections may be required to achieve appropriate levels during therapy of deep ophthalmologic fungal infections, including candidal endopthalmitis.[6,7] The exact route of elimination of AMB is not known and despite the well-known nephrotoxicity, dosing need not be adjusted in patients who have a decreased glomerular filtration rate.

The broad antifungal spectrum and experience with the use of amphotericin B accounts for its continued use despite toxicity concerns. Liposomal amphotericin B remains the recommended antifungal during the treatment of neutropenic fever after an open-label, randomized international trial comparing L-AMB to voriconazole. Although fewer breakthrough infections (including those caused by *Aspergillus* spp) occurred in patients receiving voriconazole, predetermined noninferiority criteria were not reached.[8] Additionally, a recent meta-analysis suggested L-AMB may be associated with lower morality than AmBd during the empiric treatment of neutropenic fever.[9]

AMB was previously the preferred first-line agent during the treatment of invasive aspergillosis; however, a greater therapeutic response and survival have been demonstrated when voriconazole is administered in this setting—relegating AMB to second-line or salvage therapy during the treatment of invasive aspergillosis.[10] AMB does remain the agent of choice when the

Zygomycetes are encountered. In fact, a delay in the prescribing of an AMB formulation in patients infected with one of the Zygomycetes resulted in a twofold greater risk for death.[11] Discriminating between invasive zygomycoses and aspergillosis is difficult, but the differences in the choice of antifungal agents and outcomes mandate an aggressive diagnostic strategy and prompt initiation of antifungal agents.

Before the development of alternative agents, AMB was the recommended first-line agent for invasive candidal infections.[12] AMB in combination with flucytosine remains the drug of choice in the treatment of cryptococcal meningitis and in most cases a lipid formulation is preferred because of the decreased incidence of nephrotoxicity.[5] Severe infection caused by the endemic mycoses (ie, histoplasmosis, coccidioidomycosis, blastomycosis, and sporotrichosis) should be treated with an AMB formulation. Histoplasmosis remains the only infection for which a lipid formulation of AMB (L-AMB) has demonstrated greater efficacy than the conventional form.[13]

In attempts to avoid the potential nephrotoxicity of systemic administration and to deliver higher local concentrations, different formulations of AMB have been given by way of the inhalational route. The deoxycholate used to solubilize AMB acts as a detergent and may affect alveolar surfactant. Lipid preparations are thus preferred for inhalation delivery, although no decline in pulmonary lung function from AmBd has been documented. AmBd is often difficult to effectively administer in an aerosol form because of foaming caused by the solubilizing agent.[11,14–16] Aerosol delivery has been found effective in the prevention of pulmonary fungal infections in lung transplantation and in bone marrow transplant recipients, although data supporting its efficacy in other settings are limited.

Inhaled L-AMB has been found protective against development of invasive aspergillosis when given twice weekly to neutropenic patients who have cancer.[16] Inhalation delivery is also an attractive option in the treatment of lung transplant patients and a recent retrospective series reported nebulized ABLC provided effective prophylaxis against invasive aspergillosis in 98.3% of all patients.[14]

The recommended dose of IV AmBd is between 0.7 and 1 mg/kg and only recently have clinical data emerged evaluating higher doses of lipid formulations of AMB to potentially improve efficacy. The AmBiLoad trial evaluated the efficacy of higher initial doses of L-AmB (3 mg/kg versus 10 mg/kg) in the treatment of invasive aspergillosis. Treatment success rates were similar in both treatment arms although there was a greater incidence of nephrotoxicity in those receiving the higher dose of L-AmB.[17] In severe and life-threatening disease it is the authors' experience that escalating doses of lipid formulations of AMB may be indicated when alternative agents are not available or have been found ineffective.

AmBd infusion is associated with infusion-related reactions, such as fever, chills, rigors, myalgias, bronchospasm, nausea and vomiting, tachycardia, tachypnea, and hypertension.[12] These events are less likely to occur when one of the lipid formulations is used; however, ABCD has been associated with the development of dyspnea and hypoxia and L-AMB has been associated with back pain during infusion.[6] Amphotericin B has been associated with acute kidney injury and nephrotoxicity in many studies and is a well-known potential complication of therapy occurring in up to 30% of patients. This toxicity is believed secondary to vascular smooth muscle dysfunction with resultant vasoconstriction and ischemia.[18] For this reason most advocate ensuring adequate volume status before administration. Lipid preparations of AMB have a lower incidence of renal toxicity, and studies have shown that when AmBd is replaced by a lipid formulation after the development of creatinine elevation, renal function stabilizes or improves in a significant proportion of patients.[19]

The avoidance of AmBd and use of a lipid formulation has been met with skepticism by some because of the vast price difference in compounds. The reduction in hospital days when toxicity is avoided, however, has proven the lipid formulations more cost effective than AmBd.[19]

TRIAZOLES

The triazoles also exert their effects within the fungal cell membrane. The inhibition of cytochrome P450 (CYP)-dependent 14-α-demethylase prevents the conversion of lanosterol to ergosterol. This mechanism results in the accumulation of toxic methylsterols and resultant inhibition of fungal cell growth and replication (**Fig. 1**). This class of agents has demonstrated species- and strain-dependent fungistatic or fungicidal activity in vitro and the area under the curve (AUC) to MIC ratio is the primary predictor of drug efficacy.

The indirect immunomodulatory effects are poorly understood because of the complex interaction of triazoles and phagocytic cells. Evidence suggests that ergosterol depletion increases fungal cell vulnerability to phagocytic oxidative damage[20] and voriconazole has been shown to
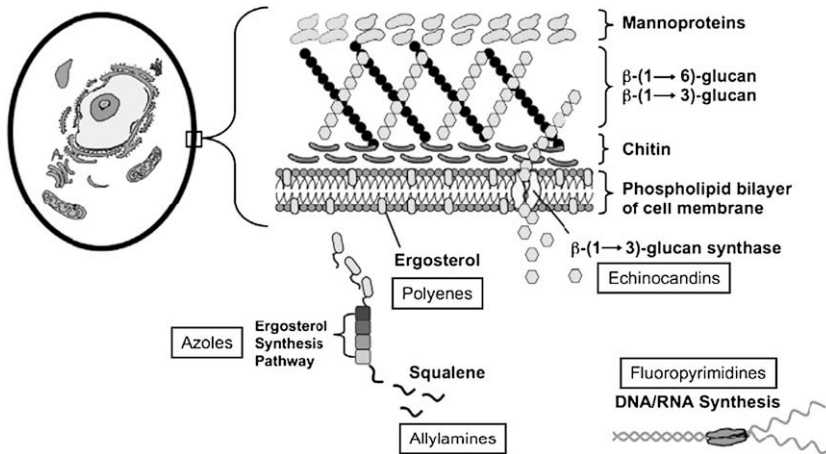
Fig. 1. Targets of systemic antifungal agents.

induce the expression of TLR2, nuclear factor-κB, and tumor necrosis factor-α.[2]

Azoles differ in their affinity for the 14-α-demethylase enzyme and this difference is largely responsible for their varying antifungal potency and spectrum of activity. Cross-inhibition of several human CYP-dependent enzymes (3A4, 2C9, and 2C19) is responsible for most of the clinical side effects and drug interaction profiles that have been described with this class. Itraconazole and posaconazole act primarily as inhibitors of 3A4 and 2C9 with little effect on 2C19. Voriconazole acts as both an inhibitor and a substrate on all three isoenzymes providing ample opportunity for drug–drug interactions because of this frequently shared metabolic pathway.

Comprehensive lists of triazole drug interactions can be found elsewhere. Briefly, caution should be used when these agents are concurrently administered with: most HMG-CoA reductase inhibitors, benzodiazepines, phenytoin, carbamazepine, cyclosporine, tacrolimus, sirolimus, methylprednisolone, buspirone, alfentanil, the dihydropyridine calcium channel blockers verapamil and diltiazem, the sulfonylureas, rifampin, rifabutin, vincristine, busulphan, docetaxel, trimetrexate, and the protease inhibitors ritonavir, indinavir, and saquinavir.[21–27]

The triazoles have also been associated with QTc prolongation[28] and coadministration with other agents known to have similar effects (cisapride, terfenadine, astemizole, mizolastine, dofetilide, quinidine, and pimozide, amongst others) should be avoided.[29–31] The triazoles are additionally embryotoxic and teratogenic and are secreted into breast milk, and thus administration should be avoided during pregnancy or while lactating.[28,32,33]

Fluconazole

Fluconazole (Diflucan) remains one of the most frequently prescribed triazoles because of its excellent bioavailability, tolerability, and side-effect profile. More than 80% of ingested drug is found in the circulation, and 60% to 70% is excreted unchanged in the urine. Oral absorption remains unchanged in patients receiving acid-suppressive therapy (proton pump inhibitors, H2-blockers). Only 10% of fluconazole is protein bound.[34]

Fluconazole also exhibits excellent tissue penetration. CSF levels are 70% of matched serum levels, and levels reported in saliva, sputum, and other sites are well within therapeutic ranges. The half-life is 27 to 34 hours in the presence of normal renal function allowing once-daily dosing. In patients who have a reduced creatinine clearance the normal dose should be reduced by 50%. Fluconazole serum levels are rarely necessary. Currently 50-, 100-, 150-, and 200-mg tablets are available and IV formulations exist in 200- or 400-mg doses.

Fluconazole is active against most *Candida* spp with the exception of *C krusei* and *C glabrata* isolates. If a *C glabrata* isolate is found susceptible to fluconazole higher doses (12 mg/kg/d) should be used.[7,35] There is no appreciable activity against *Aspergillus*, *Fusarium*, *Pseudoallescheria*, or the Zygomycetes.

Although fluconazole has substantially fewer drug–drug interactions than other triazole compounds, caution remains necessary because of increases in the serum levels of phenytoin, glipizide, glyburide, warfarin, rifabutin, and cyclosporine. Fluconazole levels are reduced in the presence of rifampin.

Fluconazole is well tolerated by most patients, even if chronic therapy is necessary.[36] Headache, alopecia, and anorexia are the side effects most common (10%) with transaminase elevation in less than 10%.

Fluconazole remains the drug of choice in the treatment of oropharyngeal candidiasis (OPC) (100 mg/d for 7–14 days).[7] Newer data suggest a one-time dose of 750 mg for the treatment of OPC with equivalent relapse rates to standard therapy.[37] Patients who have frequent relapse should remain on chronic suppressive fluconazole until immune reconstitution has been documented.

Fluconazole has also been used for prophylaxis in those at high risk for invasive fungal infections. Initiation of 400 mg/d of fluconazole for the first 75 days after bone marrow transplantation has been found effective in reducing cases of candidemia.[38] Preemptive therapy within ICUs remains controversial. The high incidence of invasive candidiasis within this setting (1%–2% of all patients) makes prophylaxis an attractive option; however, the largest randomized, multicenter, blinded clinical trial comparing empiric fluconazole therapy in ICU patients with several risk factors for invasive candidiasis to placebo showed no clear benefit to fluconazole therapy.[39]

After induction therapy with AMB and flucytosine, fluconazole is used for suppression of cryptococcosis. An initial dose of 400 mg for 10 weeks followed by 200 mg weekly pending immune reconstitution has been recommended.[5] Although recent data has accrued regarding the use of high-dose fluconazole monotherapy during the induction course of cryptococcal meningitis, this practice should be used only in resource-limited settings and not when AMB is available.[40]

Fluconazole is also useful for infections caused by *Coccidioides immitis*. In cases of meningitis or disseminated infection high-dose fluconazole (up to 2 g daily) is often necessary.[41]

Itraconazole

Itraconazole is currently available as capsules and as an oral solution suspended in hydroxypropyl-β-cyclodextrin (HPCD). Unfortunately, the IV preparation of itraconazole is no longer commercially available. Itraconazole capsules depend on an acidic environment for maximal absorption, and the concomitant administration of H_2-receptor antagonists, proton pump inhibitors, or antacids causes erratic and unpredictable drug absorption; it is thus recommended that itraconazole capsules be taken with food or a cola beverage.[42,43]

Itraconazole solution allows for greater oral bioavailability and the AUC and peak concentrations are both increased by 30% when itraconazole solution is taken in the fasting state.[44,45] The cyclodextrin carrier has minimal absorption and no systemic side effects have been attributed to its use in the oral formulation.[46] With once-daily dosing, steady state is reached in 7 to 14 days, although oral loading (200 mg three times daily for 3 days) allows for more rapid attainment of therapeutic serum levels.[47] Itraconazole is also highly protein bound with less than 1% available as free drug and has a relatively high volume of distribution.

Itraconazole is extensively metabolized by the liver and its major metabolite, hydroxy-itraconazole, does possess antifungal activity similar to that of the parent drug. Despite similar antifungal efficacy, hydroxyl-itraconazole is not measured during serum drug level determination by high performance liquid chromatography, although the active metabolite is detected by bioassay.[48]

The development of newer and more effective antifungal agents (ie, voriconazole) has relegated itraconazole to second-line therapy during the treatment of invasive aspergillosis. Itraconazole is thus licensed in the United States only for salvage therapy of invasive aspergillosis (IA).[10] Itraconazole does, however, remain the drug of choice for those who have mild to moderate infection caused by histoplasmosis and is the mainstay of secondary prophylaxis in patients who have HIV with a history of histoplasmosis before immune reconstitution with antiretrovirals.[49] Itraconazole is also approved for allergic bronchopulmonary aspergillosis.[10]

The recommended dosage of oral itraconazole in adults is 400 mg/d (capsules) and 2.5 mg/kg twice daily (HPCD solution).[10] Steady-state levels can be more rapidly attained, however, when administered as 200 mg three times daily for 3 days and then 200 mg twice daily for the duration of therapy. Considerable concern remains regarding adequate oral absorption and oral itraconazole is not recommended in seriously ill patients or patients who have life-threatening disease. Dose adjustment is not indicated when the oral formulation of itraconazole is used in patients who have renal insufficiency or those receiving hemodialysis/continuous ambulatory peritoneal dialysis. The half-life of itraconazole is prolonged in patients who have hepatic dysfunction and drug dose adjustment, liver function testing, and drug interactions need to be carefully assessed.[50]

Itraconazole is usually well tolerated and although adverse reactions have been observed in up to 39% of patients no fatalities and only rare toxicity requiring discontinuation of therapy

were reported. The most frequent side effects include: nausea and vomiting (<10%), hypertriglyceridemia (9%), hypokalemia (6%), liver enzyme elevations (5%), skin rashes/pruritus (2%), headache and dizziness (<2%), and pedal edema (1%).[51] Gastrointestinal intolerance (46%) is exceedingly common with the oral HPCD solution at doses greater than 400 mg/d with vomiting the most frequent complaint.[52] The myocardial depressant effects of itraconazole are also well known and cases of congestive heart failure have been reported.[53]

Posaconazole

Posaconazole is a lipophilic second-generation antifungal triazole with a similar molecular structure to that of itraconazole. The spectrum of activity of posaconazole includes agents of the Zygomycetes, and it has improved activity against *Aspergillus* spp compared with itraconazole.[54]

Posaconazole is insoluble in water and no IV formulation has yet been developed. It is thus administered as a cherry-flavored suspension using polysorbate 80 as the emulsifying agent.[55] Optimal dosing of posaconazole is obtained when given as two to four divided doses administered with food or a liquid nutritional supplement.[56,57] Although initial studies suggested that changes in gastric acidity do not affect posaconazole absorption subsequent work has shown H_2-receptor antagonists and proton pump inhibitors may decrease posaconazole serum levels and if possible coadministration should be avoided.[32,55,58,59]

Posaconazole has demonstrated dose-dependent pharmacokinetics with saturable absorption greater than 800 mg/d; thus oral loading is not possible and steady state is typically achieved after 7 to 10 days of therapy.[60] This prolonged time required to reach steady-state levels may affect the use of posaconazole as primary therapy for invasive fungal infections. This agent also has a large volume of distribution despite its high protein binding and a half-life of approximately 24 hours.

Peak serum concentrations have shown considerable interpatient variability for reasons that remain unclear. Some have proposed genetic polymorphisms within P-glycoprotein to play a role because posaconazole is both a substrate and inhibitor, but this remains unproven.[61] Glucuronidation plays a minor role in posaconazole metabolism and single nucleotide polymorphisms within UGT (uridine diphosphate-glucuronyl transferase) have also been proposed to account for these differences but confirmatory studies are lacking.[62] This unpredictable variation in serum posaconazole levels has heightened interest and the necessity of therapeutic drug monitoring (TDM).

Posaconazole is hepatically metabolized and undergoes minimal glucuronidation. Renal clearance plays a minor role in the clearance of posaconazole, which is predominantly eliminated fecally.

Oral posaconazole has proved effective in the prevention of proven or probable invasive aspergillosis in neutropenic patients who have acute myelogenous leukemia and in hematopoietic stem cell transplant recipients who have graft versus host disease.[63,64] The efficacy and safety of posaconazole in the treatment of invasive fungal infections has also been assessed, and although this study predates the development of echinocandins and voriconazole the statistically significant success rate of posaconazole compared with other agents allows for its use during salvage therapy.[65]

Currently, 200 mg three times daily is recommended for prophylaxis, and 800 mg divided in two or four doses is recommended in the salvage setting. For patients not tolerating food, a liquid nutritional supplement has been recommended to increase absorption.[61] Pediatric dosing schedules have yet to be established.[10] Dose adjustment by age, sex, race, and hepatic or renal insufficiency is not necessary given the minimal glucuronidation and renal clearance of posaconazole.[66]

Posaconazole is usually well tolerated and infrequently requires discontinuation because of adverse events. The most frequent side effects of posaconazole therapy are gastrointestinal (14%), with transaminase elevation and hyperbilirubinemia occurring in 3%.[64] In one trial, however, more serious adverse events were reported in patients treated with posaconazole than with fluconazole. Three cardiac events were reported among those possibly related to posaconazole treatment, including decreased ejection fraction, QTc prolongation, and torsades de pointes.[63] For most patients posaconazole is well tolerated and even long-term therapy (>6 months) is frequently without toxicity.[67]

Posaconazole is not significantly metabolized through the cytochrome P450 system and serum levels are unlikely to be increased by concomitant administration of P450 inhibitors.

Voriconazole

Voriconazole is a low molecular weight water-soluble second-generation triazole with a chemical structure similar to fluconazole. Voriconazole

exhibits a broad spectrum of activity against molds with the exception of the Zygomycetes.[68]

Voriconazole is available in oral and IV formulations. Similar to itraconazole, the IV form depends on sulfobutyl ether β–cyclodextrin for solubility.[68] When 3 to 6 mg/kg of daily voriconazole is administered, steady-state levels are reached in 5 to 6 days. If IV loading is given, however, steady state can be reached within 1 day.[69] The oral formulation obtains steady-state levels within 24 hours if appropriate loading is administered; however, fatty foods have been found to reduce bioavailability by 80%.[70]

Although voriconazole in children has demonstrated linear pharmacokinetics, in adults nonlinear metabolism is observed, likely secondary to saturable metabolic enzymes required for drug clearance.[69] Interpatient serum concentration differences have been attributed to polymorphisms within CYP2C19, the major metabolic pathway for voriconazole.[68] Up to 20% of non-Indian Asians have low CYP2C19 activity and voriconazole serum levels are thus up to four times higher than those found in white or black populations in which the ''poor metabolizer'' status is uncommon.[71] The unpredictability of patient enzymatic activity has generated an increased interest in the routine use of voriconazole serum level determination.

For IV administration 6 mg/kg twice daily on day one, followed by 4 mg/kg IV twice daily for the duration of therapy is recommended. The oral dosages in adults are also weight based. For those weighing greater than 40 kg, 400 mg twice daily on day one, followed by 200 mg twice daily until completion of therapy is suggested, whereas those weighing less than 40 kg should receive 200 mg twice daily for one day followed by 100 mg twice daily.[68] Pediatric patients are known to hypermetabolize voriconazole and for this reason an IV dose of 7 mg/kg twice daily and oral dosing of 200 mg twice daily without loading is recommended.[33] In patients who have liver dysfunction standard loading doses should be given, but the maintenance dose reduced by 50%. The safety of voriconazole use in severe liver disease remains uncertain. No dosage adjustment is required if oral drug is given to patients who have renal insufficiency. The presence of a cyclodextrin vehicle within the IV formulation has caused concerns about vehicle accumulation in renal insufficiency or dialysis dependence and IV administration is best avoided in patients who have a creatinine clearance less than 50 mL.[68]

Voriconazole is typically well tolerated, and the side-effect profile is similar to other triazoles with few exceptions. Most of those experiencing a reported adverse reaction to voriconazole describe abnormal vision (up to 23%) that is transient, infusion related, and without sequelae. This unique effect typically occurs 30 minutes after infusion and abates 30 minutes after onset.

Other well-known effects of voriconazole therapy include skin rash and transaminase elevation.[72] Baseline evaluation of hepatic function has been recommended before and during treatment, and rare cases of hepatic failure during voriconazole use have been reported.[73] Elevated voriconazole serum levels have been attributed to most side effects encountered in clinical practice, and higher levels (>5.5 mg/L), although associated with favorable outcomes, have also been suggested to be responsible for the uncommon potential side effects of encephalopathy or hallucinations.[74–76]

Voriconazole has become the drug of choice for most cases of invasive aspergillosis based on recent data comparing voriconazole to conventional amphotericin B, followed by other antifungal therapy in patients who have invasive aspergillosis.[77] Voriconazole has also been evaluated in the treatment of neutropenic fever. Although voriconazole did not meet predetermined noninferiority criteria, there were significantly fewer breakthrough infections (including those caused by *Aspergillus* spp) in patients receiving voriconazole.[8]

Voriconazole has also been evaluated for use during infection caused by *Fusarium* and *Scedosporium* spp. A retrospective series evaluated its use in these infections and reported a favorable response in 63% of patients treated with voriconazole.[33]

Therapeutic Drug Monitoring

Commercial assays are available for monitoring the serum concentrations of all currently available triazoles; however, at this time existing guidelines recommend only itraconazole TDM.[49,78,79] Itraconazole levels are typically drawn after steady state is reached to ensure therapeutic levels (>1 μg/mL) have been obtained. Fluconazole levels are infrequently monitored because of the excellent bioavailability of this agent. Clinical circumstances may dictate drug monitoring when therapeutic levels are uncertain (ie, concurrent use of rifampin, rifampicin, and so forth).

The newer triazoles, posaconazole and voriconazole, have received increased attention because of their erratic absorption (posaconazole) or concerns for toxicity and the interpatient variability of serum levels (voriconazole). No guidelines exist for posaconazole TDM; however, past

evidence supports a relationship between posaconazole serum drug level and efficacy.[80] TDM should also be considered when drug interactions are of concern, such as the aforementioned potential for acid-suppressive agents to reduce absorption. Although goal levels remain to be determined, most advocate trough concentrations 0.5 μg/mL or greater when given for antifungal prophylaxis. The interpatient variability of voriconazole also warrants consideration of TDM during use. Low concentrations (<1 mg/L) are more common in those receiving oral therapy and failure rates have been associated with low serum drug levels.[72] Conversely, levels greater than 5.5 mg/L have been associated with encephalopathy without an improvement in efficacy.[74] The frequency with which to monitor these newer triazoles remains to be determined.

ECHINOCANDINS

Echinocandins (caspofungin, micafungin, anidulafungin) are synthetic compounds that inhibit the synthesis of β-1,3 glucan, by inhibiting the activity of glucan synthase. This mechanism impairs cell wall integrity and leads to osmotic lysis.[81] Their clinical use is primarily limited to *Candida* spp and *Aspergillus* spp and they lack activity against the Zygomycetes, *Cryptococcus* spp, and other clinically important molds (see **Table 1**). Although activity is observed against all *Candida* spp, the MICs are elevated (>1 μg/mL) when *Candida parapsilosis* and *Candida guilliermondii* are encountered and susceptibility differences between the different agents in this class are minimal.[82] Echinocandins also have immunomodulatory effects. By exposing β-glucan by the disruption of fungal cell wall mannoproteins, additional antigens are exposed for antibody deposition and fungal recognition by the host immune system.[83]

Echinocandin efficacy is predicted by peak to MIC ratios, and optimal fungicidal activity is obtained when peak concentrations exceed MICs by 5- to 10-fold.[6] TDM of echinocandins is seldom required, however, and not routinely recommended. Echinocandin resistance is uncommon but may develop during therapy.[84]

Multiple in vitro studies have confirmed a paradoxical effect of the echinocandins. In this circumstance, above a certain concentration of drug decreased antifungal activity is observed. The exact mechanism responsible for this phenomenon has not been fully elucidated and the clinical significance remains uncertain.[85]

Echinocandins have poor oral absorption and current agents are available only in the IV formulation. Echinocandins are highly protein bound (anidulafungin 84%, caspofungin 97%, and micafungin 99%) and have a half-life of 26, 30, and 15 hours, respectively. Their vitreal and CSF penetration is negligible and this point is of clinical significance during the treatment of candidemia if endophthalmitis is also observed.

Caspofungin was the first available agent of this class, and is metabolized by both hepatic hydrolysis and N-acetylation. Inactive metabolites are subsequently eliminated in the urine. Severe hepatic dysfunction thus mandates caspofungin dose reduction.[6] Caspofungin has several drug interactions with agents metabolized through the cytochrome P450 system and serum levels are reduced in the presence of rifampin and may increase levels of sirolimus, nifedipine, and cyclosporine.[6] Micafungin is metabolized by nonoxidative metabolism within the liver and anidulafungin undergoes nonenzymatic degradation within the kidney. Both agents are eliminated in stool. These agents therefore do not require dosage adjustment with hepatic impairment.[6]

The side-effect profile of the echinocandins is minimal and these agents are typically well tolerated. An infusion-related reaction has been described if rapid administration is given, with tachycardia, hypotension, or thrombophlebitis.

Clinical Use

The increased incidence of triazole-resistant *Candida* spp and the fungicidal activity of the echinocandins (caspofungin, micafungin, anidulafungin) has prompted some authorities to recommend these agents as first-line therapy for invasive candidiasis. Additionally, their proven efficacy, infrequency of side effects, and favorable drug interaction profiles make them attractive options over other available antifungals.[12,86–88]

Comparative trials have found the echinocandins equally efficacious and better tolerated than AMB in the treatment of candidemia.[12] In one such trial, caspofungin (70 mg loading dose followed by 50 mg daily) was compared to amphotericin B deoxycholate (0.6–1 mg/kg) in the treatment of invasive candidiasis. Although *C albicans* was more common in the AMB arm, modified intention to treat revealed similar survival in each group, with a trend toward increased survival and a statistically significant decrease in drug side effects in those receiving caspofungin.[12]

Similarly, micafungin (100 mg IV daily) has been compared to L-AMB 3 mg/kg IV daily in an international, double-blind trial. In this study assigning patients to 14 days of IV treatment, successful treatment was equivalent in each group. There were fewer treatment-related adverse events,

including those that were serious or led to treatment discontinuation, with micafungin than there were with liposomal amphotericin.[86]

Only one comparative trial of different echinocandins has been performed in invasive candidiasis. In this trial patients were enrolled to one of three treatment groups: micafungin 100 mg IV daily, micafungin 150 mg IV daily, or caspofungin 70 mg IV loading dose followed by 50 mg IV daily. Intention to treat analysis found no differences in response to therapy, treatment or microbiologic failure, or all-cause mortality.[88] Although this trial found that higher doses of an echinocandin may not equate to a greater therapeutic response, no increase in toxicity was seen with higher doses, and dose escalation can thus be safely used in unusual circumstances or in obesity.

Anidulafungin has been compared with fluconazole for the treatment of invasive candidiasis. At the end of IV therapy, treatment was successful in 75.6% of patients treated with anidulafungin, as compared with 60.2% of those treated with fluconazole. Despite a greater response rate and a lower rate of death from all causes in the anidulafungin group, however, predetermined criteria for statistical superiority were not reached and only noninferior status granted.[87]

It is common practice from the results of these trials for local resistance patterns and the severity of infection to be taken into account and echinocandins are frequently used as first-line therapy. After clinical improvement is obtained or the absence of fluconazole resistance documented, therapy is often changed to a triazole, such as fluconazole. As noted previously, CNS and intraocular infections should not be treated with echinocandin monotherapy because of their poor penetration into these sites.

Although clinical trials have been primarily limited to patients who have candidemia, observational data have shown efficacy in candidal osteomyelitis, peritoneal infections, and abdominal abscesses.[89] Additional retrospective data have also shown a potential role for the echinocandins in infective endocarditis caused by Candida spp.[90]

The echinocandins have also been found efficacious in the treatment of invasive aspergillosis, although they are fungistatic against this agent. The growing number of patients who are at risk for this infection has prompted a greater interest in the use of other agents that may be of clinical use against this devastating infection. The known toxicity of AMB and its different formulations and the potential for voriconazole-induced drug–drug interactions or toxicity has also increased interest in the echinocandins for use during treatment of IA.[91]

Caspofungin as a potential first-line agent has been evaluated only in limited settings and although acceptable responses have been observed, data are not sufficient to recommend caspofungin for first-line use during the treatment of IA.[10] Patients who are unresponsive or intolerant to voriconazole may benefit from a change to caspofungin.[91] In vitro studies and limited clinical data have also shown the potential role for combination therapy (an echinocandin plus AMB or an azole) and prospective studies are ongoing.

ANTIMETABOLITES
Flucytosine

Flucytosine (5FC; Ancobon) is deaminated to 5-fluorouracil by fungal cytosine deaminase. 5-fluorouracil is further converted to 5-fluorodeoxyuridylic acid, which interferes with DNA synthesis. Mammalian cells lack cytosine deaminase allowing for a selective inhibition of fungal organisms (see **Fig. 1**).[92] This agent may be either fungistatic or fungicidal depending on fungal species and strain.

Activity has been observed against most fungal pathogens, including Candida, Cryptococcus, Cladosporium, Phialophora, and Saccharomyces spp. Aspergillus spp, the Zygomycetes, dermatophytes, and the endemic mycoses are all resistant to 5FC (see **Table 1**). Additionally, resistance commonly develops when 5FC is used as monotherapy even in susceptible organisms and it should not be used as such except during the treatment of chromoblastomycoses or during the treatment of localized candidal infections when alternative agents are unavailable or contraindicated.

5FC has excellent oral bioavailability with greater than 80% to 90% absorption. Peak serum levels occur 1 to 2 hours after ingestion (30–45 µg/mL) of a single dose. The volume of distribution of 5FC is 0.6 to 0.9, yet bone, peritoneal, and synovial fluid 5FC levels have been demonstrated and urinary levels are several-fold higher than concurrent serum levels. Greater than 95% of 5FC is eliminated unchanged in the urine. 5FC is typically administered by mouth at 100 or 150 mg/kg/d divided in four doses.

Side effects of therapy include rash, diarrhea, hepatic transaminase elevation, and bone marrow suppression. The marrow suppressive effects are more common if blood levels exceed 100 to 125 µg/mL.[93] In the presence of prolonged therapy (>7 days) or with alterations in renal function serum drug monitoring is recommended. Other less common side effects, such as abdominal pain or diarrhea, are frequently indirect markers of elevated flucytosine levels and therapy is typically

stopped in these circumstances. 5FC is terato-
genic and should not be administered during
pregnancy.

5FC is primarily used only in the treatment of
cryptococcus (combined with AMB) and chromo-
blastomycosis. Despite concerns for additive
toxicity the synergistic effects of dual therapy in
cryptococcus allow for more rapid CSF
clearance.[94]

SUMMARY

The incidence of infection with invasive mycoses
continues to increase with the increasing immuno-
suppressed patient population. The recently
expanded antifungal armamentarium offers the
potential for more effective and less toxic therapy
and these agents offer distinct pharmacologic
profiles and indications for use.

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