

## Current Concepts in Antifungal Pharmacology

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*On completion of this article, the reader should be able to: (1) compare and contrast the spectrum of activity and mechanism of action of current systemic antifungal agents to select appropriate therapy for invasive mycoses, (2) identify common pharmacokinetic/pharmacodynamic problems with systemic antifungal therapy and recommend appropriate strategies for therapeutic drug monitoring, and (3) identify common short-term adverse effects and less common long-term adverse effects with triazole therapy.*

**The introduction of new antifungal agents (eg, echinocandins, second-generation triazoles) in the past decade has transformed the management of invasive mycoses to the point that drug toxicity is no longer the major limiting factor in treatment. Yet, many of these newer antifungal agents have important limitations in their spectrum of activity, pharmacokinetics, and unique predisposition for pharmacokinetic drug-drug interactions and unusual toxicities associated with long-term use. This article reviews key pharmacological aspects of systemic antifungal agents as well as evolving strategies, such as pharmacokinetic-pharmacodynamic optimization and therapeutic drug monitoring, to improve the safety and efficacy of systemic antifungal therapy.**

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**AUC = area under the curve; CYP = cytochrome P450; 5-FC = flucytosine; GI = gastrointestinal; MIC = minimum inhibitory concentration; TDM = therapeutic drug monitoring**

The era of systemic antifungal chemotherapy effectively began with the introduction of amphotericin B-deoxycholate in 1958 by Squibb Laboratories, after exhaustive attempts to develop orally bioavailable formulations of more than 200 polyene macrolide antibiotics produced by the soil actinomycete *Streptomyces*.<sup>1</sup> Although amphotericin B was to become the criterion standard treatment for serious fungal infections for more than 40 years, infusion-related adverse effects and dose-limiting nephrotoxicity prompted the continued search for equally effective but less toxic alternatives that could be administered both intravenously and orally.

This goal was not realized until more than 3 decades later with the introduction of fluconazole in 1990 (Figure 1). Unlike amphotericin B and the earlier imidazole antifungal agents (miconazole, ketoconazole), fluconazole possessed excellent oral bioavailability; predictable linear pharmacokinetics with wide distribution into many tissues, including the cerebral spinal fluid and vitreous chamber of the eye; and a much lower risk of drug interactions and toxicity in critically ill patients compared with earlier azoles.<sup>2</sup> Fluconazole was also effective for the treatment of oropharyngeal candidiasis in patients with AIDS; however, resistance could be problematic in patients receiving prolonged treatment who had declining CD4<sup>+</sup> cell counts.<sup>3</sup> Fluconazole

quickly became one of the most widely prescribed antifungal agents for mucosal and systemic yeast infections. However, the lack of activity against opportunistic molds (ie, *Aspergillus*, Mucorales, and *Fusarium* species) and intrinsic resistance among some *Candida* species (eg, *Candida glabrata*, *Candida krusei*) created a need for broader-spectrum alternatives. Itraconazole (1992) was a partial solution to the limitations of fluconazole because the drug had improved activity against endemic fungi and *Aspergillus* species, but the oral dosing formulations were plagued by erratic absorption (capsules)<sup>4</sup> or adverse gastrointestinal (GI) effects (solution formulation)<sup>5</sup> that limited its effectiveness in cancer patients with mucositis or nausea and vomiting.<sup>6</sup>

The introduction of the broader-spectrum triazoles voriconazole (2002) and posaconazole (2006) transformed the management of invasive mold infections in severely immunocompromised patients. Voriconazole was shown to be more effective than conventional amphotericin B for the treatment of invasive aspergillosis<sup>7</sup> and is a useful agent for fusariosis,<sup>8</sup> whereas posaconazole had a spectrum of activity that included not only *Aspergillus* and *Fusarium* species but also many Mucorales.<sup>9,10</sup> Both agents could be administered orally, paving the way for their use not only for the treatment of suspected or documented mold infections but also as prophylaxis in severely immunocompromised patients.<sup>11-13</sup> Unfortunately, the broader spectrum of activity with triazole antifungal agents often comes at the expense of increased pharmacokinetic variability and risk of drug interactions. Newer triazoles currently under investigation (ie, isavuconazole) appear to have a spectrum of activity

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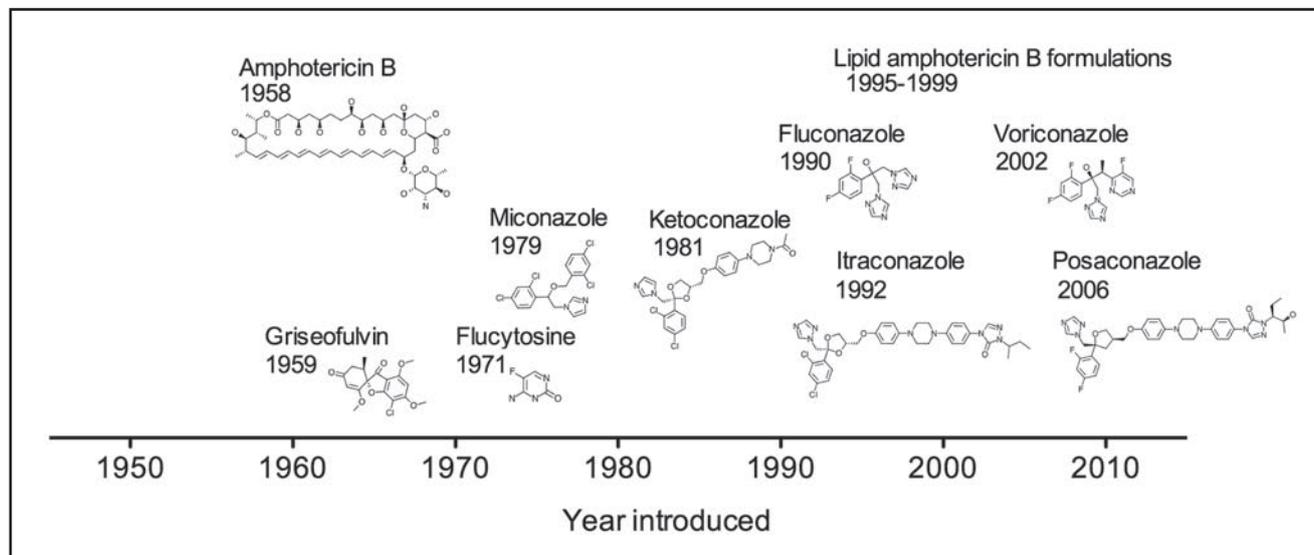


FIGURE 1. Timeline of systemic antifungal drugs.

similar to voriconazole and posaconazole, with less pharmacokinetic variability and drug interactions.<sup>14</sup> Efforts under way to reformulate the posaconazole suspension into better oral and intravenous dosage forms could address many of the drug's pharmacokinetic shortcomings.

The final milestone of antifungal drug discovery in the 20th century was the identification and development of echinocandin antifungal agents. Echinocandins are semisynthetic lipopeptides that inhibit synthesis of  $\beta$ -1,3-D-glucan in susceptible fungi, leading to damage of the fungal cell wall. Because a glucan-rich cell wall is a target not found in mammalian cells, these agents were predicted to be effective antifungal agents with very little collateral toxicity in mammalian cells—a prediction that has been proven true in clinical trials of patients with invasive candidiasis<sup>15-17</sup> and aspergillosis.<sup>18</sup> However, echinocandins still lack activity against some common opportunistic yeasts (*Cryptococcus* species) and less common molds (ie, *Fusarium*, *Scedosporium*, and Mucorales) that often develop as breakthrough infections in severely immunocompromised patients.

Therefore, although considerable progress has been achieved since the dawn of systemic antifungal therapy in the 1950s, the current antifungal armamentarium is far from perfect. No single antifungal agent is appropriate for all patients for a given mycosis because of patient-specific comorbid conditions, hypersensitivities, risk of drug interactions, immunosuppression, site of infection, and risk of infection with more intrinsically antifungal-resistant pathogens. This article reviews key aspects of the clinical pharmacology of older vs newer antifungal agents, with a particular emphasis on pharmacokinetic issues that arise

with newer agents and emerging data on toxicity with longer-term therapy.

#### OVERVIEW OF ANTIFUNGAL PHARMACOLOGY

Despite differences in the composition of the cell membrane and the presence of the cell wall, fungi are metabolically similar to mammalian cells and offer few pathogen-specific targets. Systemic antifungal agents can be generally grouped on the basis of their site of action in pathogenic fungi (Figure 2). Azole and polyene antifungal agents exert their antifungal effects by targeting ergosterol—the principal cell membrane sterol of many pathogenic fungi. By inhibiting  $14\alpha$ -demethylase (lanosterol demethylase), a fungal cytochrome P450 (CYP)-dependent enzyme, azole antifungal agents deplete cell membrane ergosterol, impair membrane fluidity, and lead to accumulation of toxic  $14\alpha$ -methylated sterols, resulting in growth arrest and eventual fungal cell death.<sup>19</sup> However, this inhibition is not entirely selective to fungi; indeed, collateral inhibition of human CYP enzymes by azoles is often responsible for pharmacokinetic drug-drug interactions. The fungal target for azole binding is a heme-containing pocket on the  $14\alpha$ -demethylase enzyme.<sup>20</sup> Differences in the conformation of the  $14\alpha$ -demethylase binding pocket and azole structure largely define the binding affinity of each drug, and in some fungal species, the potential for cross-resistance among triazoles.<sup>20</sup> For molecules derived from ketoconazole (ie, itraconazole, posaconazole), extension of the nonpolar side chains enhances azole binding to the  $14\alpha$ -demethylase apoprotein, resulting in an enhanced

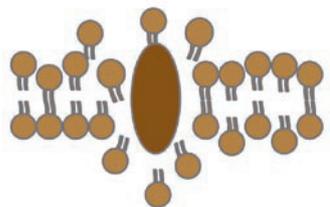
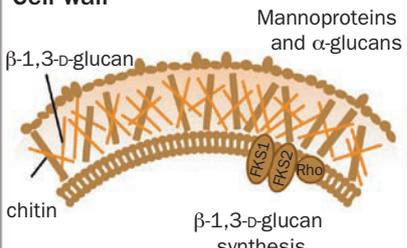
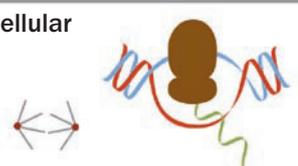
Mechanism	Drug class	Drugs
<b>Cell membrane</b>  <i>Ergosterol inhibitors/binders</i>	Azoles (14- $\alpha$ -demethylase inhibitors)	<b>Imidazoles</b> Ketoconazole, miconazole <b>Triazoles</b> Fluconazole, itraconazole, voriconazole, posaconazole, isavuconazole*
	Polyenes (ergosterol binding)	Amphotericin B
	Allylamines (squalene monooxygenase)	Terbinafine
<b>Cell wall</b>  Mannoproteins and $\alpha$ -glucans $\beta$ -1,3-D-glucan chitin $\beta$ -1,3-D-glucan synthesis FKS1, FKS2, Rho	Echinocandins ( $\beta$ -1,3-D-glucan synthesis inhibitors)	Anidulafungin, caspofungin, micafungin
<b>Intracellular</b> 	Pyrimidine analogues/ thymidylate synthase inhibitor	Flucytosine
	Mitotic inhibitor	Griseofulvin

FIGURE 2. Sites of action and mechanisms of systemic antifungal agents. FKS1, FKS2 catalytic subunits of the glucan synthase complex are the putative target binding site of echinocandins. Rho is a cell wall-regulating protein.

\*Isavuconazole is still in phase 3 trials.

spectrum of activity against molds (Figure 3).<sup>21</sup> Voriconazole, a derivative of fluconazole, possesses an  $\alpha$ -o-methyl group that confers activity against *Aspergillus* species and other filamentous fungi.<sup>21,22</sup> Resistance to triazole antifungal agents is most commonly the result of mutations in the azole binding pocket of 14 $\alpha$ -demethylase<sup>21,22</sup> and/or the overexpression of *MDR1* efflux pumps that expel fluconazole or the multidrug adenosine triphosphate-dependent efflux pumps *CDR1* and *CDR2*, which expel all triazoles, thereby leading to cross-resistance.<sup>3</sup> Because intrinsic resistance in *C krusei* is a result of impaired binding of fluconazole to 14 $\alpha$ -demethylase, newer triazoles with enhanced binding to the enzyme retain activity against fluconazole-resistant strains such as *C krusei*.<sup>23</sup> However, fluconazole resistance in *C glabrata* is frequently a result of the expression of multidrug efflux pumps; hence, cross-resistance may be observed with all azole antifungal agents.<sup>24</sup>

Similar to azole antifungal agents, the allylamine terbinafine inhibits ergosterol biosynthesis by inhibiting

squalene monooxygenase—an enzyme in fungi responsible for conversion of squalene to squalene epoxide, which is a precursor to lanosterol in the ergosterol synthesis pathway.<sup>20</sup> Although allylamines do not seem to have the same collateral effects on human CYP enzymes as azole antifungal agents, drugs such as rifampin that strongly induce CYP metabolism in mammals will increase the metabolism of terbinafine.<sup>25</sup> Once taken orally, terbinafine concentrates in the skin and nail beds and has relatively low bloodstream concentrations.<sup>26</sup> Consequently, its use as a systemic antifungal agent is primarily restricted to the treatment of onychomycosis and cutaneous fungal infections.<sup>26</sup>

The broad-spectrum polyene amphotericin B is the only other antifungal agent that targets the fungal cell membrane (Figure 2). Amphotericin B directly binds to ergosterol, forming complexes that intercalate the cell membrane, thereby resulting in pore formation and leakage of intracellular contents.<sup>27</sup> Amphotericin B has greater avidity for ergosterol-rich fungal cell membranes vs cholesterol-rich

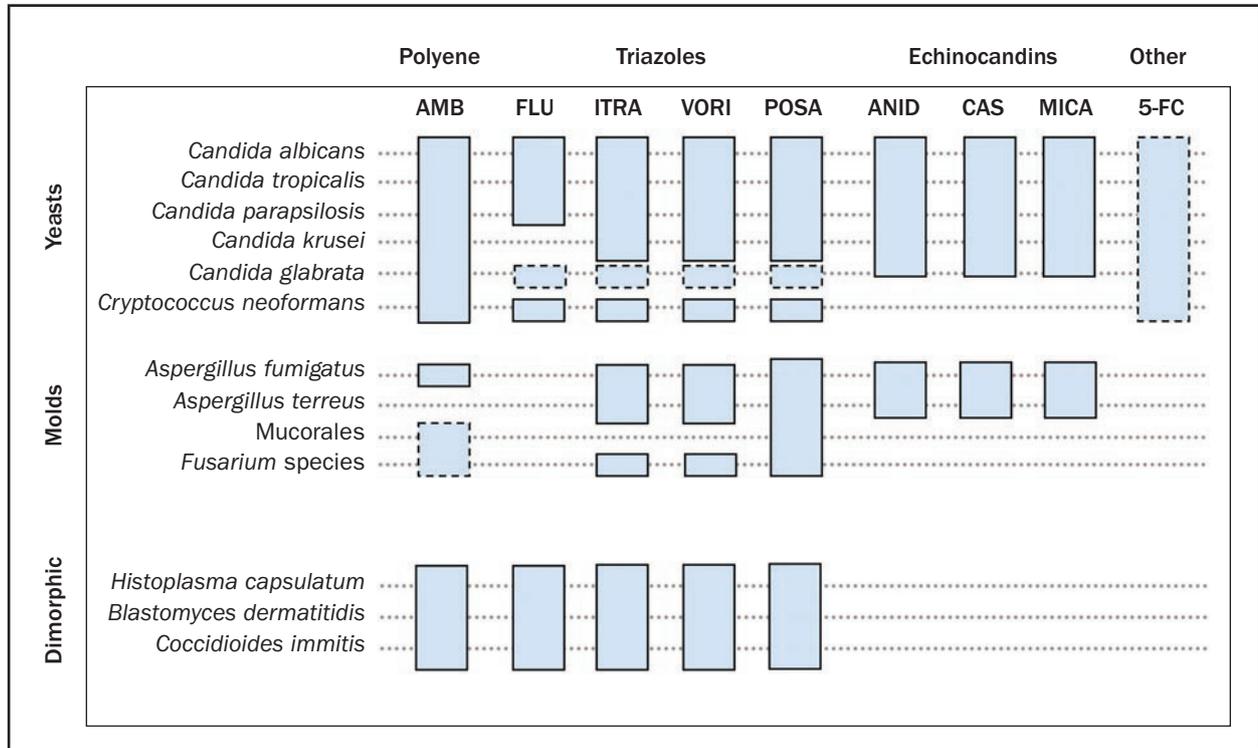


FIGURE 3. Spectrum of action of systemic antifungal agents. Solid blocks represent species in which the antifungal agent has demonstrated microbiological and clinical efficacy. Blocks with dotted lines indicate fungal genera/species in which resistance is common. AMB = amphotericin; ANID = anidulafungin; CAS = caspofungin; 5-FC = flucytosine; FLU = fluconazole; ITRA = itraconazole; MICA = micafungin; POSA = posaconazole; VORI = voriconazole.

mammalian cell membranes; however, this specificity may be lost when the drug accumulates to high concentrations in organs such as the kidney, where the drug causes direct damage to distal tubular membranes.<sup>28</sup> Consequently, nephrotoxicity is a common dose-limiting adverse effect of amphotericin B therapy. Amphotericin B also directly stimulates release of proinflammatory cytokines by mononuclear phagocytic cells, often resulting in fever, rigors, and chills during drug infusion.<sup>29,30</sup> This infusion reaction can be attenuated to varying degrees by reformulation of amphotericin B into lipid carriers. However, the principal advantage of lipid amphotericin B formulations are their reduced distribution of amphotericin B to the kidneys, which reduces but does not eliminate the nephrotoxicity of amphotericin B.<sup>31</sup> Two formulations of amphotericin B—a liposomal formulation and a lipid complex—are now commonly used to treat a wide range of invasive fungal infections. Although development of amphotericin B resistance during therapy is a rare clinical phenomenon, substitution of alternative cell wall sterols<sup>3,32</sup> and increased resistance to oxidative damage in the cell membrane through increased production of neutralizing enzymes<sup>33</sup> are 2 mechanisms that have been identified in clinical isolates exhibiting innate or acquired resistance to amphotericin B.

Of the antifungal agents currently in clinical use, echinocandins are the only ones that target the fungal cell wall by competitively inhibiting the synthesis of  $\beta$ -1,3-D-glucan polymers—key cross-linking structural components of the cell wall in some pathogenic fungi (Figure 2).<sup>34</sup> Echinocandins bind to the  $\beta$ -1,3-D-glucan synthase enzyme complex in susceptible fungi, resulting in a glucan-depleted cell wall that is susceptible to osmotic lysis, especially in rapidly growing cells.<sup>35</sup> The degree of  $\beta$ -1,3-D-glucan polymerization in the fungal cell wall and the expression of the glucan synthase enzyme target largely define the spectrum of this antifungal class, which is generally considered to have fungicidal activity against *Candida* species and fungistatic activity against *Aspergillus* species (Figure 3).<sup>36</sup> Although bona fide echinocandin resistance remains a relatively rare clinical phenomenon, mutations in defined “hot spot” regions of the *FKS1* and *FKS2* catalytic subunits of the glucan synthase are associated with reduced echinocandin inhibitory activity against the enzyme, higher minimum inhibitory concentrations (MICs), and an increased risk of treatment failure.<sup>37</sup>

Two groups of antifungal agents selectively target intracellular processes in fungi via mechanisms analogous to

TABLE 1. Comparative Pharmacokinetic and Pharmacodynamic Properties of Systemic Antifungal Agents<sup>a</sup>

Drug	Typical adult dosing	Oral bioavailability	C <sub>max</sub> (µg/mL)	AUC (mg × h/L)	Protein (%)	CSF (%)	Vitreous (%)	Urine (%)	Metabolism	Elimination	T <sub>1/2</sub> (h)	PK:PD (total drug unless indicated)
AMB	0.6-1.0 mg/kg/d	<5	0.5-2.0	17.0	>95.0	0-4	0-38 <sup>b,c</sup>	3-20	Minimal	Feces	50	C <sub>max</sub> :MIC 4-10 or AUC:MIC >100
ABCD	4 mg/kg/d	<5	4.0	43.0	>95.0	<5	0-38 <sup>b,c</sup>	<5	Minimal	ND	30	ND
ABLC	5 mg/kg/d	<5	1.7	14.0	>95.0	<5	0-38 <sup>b,c</sup>	<5	Minimal	ND	173	C <sub>max</sub> :MIC >40 or AUC:MIC >100
LAMB	3-5 mg/kg/d	<5	83	555	>95.0	<5	0-38 <sup>b,c</sup>	5	Minimal urine; feces	Minor	100-153	C <sub>max</sub> :MIC >40 or AUC:MIC >100
FLU	6-12 mg/kg/d	>90	6-20	400-800	10.0	>60	28-75 <sup>b,c</sup>	90	Minor hepatic	Renal	31	AUC:MIC >25
ITRA <sup>d</sup>	200 mg twice daily	50	0.5-2.3	29.2	99.8	<10	10 <sup>b</sup>	1-10	Hepatic	Hepatic	24	AUC:MIC >25
VOR	6 mg/kg every 12 h for 2 doses, then 4 mg/kg every 12 h	>90	3.0-4.6	20.3	58.0	60	38 <sup>b,c</sup>	<2	Hepatic	Renal	6	AUC:MIC >25
POS	600-800 mg/d in divided doses	ND	1.5-2.2	8.9	99.0	ND	26 <sup>b,c</sup>	<2	Modest hepatic	Feces	25	AUC:MIC >400 (8-25 free drug)
ANI <sup>e</sup>	200 mg × 1 loading dose, then 100 mg/d	<5	6-7	99	84.0	<5	0 <sup>c</sup>	<2	None	Feces	26	C <sub>max</sub> :MIC >10 or serum (unbound) AUC:MIC >20
CAS	70-mg loading dose, then 50 mg/d	<5	8-10	119	97.0	<5	0 <sup>b</sup>	<2	Hepatic	Urine	30	C <sub>max</sub> :MIC >10 or serum (unbound) AUC:MIC >20
MICA <sup>b</sup>	100-150 mg/d; 50 mg/d (prophylaxis)	<5	10-16	158	99.0	<5	<1 <sup>c</sup>	<2	Hepatic	Feces	15	C <sub>max</sub> :MIC >10 or serum (unbound) AUC:MIC >20
5-FC	100 mg/kg/d in divided doses	80	30-40	30-62	4.0	60-100	49 <sup>c</sup>	90	Minor intestinal	Renal	3-6	Time > MIC 20%-40%

<sup>a</sup> ABCD = amphotericin B colloidal dispersion; ABLC = amphotericin lipid complex; AMB = amphotericin B; ANI = anidulafungin; AUC = area under the curve; CAS = caspofungin; C<sub>max</sub> = maximum concentration; CSF = cerebrospinal fluid; 5-FC = flucytosine; FLU = fluconazole; ITRA = itraconazole; LAMB = liposomal AMB; MIC = minimum inhibitory concentration; MICA = micafungin; ND = not determined; PK-PD = pharmacokinetics-pharmacodynamics; POS = posaconazole; VOR = voriconazole; T<sub>1/2</sub> = half-life.

<sup>b</sup> Data derived from human studies.

<sup>c</sup> Data derived from animal studies.

<sup>d</sup> Oral solution formulation.

<sup>e</sup> Data are for the 100-mg dose.

those of cancer chemotherapeutic agents and are generally not effective as monotherapy for systemic mycoses (Figure 2). Flucytosine (5-FC) is selectively taken up by 2 fungus-specific enzymes, cytosine permease and cytosine deaminase, and is converted to cytostatic 5-fluorouracil in fungal cells, where the active drug inhibits thymidylate synthase and causes RNA miscoding.<sup>28,38</sup> However, resident intestinal bacterial flora in the human gut can convert 5-FC to 5-fluorouracil, resulting in nausea, vomiting, diarrhea, and bone marrow suppression.<sup>28,39</sup> Flucytosine is primarily active against yeasts but must be given in combination with other drugs to avoid resistance that arises with mutations in cytosine permease and cytosine deaminase, resulting in decreased importation and conversion of the drug to its active form (Figure 3).<sup>39</sup> Griseofulvin is a systemic antifungal agent that binds to tubulin, interfering with microtubule formation. Because the drug concentrates in keratinocytes, it is

only used for noninvasive dermatophyte infections. Interestingly, griseofulvin inhibits the proliferation of many types of cancer cells in vitro, which has led to renewed interest in this agent as a potential adjunctive treatment for breast cancer.

## PHARMACOKINETIC CONSIDERATIONS

Besides spectrum of activity, antifungal pharmacokinetic properties are often the most important consideration in drug selection because impaired GI tract function or reduced renal/hepatic drug clearance can profoundly influence the safety and efficacy of antifungal therapy. Key pharmacokinetic characteristics of systemic antifungal agents are summarized in Table 1.

Several classes of antifungal agents must be administered intravenously, including amphotericin B and the echinocandins, because these agents are not sufficiently

TABLE 2. **Cytochrome P450 (CYP) Inhibition Profile of Triazole Antifungal Agents**

Mechanism	Fluconazole	Itraconazole	Posaconazole	Voriconazole
<b>Inhibitor</b>				
CYP2C19	+	-	-	+++
CYP2C9	++	+	-	++
CYP3A4	++	+++	+++	++
<b>Substrate</b>				
CYP2C19	-	-	-	+++
CYP2C9	-	-	-	+
CYP3A4	+	+++	-	+

- = no activity; + = minimal activity; ++ = moderate activity; +++ = strong activity.

Data are derived from reference 57.

absorbed from the GI tract. This problem has been solved with the introduction of triazole antifungal agents; however, the degree of absorption varies considerably from one drug to the next (Table 1). Fluconazole and voriconazole both have oral bioavailability exceeding 90% and can be administered without regard to food (fluconazole) or preferably on an empty stomach (voriconazole).<sup>40</sup> Itraconazole capsules and posaconazole suspension require food to prolong gastric residence time to enhance drug dissolution, which is not an issue with the oral cyclodextrin formulation of itraconazole that is administered on an empty stomach. However, patients may prefer to take itraconazole solution with food because of GI intolerance and the unpalatable aftertaste of the solution.<sup>41</sup>

The oral absorption of a posaconazole suspension can be unpredictable in patients with poor appetite, nausea, diarrhea, and GI dysfunction associated with cancer chemotherapy (mucositis) or transplant (graft-vs-host disease involving the gut, colitis) or in patients taking acid suppression therapy, especially with potent agents such as proton pump inhibitors.<sup>42,43</sup> Absorption of posaconazole is dose limited at 800 mg/d but can be maximized when the drug is administered with a high-fat (>50% of the calories from fat) food or nutritional supplement.<sup>44</sup> Administration of the drug in divided doses improved the exposure by 180% compared with a single daily dose.<sup>42,45</sup> Therefore, posaconazole is usually initiated at doses of 200 mg 3 to 4 times daily with food in patients with suspected or documented infections until infection stabilizes or adequate serum levels can be verified (see Therapeutic Drug Monitoring section). Dosing can then be transitioned to 400 mg twice daily. Inadequate posaconazole concentrations are better addressed with clinical approaches that improve drug dissolution and absorption (eg, administration with acidic cola or fruit juice or a high-fat meal, discontinuation of acid suppression therapy) than increasing drug doses above 800 mg/d.

Unlike posaconazole, genetic variability in metabolism plays a more important role in the patient-to-patient phar-

macokinetic variability of voriconazole.<sup>46</sup> Polymorphisms in the CYP2C19-encoding gene result in 3 populations of patients with markedly different rates of nonlinear voriconazole clearance despite the administration of the same fixed daily dose: (1) homozygous patients who extensively metabolize voriconazole, (2) heterozygous patients with moderate clearance rates of voriconazole, and (3) homozygous patients who metabolize drug poorly through this pathway and have slow rates of voriconazole clearance.<sup>47</sup> The poor metabolism genotype is more common in some ethnic groups, such as patients of Asian or Pan-Pacific origin (14%-19%), than in patients of African origin or whites (2%).<sup>47</sup> In contrast, pediatric patients often exhibit more rapid linear clearance of voriconazole, which may result in low or undetectable serum drug concentrations at standard adult doses.<sup>48,49</sup> Therefore, higher weight-based doses are recommended in children (7 mg/kg every 12 hours, sometimes increased up to 12 mg/kg every 12 hours without a loading dose) (Table 1).

Drug interactions are another important cause of pharmacokinetic variability because coadministration of any triazole or caspofungin with potent inducers of phase 1 (CYP) and phase 2 metabolism (ie, rifampin, phenytoin) can potentially result in low (fluconazole, caspofungin, posaconazole) or undetectable (itraconazole, voriconazole) bloodstream concentrations of the antifungal agent and an increased risk of treatment failure.<sup>50</sup> In the case of itraconazole, voriconazole, and posaconazole, interactions with potent inducers of CYP3A4 cannot always be overcome with higher antifungal drug doses.<sup>51-54</sup>

Pharmacokinetic drug-drug interactions are further compounded by the fact that some antifungal agents inhibit the clearance or metabolism of other drugs. Nephrotoxicity associated with amphotericin B therapy (often accelerated by calcineurin inhibitors, aminoglycosides, intravenous radiocontrast agents, foscarnet, or aggressive diuresis) will reduce the clearance of other renally eliminated drugs.<sup>55</sup> Pharmacokinetic drug-drug interactions are most problematic, however, with triazole antifungal agents because all of these agents inhibit human CYP enzymes to varying degrees (Table 2).<sup>56,57</sup> These interactions can be dangerous if not anticipated in patients receiving drugs with a narrow therapeutic index, such as chemotherapeutic agents, immunosuppressants, and some cardiovascular medications. Although a detailed discussion of drug interactions is beyond the scope of this review, several recent reviews have been published on this topic.<sup>50,57-59</sup>

Finally, the site of infection is an important consideration in the selection of antifungal therapy because some antifungal agents have limited distribution to anatomically privileged sites, such as the central nervous system and vitreous fluid, or, in the case of oral itraconazole and

posaconazole, may not achieve sufficient concentrations in the bloodstream to treat hematogenous infection (Table 1). Fungal infections involving the central nervous system are notoriously difficult to treat, and many antifungal agents have high molecular weights and a large degree of protein binding that limit their ability to penetrate the blood-brain barrier.<sup>60,61</sup> Of the currently available antifungal agents, 5-FC, fluconazole, and voriconazole have the best penetration in the cerebrospinal fluid and vitreous chamber of the eye.<sup>62</sup> However, liposomal amphotericin B and perhaps other triazoles and echinocandins may still achieve concentrations in the brain parenchyma sufficient to be clinically effective.<sup>28,63</sup> Lipid formulations of amphotericin B, newer triazole antifungal agents, and echinocandins have no role in the treatment of candiduria because only small amounts of microbiologically active drug are excreted in the urine.<sup>58</sup>

### PHARMACODYNAMIC CONSIDERATIONS

Similar to antibacterial agents, antifungal agents display different patterns of activity in vivo (ie, concentration-independent or concentration-dependent as determined by the shape of the dose-response curve at clinically achieved concentrations).<sup>64</sup> These patterns of activity in vivo can often be correlated with the drug dose and the pathogen MIC to identify dosing strategies that maximize antifungal efficacy while reducing the risk of toxicity. Pharmacodynamic data may also be useful for predicting sites of infection where antifungal drugs have a higher risk of treatment failure (ie, cerebrospinal fluid, vitreous fluid, urine) because inadequate distribution leads to ineffective drug concentrations.

Flucytosine displays concentration-independent pharmacodynamic characteristics in vitro and in vivo against *Candida* and *Cryptococcus* species; ie, increases in serum drug concentrations above the pathogen MIC do not appreciably increase the rate or extent of fungal killing.<sup>65</sup> In dose fractionation studies in animals, the ability of a dosage regimen to maintain serum drug concentrations above the MIC (percent of time greater than MIC of 20%-40%) was the best predictor of 5-FC activity against *Candida albicans*.<sup>65</sup> This realization led in part to studies that used lower doses of 5-FC (100 mg/kg daily) in combination with higher amphotericin B treatment doses for cryptococcal meningitis, even though pharmacodynamic data for 5-FC in the treatment of *Cryptococcus neoformans* are limited.<sup>66</sup>

Both in vitro and in vivo amphotericin B and lipid amphotericin B formulations generally display concentration-dependent fungicidal activity that begins to plateau once concentrations surpass the MIC of the infecting pathogen by 4- to 10-fold.<sup>67,68</sup> Animal models<sup>69</sup> and limited clinical

data<sup>70</sup> suggest that a ratio of maximum concentration in serum to MIC of greater than 40 is associated with a higher probability of treatment response with liposomal amphotericin B. For most adults, standard liposomal amphotericin B doses of 3 to 5 mg/kg should surpass the maximum concentration to MIC ratio of 40 unless the pathogen has an MIC of 2 µg/mL or greater. Moreover, a recent study that examined the benefits of dosage escalation to 10 mg/kg daily of liposomal amphotericin B in patients with proven or probable aspergillosis found that the escalated dosage provided no benefit over the 3 mg/kg daily dosage and nearly doubled the rate of nephrotoxicity and severe hypokalemia.<sup>71</sup>

The concentration-dependent activity of echinocandins against *Candida*<sup>72,73</sup> and *Aspergillus*<sup>74</sup> species is optimized when the free-drug (non-protein-bound) serum area under the curve (AUC):MIC ratio approaches 20 for *C albicans* or 7 for less virulent isolates of *C glabrata* and *Candida parapsilosis*.<sup>72</sup> These pharmacokinetic-pharmacodynamic targets are generally achieved with currently recommended echinocandin dosages for greater than 90% of isolates with MICs less than 0.5<sup>75</sup> (Table 1). However, initial echinocandin breakpoints for defining nonsusceptible MICs were set at greater than 2 µg/mL, suggesting that a portion of isolates with MICs of 1 to 2 µg/mL that are classified as "susceptible" may not be treatable with currently recommended echinocandin dosages.<sup>75</sup> A reassessment of echinocandin breakpoints on the basis of analysis of resistant isolates and molecular-biochemical resistance mechanisms suggested that nonsusceptibility breakpoints should be lowered to 0.25 µg/mL for susceptible, 0.5 µg/mL for intermediate, and 1 µg/mL for resistant *C albicans*, with breakpoints of less than 2 µg/mL, 4 µg/mL, and greater than 8 µg/mL for susceptible, intermediate, and resistant *C parapsilosis*, respectively.<sup>75</sup>

Triazole antifungal agents have perhaps the largest body of experimental and clinical literature establishing a correlation between drug dose, organism MIC, and outcome.<sup>76</sup> Experimental studies in animals and clinical studies with fluconazole in the treatment of mucosal and invasive candidiasis suggest that achieving a serum free-drug AUC:MIC ratio of greater than 25 is the parameter most closely linked to successful treatment.<sup>76-78</sup> Although less data are available for other triazoles and mold infections, studies in animal models of aspergillosis also suggest that the AUC:MIC ratio is the best predictor of treatment response to posaconazole, with 50% survival at total-drug AUC:MIC ratios of 100 to 150 and maximal responses at a ratio greater than 440 (free-drug AUC:MIC ratio of approximately 8-25).<sup>79,80</sup>

Clinical trial data for candidal infections have suggested that this pharmacokinetic-pharmacodynamic relationship may be helpful for predicting treatment efficacy in

humans<sup>77,81-83</sup> and have formed the basis for susceptibility testing breakpoints in *Candida* species. For example, isolates with fluconazole MICs of 16 or greater would be difficult to treat with a standard dosage of 6 mg/kg daily (ie, 400 mg dose with an AUC of 400 µg/h per liter) because the AUC:MIC falls below 25 at this MIC with the standard dosage. Therefore, isolates with fluconazole MICs of 16 to 32 µg/mL are categorized as “susceptible-dose dependent” instead of “intermediate” because they may still be treatable provided higher daily dosages of fluconazole are used (ie, 12 mg/kg daily or approximately 800 mg/d). *Candida* isolates with MICs greater than 64 µg/mL would require fluconazole dosages of 1600 mg/d or greater and therefore are classified as “resistant.”<sup>83</sup> Recent studies using epidemiological cut-off analysis of wild-type susceptible and fluconazole-resistant *Candida* species, however, have prompted reconsideration of these pharmacodynamics-driven breakpoints because they may not be sufficiently sensitive to detect emerging resistance, especially among non-*C glabrata* isolates.<sup>84</sup> Therefore, new species-specific MIC breakpoints for fluconazole have been proposed for *C albicans*, *C parapsilosis*, and *Candida tropicalis* (susceptible, ≤2 µg/mL; susceptible-dose dependent, 4 µg/mL; resistant, ≥8 µg/mL) while maintaining current breakpoints for *C glabrata* (susceptible-dose dependent, ≤32 µg/mL; resistant ≤64 µg/mL).<sup>84</sup>

### THERAPEUTIC DRUG MONITORING OF ANTIFUNGAL AGENTS

Because some antifungal agents exhibit marked variability in bloodstream concentrations that are difficult to predict on the basis of dosing alone, recent treatment guidelines and expert reviews<sup>85-88</sup> have recommended therapeutic drug monitoring (TDM) for some antifungal agents in select patient populations. Therapeutic drug monitoring has long played an important role in improving the safety of 5-FC because the drug is frequently administered with nephrotoxic agents such as amphotericin B that cause wide fluctuations in drug clearance. Bone marrow suppression and hepatotoxicity are the most common dose-limiting toxicities of 5-FC and have been strongly linked to serum peak concentrations greater than 100 µg/mL. In an analysis of 1000 5-FC concentrations from 233 patients with invasive fungal infections, only 20% of patients were found to have “therapeutic” serum concentrations, 5% had undetectable levels, and 39% had serum concentrations that are generally considered to be toxic (>100 µg/mL).<sup>89</sup> Therefore, standard weight-based dosages of 5-FC (100 mg/kg daily) should be individualized on the basis of the patient’s renal function and serum 5-FC levels, which are determined 2 hours after the ad-

ministration of an oral dose.<sup>86,89</sup> Target blood concentrations should fall between 20 to 50 µg/mL and be checked during the first week of therapy and 1 to 2 times weekly thereafter if the patient is receiving other nephrotoxic agents or has fluctuations in renal function.<sup>86</sup>

Mold-active triazole antifungal agents (itraconazole, voriconazole, and posaconazole) are the other antifungal class most frequently recommended for TDM because of erratic absorption (itraconazole and posaconazole), variable hepatic clearance (voriconazole), and propensity for multiple drug interactions.<sup>86</sup> Several studies have examined the association between itraconazole efficacy and serum drug levels when the drug is administered as prophylaxis<sup>90,91</sup> or for the treatment<sup>5,92-94</sup> of documented infections due to *Candida*, *Aspergillus*, *Cryptococcus*, and *Coccidioides immitis*. All of these studies found a higher probability of treatment response when serum trough concentrations determined by bioassay surpassed 6 µg/mL (>1-2 µg/mL by high-performance liquid chromatography). According to studies by Glasmacher et al<sup>90,91</sup> in patients with hematologic malignancy receiving itraconazole prophylaxis, patients who did not achieve trough concentrations of greater than 0.5 µg/mL (determined by high-performance liquid chromatography) by the first week were at significantly higher risk of subsequent breakthrough aspergillosis. A recent analysis of the association between itraconazole serum concentrations and toxicity reported that serum concentrations greater than 5 µg/mL (determined by high-performance liquid chromatography) or 17 µg/mL (determined by bioassay) were associated with an increased risk of GI adverse effects and peripheral edema.<sup>95</sup>

Voriconazole serum concentrations may vary up to 100-fold from one patient to the next depending on age, drug dose, concurrent illness, underlying liver function, drug-drug interactions, and genetic polymorphisms affecting CYP2C19 metabolism.<sup>46</sup> Pharmacokinetic variability can be especially problematic in patients undergoing hematopoietic or solid organ transplant because these patients have multiple concomitant conditions affecting voriconazole clearance and are at higher risk of severe drug interactions.<sup>96,97</sup>

Common adverse effects reported with voriconazole (ie, photopsia, liver function test abnormalities) can be retrospectively correlated with serum drug concentrations, but data are conflicting as to whether specific threshold serum voriconazole concentrations are *predictive* of toxicity. For example, an analysis of the association between hepatotoxicity and serum voriconazole concentrations from phase 3 clinical trials revealed the odds of a greater than 3 times the upper limit of normal increase in levels of aspartate aminotransferase, alkaline phosphatase, and

bilirubin to be 13.1%, 16.5%, and 17.2%, respectively, for every 1- $\mu\text{g}/\text{mL}$  increase in voriconazole plasma concentrations, especially in recipients of hematopoietic stem cell transplants.<sup>98</sup> However, no single concentration was *predictive* of subsequent hepatotoxicity by receiver operator curve analysis, suggesting that elevated voriconazole concentrations were a consequence (not necessarily a cause) of hepatic dysfunction. Although less common toxicities have been reported in the setting of high voriconazole exposures (eg, encephalopathy, hallucinations, hypoglycemia, electrolyte disturbances, pneumonitis), their association with plasma voriconazole concentrations are less well established.

A stronger case for TDM of voriconazole can be made on the basis of clinical efficacy because inadequate drug exposures that cannot be predicted on the basis of dose alone could increase the probability of treatment failure. Exploratory pharmacokinetic-pharmacodynamic analysis of 3736 plasma samples from 1053 patients enrolled in voriconazole therapeutic studies found that the rate of treatment success appeared proportionately lower in patients with mean plasma concentrations less than 0.5  $\mu\text{g}/\text{mL}$  than in patients with concentrations between 0.5 and 5  $\mu\text{g}/\text{mL}$ .<sup>99</sup> The difference in clinical outcome was not statistically significant, however, because of the heterogeneous response rates in each quartile of drug exposure—a reflection of the varied response rate among different patient groups included in the analysis (ie, those receiving transplants, those with lymphoma, those with leukemia). Similarly, patients with possible or proven invasive aspergillosis who have random voriconazole serum concentrations less than 2.05  $\mu\text{g}/\text{mL}$  were shown to have poorer treatment responses.<sup>100</sup> Subsequent studies in adults<sup>101</sup> and pediatric patients<sup>48</sup> have also demonstrated that the probability of successful outcome while receiving voriconazole therapy declines when trough serum concentrations in patients are less than 1  $\mu\text{g}/\text{mL}$ . Therefore, many experts currently recommend dosing voriconazole to achieve trough concentrations of 1 to 5  $\mu\text{g}/\text{mL}$ .<sup>86</sup>

Collectively, most data from single-institution studies and randomized trials suggest that nearly one-third of patients who receive voriconazole at currently approved dosing may be at increased risk of therapeutic failure due to suboptimal drug exposures.<sup>86</sup> The absolute threshold voriconazole concentration (ie, 0.5, 1.0, or 2.0  $\mu\text{g}/\text{mL}$ ) required for clinical efficacy is not well established and probably varies by infecting pathogen. However, trough concentrations of less than 0.5  $\mu\text{g}/\text{mL}$  in patients receiving voriconazole prophylaxis, or trough concentrations of less than 1 to 2  $\mu\text{g}/\text{mL}$  in patients receiving treatment for suspected or documented infection, should prompt an increase in the voriconazole dose by 50- to

100-mg increments or a switch to an alternative agent(s), especially if there is evidence of progressing infection.<sup>86</sup>

Risk factors for impaired posaconazole absorption and suboptimal serum concentrations include graft-vs-host disease of the gut or chemotherapy-associated mucositis, severe nausea and/or diarrhea, poor appetite, and treatment with potent acid suppression therapy or inducers of hepatic phase 1/2 metabolism.<sup>42,102-105</sup> In 2 pivotal phase 3 trials that evaluated the effectiveness of posaconazole (200 mg 3 times daily) as antifungal prophylaxis in patients with graft-vs-host disease after hematopoietic stem cell transplant<sup>13</sup> or with neutropenia after remission induction chemotherapy for acute myeloid leukemia/myeloid dysplastic syndrome,<sup>12</sup> the probability of breakthrough infections while receiving posaconazole therapy increased significantly when random plasma concentrations fell below 0.719  $\mu\text{g}/\text{mL}$ .<sup>106</sup> Similarly, in an open-label study evaluating posaconazole as salvage therapy for invasive aspergillosis,<sup>105</sup> the highest clinical response rates were observed in a cohort of patients who had plasma posaconazole exposures of at least 0.719 to 1.250  $\mu\text{g}/\text{mL}$ .

Taken together, these studies indicate that plasma concentrations of posaconazole may serve as a useful surrogate end point for identifying patients at higher risk of drug failure due to inadequate drug absorption. In the absence of more definitive data, trough concentrations greater than 0.5  $\mu\text{g}/\text{mL}$  could be considered a practical provisional target trough concentration for patients receiving posaconazole prophylaxis, with targets of 0.5 to 1.5  $\mu\text{g}/\text{mL}$  for patients with documented mold infections.<sup>86</sup>

The frequency and timing of serum sampling for triazole TDM is not well established. Sampling of the trough concentration (immediately before the next dose) once the patient reaches steady state (5-7 days into therapy) is the most practical approach and is less prone to sampling error.<sup>86,87</sup> Trough concentrations do not provide sufficient information about drug absorption or AUC but can help identify patients with overall low exposures and excessively rapid drug clearance.<sup>87</sup> For drugs such as posaconazole that have a long half-life but are administered in divided daily doses, the serum concentration curve is relatively flat, so even random samples can identify patients with suboptimal plasma concentrations because of poor drug absorption.

## TOXICITIES OF ANTIFUNGAL AGENTS

Although the safety and tolerability of systemic antifungal therapy has improved considerably, a growing proportion of heavily immunocompromised patients are receiving systemic antifungal agents for progressively longer treatment

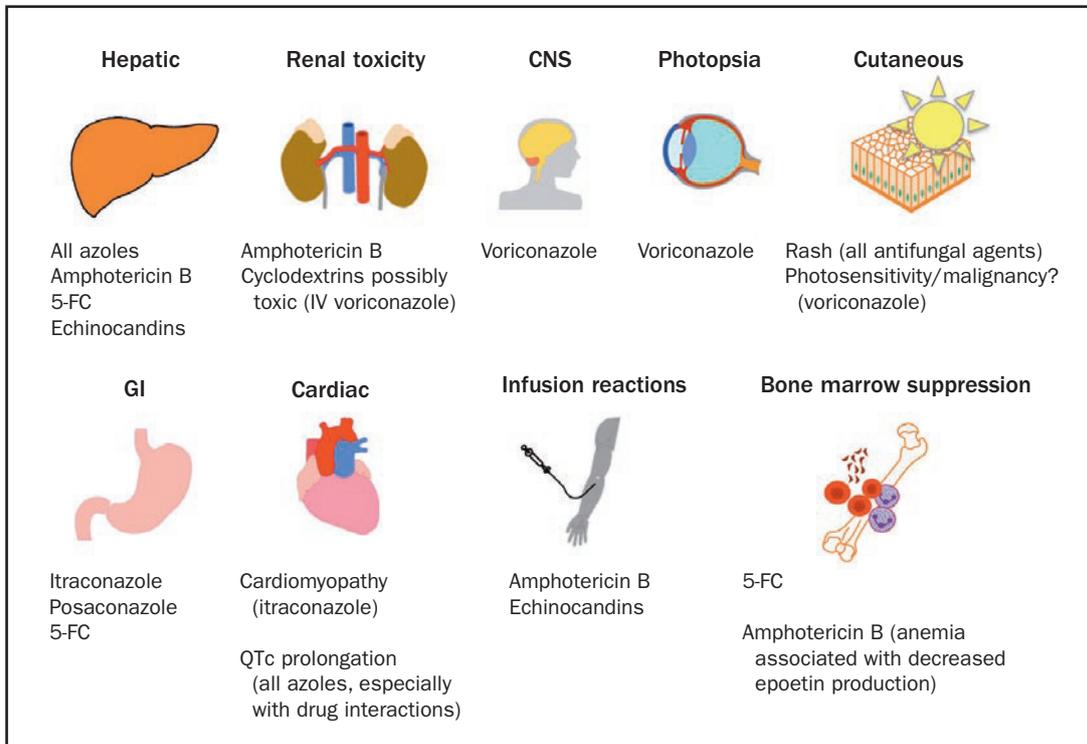


FIGURE 4. Common toxicities of antifungal agents. CNS = central nervous system; 5-FC = flucytosine; GI = gastrointestinal; IV = intravenous; QTc = corrected QT interval.

courses. As a result, clinicians need to be aware of not only the more familiar dose-limiting toxicities associated with systemic antifungal agents (ie, infusion-related toxicities and nephrotoxicity with amphotericin B, hepatotoxicity with triazole antifungal agents) but also longer-term risks, including recurrent drug interactions, organ dysfunction, and cutaneous reactions and malignancies<sup>31,50</sup> (Figure 4). Oral itraconazole can cause nausea and GI disturbances associated with the cyclodextrin excipient, making it difficult to tolerate for prolonged treatment courses. Itraconazole has also been described as causing (mostly in older adults) a unique triad of hypertension, hypokalemia, and edema that may be related to a negative inotropic effect of the drug or adrenal suppression.<sup>107</sup> Therefore, prolonged administration of itraconazole is not recommended in patients with a history of heart failure.

Although rash is reported with all antifungal classes in 5% to 15% of patients, voriconazole treatment in ambulatory patients has been associated with unique retinoid-like phototoxic reactions that present with cheilitis, erythema, and occasional blistering.<sup>108</sup> This phototoxic reaction is not prevented through the use of sunscreens but is generally reversible after discontinuation of therapy. However, recent reports have linked this phototoxic reaction to the subsequent development of squamous

cell carcinoma<sup>109</sup> and melanoma,<sup>108</sup> suggesting that all patients who receive long-term voriconazole treatment should undergo careful screening for skin cancer, especially if they manifest evidence of photosensitivity or cutaneous photodamage.

## CONCLUSION

The introduction of new systemic antifungal agents during the past decade has revolutionized the treatment of invasive mycoses. However, with these new therapies comes a need for increased awareness of the limitations in their spectrum of activity, pharmacokinetics, and risk for pharmacokinetic drug interactions. Newer broad-spectrum triazoles, in particular voriconazole and posaconazole, display significant variability in bloodstream concentrations from one patient to the next that may necessitate TDM in select situations to guide drug therapy and dosing. Long-term toxicities have become more of a concern because ambulatory patients with long-term immunosuppression are taking antifungal therapies for prolonged periods. For most patients, however, the benefits of safer and more effective antifungal therapy vastly outweigh the manageable risks of developing toxicity and undertreating a life-threatening systemic fungal infection.

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