Introduction to Antifungal Drugs

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In the United States, only 10 antifungal drugs are currently approved by the Food and Drug Administration (FDA) for the therapy of systemic fungal infections. As shown in table 1, these drugs belong to 3 principal classes: polyenes, pyrimidines, and azoles. Drugs that belong to other classes are also approved as topical antifungal drugs, but will not be considered further here.

Although conventional amphotericin B (Fungizone) remains the standard therapy for many invasive or life-threatening mycoses, this polyene drug is associated with significant toxicity, including infusion-related events, such as chills, fever, headache, nausea and vomiting, and dose-limiting nephrotoxicity [1]. In addition, the clinical efficacy of amphotericin B in some settings (e.g., mold disease such as invasive aspergillosis in severely immunocompromised patients) is suboptimal.

Consequently, 3 new lipid formulations of amphotericin B (amphotericin B lipid complex, amphotericin B cholesteryl sulfate, and liposomal amphotericin B) have been developed and recently approved by the FDA. These lipid formulations offer several advantages over conventional amphotericin B, including increased daily dose of the parent drug (up to 10-fold), high tissue concentrations in the primary reticuloendothelial organs (lungs, liver, and spleen), decrease in infusion-associated side effects (especially liposomal amphotericin B), and marked decrease in nephrotoxicity [2–3]. Although the therapeutic : toxic ratio of these compounds is clearly improved, superiority in clinical efficacy has not been definitively established in head-to-head comparative trials, either a lipid formulation versus conventional amphotericin B or 1 lipid formulation versus another lipid formulation [4–11]. Moreover, these lipid formulations of amphotericin B are considerably more expensive than conventional amphotericin B, ranging from 10- to 20-fold higher in cost per dose [3]. In addition, the optimum daily or total dose of these lipid compounds has not been established.

Accordingly, unanswered questions and controversy abound about several issues relating to these 3 lipid agents [11]. For example, is 1 drug superior by pharmacologic and efficacy parameters to the other 2 drugs? What is the appropriate indication(s) to justify initiation of therapy with 1 of the lipid formulations rather than conventional amphotericin B? What is the most appropriate initial dose? Does the dose differ for each of the 3 drugs? Do pharmacoeconomic parameters justify the higher cost of the lipid formulations?

Although studies aimed at providing answers to these and related questions are forthcoming, infectious disease physicians and others who treat systemic fungal diseases must keep in mind current FDA approved indications for these new drugs. All 3, amphotericin B lipid complex, amphotericin B cholesteryl sulfate, and liposomal amphotericin B, are indicated for patients with systemic mycoses, primarily invasive aspergillosis, who are intolerant of or refractory to conventional amphotericin B, defined as follows: (1) development of renal dysfunction (serum Cr >2.5 mg/dL) during antifungal therapy; (2) severe or persistent infusion-related adverse events despite premedication or comedication regimens; and (3) disease progression after ⩾500 mg total dose of amphotericin B. In addition, liposomal amphotericin B is approved as empiric therapy for the neutropenic patient who has persistent fever, despite broad spectrum antibiotic therapy [9]. However, there is no consensus among authorities about preference for lipid-based amphotericin B over conventional amphotericin B as initial therapy in this setting. Pharmacoeconomic data are especially needed for guidance here.

For patients who require treatment with amphotericin B for proven or probable systemic fungal disease but have preexisting renal dysfunction (serum creatinine >2.5 mg/dL), most infectious disease experts advocate a lipid formulation of amphotericin B as initial therapy. For the majority of patients with systemic candidiasis, cryptococcosis and the endemic mycoses (blastomycosis, histoplasmosis, coccidioidomycosis, and paracoccidioidomycosis), initial treatment with lipid-based amphotericin B drug cannot be justified. In such patients, conventional amphotericin B or an azole drug is the initial treatment of choice. For immunocompromised patients with invasive, life-threatening mold disease (e.g., aspergillosis and zygomycosis), controversy persists among experts about initial therapy. Some authorities initiate therapy with a lipid-based formulation of amphotericin B, regardless of the status of the patient's renal function, whereas other authorities initiate therapy with conventional amphotericin B and switch to a lipid formulation only for patients who are intolerant of or refractory to it. For more detailed information about indications for the lipid-based drugs, the reader should see the specific disease-focused guideline (e.g., aspergillosis or candidiasis).

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Table 1. Drugs approved for treatment of systemic fungal diseases in the United States.

Class	Generic name	Brand name	Available formulation(s)	Year initially approved
Polyene	Amphotericin B	Fungizone (Apothecon Products, Princeton, NJ)	Intravenous, oral solution	1958
Polyene	Amphotericin B lipid complex	Abelcet (Liposome, Princeton, NJ)	Intravenous	1995
Polyene	Amphotericin B cholesteryl sulfate	Amphotec (SEQUUS Pharmaceuticals, Menlo Park, CA)	Intravenous	1996
Polyene	Amphotericin B liposomal	AmBisome (Fujisawa Healthcare, Deerfield, IL)	Intravenous	1997
Pyrimidine	Flucytosine	Ancoban (ICN Pharmaceuticals, Costa Mesa, CA)	Oral tablet	1972
Azole	Ketoconazole	Nizoral (Janssen Pharmaceutica, Titusville, NJ)	Oral tablet	1981
Azole	Fluconazole	Diflucan (Pfizer, New York, NY)	Intravenous, oral tablet, oral suspension	1990
Azole	Itraconazole	Sporanox (Janssen Pharmaceutica, Titusville, NJ)	Intravenous, oral capsule, oral solution	1992

Regardless of which amphotericin B formulation (conventional or lipid) is used, clinical experience and personal preference of the treating physician often determine the approach to administration of the drug, especially since few studies have carefully addressed the issues. For example, available data do not provide definitive answers to several questions: whether a test dose of amphotericin B should be given at the start of therapy; whether the daily dose should be increased gradually to the maximum dose over several days or the maximum dose should be given on the first day; and whether the maximum daily dose or the total dose over time is most important with regard to outcome. Many authorities do not recommend a separate test dose, but do use a cautious infusion of the first dose (quasi–test dose). Moreover, patient response to a test dose does not necessarily predict major allergic reactions to subsequent doses. For patients with serious life-threatening fungal disease (e.g., rhinocerebral mucormycosis associated with diabetic ketoacidosis or invasive pulmonary aspergillosis in a neutropenic compromised host), most authorities recommend giving the maximum or target daily dose, 1–1.5 mg/kg of conventional amphotericin B at initial infusion or 3–6 mg/kg of 1 of the lipid formulations. For the larger group of patients with more indolent subacute disease, a somewhat less aggressive dosing schedule is usual (e.g., half of the anticipated maximum dose on the first day and the maximum dose on the second day).

By contrast, studies that address the issue of rapid (over 1–2 h) versus prolonged (over 3–6 h) infusion of conventional amphotericin B indicate that rapid infusion is as safe and well tolerated as prolonged infusion and greatly facilitates outpatient and home administration of the drug [12, 13]. Rapid infusion should *not* be used in patients with azotemia (creatinine clearance <25 mL/min), hyperkalemia, or dose >1 mg/kg, or in patients who receive drug therapy via a central catheter that extends into the right heart. The duration of infusion also varies for the lipid-based formulations [3]. Liposomal amphotericin B can be infused over 30–60 min, more rapidly than amphotericin B lipid complex and amphotericin B cholesteryl sulfate. Studies have demonstrated that amphotericin B (especially conventional amphotericin B)–associated nephrotoxicity can be ameliorated or prevented by maintenance of intravascular volume, by avoiding diuretic drugs and saline-loading with 500–1000 mL of normal saline before infusion of amphotericin B [14]. Avoidance of concurrent potentially nephrotoxic agents such as radiocontrast dyes, nonsteroidal anti-inflammatory drugs, aminoglycoside antibiotics, and immunosuppressive agents, such as cyclosporine and tacrolimus, also appears to be important.

There is much variability in physician practices regarding premedication or comedication regimens aimed at preventing or minimizing infusion-related side effects such as fever, chills, headache, nausea and vomiting. Available data indicate that the most common pretreatment regimens that include diphenhydramine, acetaminophen, a corticosteroid and heparin, alone or in various combinations, are similar in efficacy to no pretreatment in the prevention of infusion-related effects [15]. Importantly, most patients develop tolerance over time to the acute infusion-related toxicities of both conventional amphotericin B and the lipid-based formulations. Hence, routine premedication to prevent such events cannot be recommended. If infusion-related events do develop, premedication for subsequent infusions is appropriate. For the occasional patient who has persistent fever and chills, despite the conventional premedication regimen described above, meperidine, ibuprofen, or dantrolene may be beneficial. Since the current, common practice of placement of central venous catheters for administering amphotericin B, heparin is rarely needed nowadays to prevent phlebitis.

Among the pyrimidine class of antifungal drugs, only flucytosine (5-fluorocytosine) is approved. However, this drug's utility is hampered by its somewhat limited spectrum of activity (*Candida* species, *Cryptococcus neoformans*, and some molds), and its significant potential for toxic effects (skin rash, nausea,

Table 2. Selected pharmacologic properties of oral azole agents.

Dose	Fluconazole, 200 mg po	Itraconazole, 200 mg po	Ketoconazole, 200 mg po
Oral bioavailability, %	>80	>70	75
Peak plasma concentration, μg/mL	10.2	0.2–0.4	1.5–3.1
Time to peak plasma concentration, h	2–4	4–5	1–4
Protein binding, %	11	>99	99
CSF penetration, %	>70	<1	<10
Terminal elimination half-life, %	22–35	24–42	7–10
Active drug in urine, %	80	<1	2–4

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vomiting, diarrhea, liver dysfunction, and bone marrow suppression) [16, 17]. In addition, emergence of resistance during flucytosine therapy, especially among *Candida* species, is a troublesome feature. Consequently, flucytosine has limited clinical indications; it is used primarily in combination with amphotericin B as therapy for cryptococcal meningitis and selected life-threatening *Candida* syndromes such as endocarditis, meningitis, and hepatosplenic disease [17]. Over recent years, "lower dose" flucytosine, 100 mg/kg/day with adjustments for renal dysfunction, has been advocated [18].

The availability over the past 2 decades of the azole antifungal agents represents a major advance in the management of systemic fungal infections. Miconazole, the first azole drug to be approved and now recently withdrawn from the market, was available only as a highly toxic iv formulation; consequently, it was only rarely used. By contrast, the 3 oral azoles, ketoconazole, an imidazole, and, especially, itraconazole and fluconazole (both triazoles), have become frequently used therapeutic alternatives to amphotericin B [19, 20]. The relative broad spectrum of activity of the azoles against common fungal pathogens (e.g., *Candida* species, *Cryptococcus neoformans, Blastomyces dermatitidis, Histoplasma capsulatum, Coccidioides immitis, Paracoccidioides brasiliensis, Sporothrix schenckii,* and *Aspergillus* species [only itraconazole is active]), ease of administration, and limited toxicity are highly attractive features. As shown in table 2, among the oral azoles, fluconazole (also available as an iv formulation) possesses the most desirable pharmacologic properties, including high bioavailability, high water solubility, low degree of protein binding, wide volume of distribution into body tissues and fluids, including cerebrospinal fluid, and urine, and long half-life [21–23]. In addition, fluconazole and itraconazole are better tolerated and more effective than ketoconazole.

One potential limitation of the azole antifungal drugs is the frequency of their interactions with coadministered drugs, which results in adverse clinical consequences [19, 20, 24]. One type of azole-drug interaction may lead to decreased plasma concentration of the azole, related to either decreased absorption or increased metabolism of the azole. A second type of azole-drug interaction may lead to an unexpected toxicity of the coadministered drug, relating to the ability of the azoles to increase plasma concentrations of other drugs by altering hepatic metabolism via the cytochrome P-450 system. Examples of these potential azole-drug interactions and their consequences are shown in table 3.

A second potential limitation of the azoles is the emergence of resistance of fungal organisms, especially *Candida* species, to fluconazole. Two situations illustrate this problem. First, several epidemiologic studies have correlated the increased frequency of non–*albicans Candida* species as causes of bloodstream infections with increased use of fluconazole for both prophylactic and therapeutic purposes. These non–*albicans Candida* isolates are often more resistant to fluconazole, compared with *C. albicans* isolates. Second, an increasing number of reports document clinical and/or microbiologic resistance to fluconazole in AIDS patients with oropharyngeal candidiasis, especially those who have a history of prolonged exposure to prior fluconazole and progressive immunosuppression. Available data indicate that the annual incidence of fluconazole resistant oropharyngeal candidiasis in AIDS patients is ~5%. These limitations of the azoles will become more problematic if fluconazole and other azoles continue to be used injudiciously (e.g., as prophylactic and empiric therapy in various patient groups without established indications).

Extensive resources have been devoted to develop reproducible and clinically relevant techniques for using *in vitro* susceptibility testing to predict *in vivo* response of mycoses to antifungal agents. As a result of multiple collaborative studies coordinated by the National Committee for Clinical Laboratory Studies, the M27-A broth dilution method has emerged as a reproducible tool for testing yeasts [25]. By correlating results obtained by this method with outcome of therapy in both mucosal and bloodstream *Candida* infections, data-driven interpretive breakpoints for fluconazole, itraconazole, and flucytosine have recently been proposed [26]. On the other hand, reliable identification of amphotericin B–resistant isolates of *Candida* has proven technically difficult. Although recent results suggest that modifications of the underlying techniques of M27-A may produce clinically relevant results, convincing interpretive breakpoints have not yet been proposed [27, 28]. Likewise, meaningful determination of the susceptibility of *Cryptococcus neoformans* to any antifungal agent has proven technically difficult, and convincing interpretive breakpoints using the M27-A or any other method have not been proposed. Susceptibility

Table 3. Drug interactions involving oral azole antifungal drugs.

Effect	Azole(s) involved	Potential clinical sequelae
Decreased plasma concentration of azole		
Decreased absorption of azole		
Antacids	Ketoconazole, itraconazole	
H_2 receptor antagonists	Ketoconazole, itraconazole	
Sucralfate	Ketoconazole, itraconazole	
Omeprazole	Ketoconazole, itraconazole	
Didanosine (oral)	Itraconazole	
Increased metabolism of azole		
Isoniazid	Ketoconazole	
Rifampin	Ketoconazole, itraconazole, fluconazole	
Phenytoin	Ketoconazole, itraconazole	
Carbamazepine	Itraconazole	
Phenobarbital	Ketoconazole, itraconazole	
Increased plasma concentration of coadministered drug		
Cyclosporine	Ketoconazole, itraconazole, fluconazole	Nephrotoxicity
Tacrolimus	Fluconazole	Nephrotoxicity
Phenytoin	Ketoconazole, itraconazole, fluconazole	Phenytoin, toxicity
Sulfonylureas	Ketoconazole, itraconazole, fluconazole	Hypoglycemia
Loratadine	Ketoconazole, itraconazole	Cardiac arrhythmias
Warfarin	Ketoconazole, itraconazole, fluconazole	Potentiation of anticoagulant effect
Chlordiazepoxide	Ketoconazole	Sedation
Triazolam, alprazolam, midazolam	Ketoconazole, itraconazole, fluconazole	Sedation
Nortriptyline	Fluconazole	Sedation, cardiac arrhythmias
Felodipine	Itraconazole	Edema
Nifedipine	Itraconazole	Edema
Rifabutin	Fluconazole	Uveitis
Lovastatin	Itraconazole	Rhabdomyolysis
Zidovudine	Fluconazole	Zidovudine toxicity
Indinavir	Ketoconazole	Indinavir toxicity
Saquinavir	Fluconazole	Saquinavir toxicity
Ritonavir	Ketoconazole	Ritonavir toxicity
Digoxin (mechanism unknown)	Itraconazole	Digoxin toxicity

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testing methods for molds are still in the early stages of development.

Based on these data, it is now reasonable to propose the use of antifungal susceptibility testing under certain scenarios. First, testing susceptibility of invasive (bloodstream or other sterile site) isolates of *Candida* against fluconazole should be performed on *C. albicans* isolates from patients with persistent candidemia or progressive disseminated candidiasis, despite fluconazole therapy, and on non–*albicans Candida* isolates (e.g., *C. glabrata, C. krusei,* or *C parapsilosis*) from patients with candidemia or invasive disease. Second, periodic testing of sterile site isolates of *Candida* may be useful to establish a local antibiogram that is helpful during selection of empirical therapy. Finally, susceptibility testing of mucosal *Candida* isolates from patients who have failed conventional therapy may be used to assist in determining the cause of the therapeutic failure.

This brief overview of the available antifungal drugs is provided as a general background for the individual sections that deal with the management of specific fungal diseases, namely, aspergillosis, candidiasis, blastomycosis, coccidioidomycosis, cryptococcosis, histoplasmosis, and sporotrichosis. Each section will provide details of management, including objectives, outcomes, specific dosages, duration of treatment, options, etc. For more information about other aspects of the antifungal drugs, including mechanism of action, pharmacology, toxicity, drug interactions, and resistance, a list of pertinent references is provided.

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