

SYSTEMIC ANTIFUNGAL THERAPY: PAST, PRESENT AND FUTURE

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The prevalence of systemic fungal infections has increased significantly during the past decade.¹⁻⁶ This increase is due to greater use of broad-spectrum antibiotics, immunosuppressive agents, hyperalimentation products and central venous catheters, intensive care of low birth weight infants, organ transplantation, and the acquired immunodeficiency syndrome (AIDS) epidemic.⁶⁻¹⁹ *Candida* spp. are the second most frequent isolates from blood cultures in hospitals with large populations of immunocompromised patients, second only to coagulase-negative staphylococcus.^{20,21} According to surveillance studies, nosocomial candidemia now accounts for 10% to 15% of all hospital-acquired bloodstream infections.^{9,21,22} Systemic candidiasis has been reported to occur in up to 10% of infants weighing <1 kg.¹⁸

Significant antifungal chemotherapy began in 1903, with the successful use of potassium iodide (KI) for the treatment of sporotrichosis. There was little progress for the next 50 years until nystatin, the first useful polyene, was introduced in 1951. This was soon followed by amphotericin B in 1956, still the standard against which new systemic antifungals are compared.^{23,24} Except for the development of flucytosine (1964), there was little progress until the early 1970s and the development of the azole drugs. The current era, which is characterized largely by the modifications of azole drugs, began with miconazole (1978), and ketoconazole (1981) and brought the agents fluconazole (1990) and itraconazole (1992), which can be given orally and have increasing potency, decreased toxicity and a broader spectrum of activity. Recent studies have examined ways to ameliorate the well-known toxicities of amphotericin B. A new approach has been to complex the drug with lipids or entrap it in liposomes.^{1,4,23-26}

Classification

Two groups of drugs are now used: 1) those produced by various organisms, and 2) those made synthetically. In the first group, only amphotericin B administered systemically is active in numerous deep mycoses. Although toxicity limits the use of amphotericin B, it is still the drug of choice for systemic mycoses.²⁷ The second group are synthetic drugs and include flucytosine and azoles. The azoles include imidazoles and the new generation, the triazoles, itraconazole and fluconazole.²⁸

Amphotericin B remains the effective therapy in many severe disseminated mycoses but problems with toxicity (especially nephrotoxicity), resistance, and non-availability of an absorbable oral form for long-term maintenance therapy in the immunocompromised patient create important drawbacks. Flucytosine is not effective when used alone, and is only used in combination with amphotericin B and fluconazole. Ketoconazole is available in oral form for systemic antifungal use and is an effective therapy for oropharyngeal candidiasis. Itraconazole is a new triazole antifungal with a better pharmacokinetics profile than ketoconazole, and is currently the drug of choice in some non-life-threatening endemic mycoses and is also useful in some deep opportunistic mycoses. Fluconazole is also a new triazole antifungal drug which has the best pharmacokinetics profile and least incidence of adverse effects among all the systemic antifungals available today. It is a first-line therapy for certain deep candida and cryptococcal infections in both the immunocompetent and immunocompromised host. It is also a first-line maintenance therapy for these infections in the immunocompromised host.²⁷⁻³¹ Important consideration in drug selection includes the spectrum of activity, efficacy in eliciting a clinical response and cure, ease of administration and the extent of adverse effects (Table 1).

Amphotericin B

Amphotericin B is a polyene macrolide class of antibiotics introduced in 1956. It has since remained the gold standard for antifungal therapy and has a long history of both efficacy and toxicity because it was the only

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TABLE 1. *Clinical situation and drug of choice.*

| Infection | Drug of choice | Alternative treatment |
|----------------------------------|--|---|
| Invasive aspergillosis | Amphotericin B or liposomal amphotericin B | Itraconazole |
| Candidemia* | Amphotericin B or fluconazole | Fluconazole or amphotericin B |
| Disseminated candidiasis | Fluconazole or amphotericin B±5-FC | Amphotericin B or fluconazole |
| Blastomycosis | Itraconazole | Amphotericin B, fluconazole or ketoconazole |
| Histoplasmosis | Itraconazole** | Amphotericin B, fluconazole or ketoconazole |
| Coccidioidomycosis | Fluconazole | Amphotericin B IV+IT |
| Coccidioidomycosis nonmeningitis | Itraconazole | Ketoconazole |
| Cryptococcosis meningitis | Amphotericin B±5-FC | Fluconazole |
| Chromomycosis | Itraconazole | |
| Fusarium infection | Liposomal amphotericin B | Amphotericin B |
| Mucormycosis | Amphotericin B | Liposomal ampho B |
| Pseudoallescheriasis | Itraconazole or miconazole | |

**C. krusei* resistant to fluconazole and *C. lusitanae* resistant to amphotericin B; **in severe cases amphotericin B is the drug of choice.

available systemic agent for many years.⁷ Amphotericin A and B are isolated by-products from a fermentation process of *Streptomyces nodosus*, a soil actinomycete.^{27,32}

Mode of Action

The mechanism of action is due in part to its selective binding to ergosterol, the major fungal sterol, in the cell membrane of susceptible fungi, inducing changes in membrane permeability and leakage of cell components and, ultimately, cell death.²⁷ A second effect of amphotericin B is thought to be cell damage secondary to drug auto-oxidation.³³

Distribution

Amphotericin B is poorly absorbed orally, with less than 5% bioavailability, necessitating intravenous administration to achieve and maintain adequate serum concentrations. It is formulated as a colloidal suspension with sodium deoxycholate.²⁷ Because it precipitates in normal saline, it must be given in solution with 5% dextrose in water. Peak levels generally occur during the first hour of a four-to-six-hour infusion, with high levels persisting for six to eight hours.²⁷ Levels in serum are not affected by hepatic or renal failure, and hemodialysis does not affect drug clearance.³⁴ There is at present no established relationship with amphotericin B serum concentrations and clinical outcome, and there is no clear

indication for measurement of serum concentrations.³⁵ The highest concentrations of amphotericin B are found in liver, spleen, kidney and lung.²⁷ In contrast to adults, in whom the amphotericin B concentration in cerebrospinal fluid (CSF) may be only 2% to 4% of that in the serum,³⁶ infants may have CSF levels from 40% to 90% of those in serum.³⁷ However, animal model data suggest that meningeal concentrations may be higher than CSF concentration, which may account for the success of amphotericin B in the therapy of fungal meningitis.³⁸ Amphotericin B is known to cross the placental barrier, with cord blood and amniotic fluid levels reported to be less than that of the maternal serum concentration. The elimination of the agent is biphasic, with a rapid initial serum half-life of 24 to 48 hours, followed by a terminal phase half-life of up to 15 days. Levels have been detected in bile for up to 12 days and in urine for 27 to 35 days after administration.³⁴ The clearance is more rapid in infants.⁶

Spectrum of Activity

Amphotericin B is active against a wide variety of fungal species of both yeast and filamentous forms. Certain species of *Candida* may develop tolerance, and are less susceptible than the most frequently isolated *C. albicans*. Variable activity is shown against *Aspergillus* and *Mucorales* spp.³² *C. lusitanae*, *Trichosporon beigeli* and *Pseudoallescheria boydii* are usually resistant to amphotericin B.

Mode of Administration

Clinicians commonly initiate treatment with a test dose of 0.1 mg/kg or 1 mg given over 20 to 30 minutes to estimate the potential for a serious reaction, such as anaphylaxis. The need for a test dose has been questioned by some clinicians because of the infrequent occurrence of these reactions.²⁷ If this dose is well tolerated, the next dose then is increased progressively from 0.25 mg/kg to a maximum of 1.0 to 1.5 mg/kg, depending on the severity of infection and the pathogen involved, given once daily as an intravenous infusion over two to four hours. The rapidity of dose escalation depends on the severity of the infusion reaction and the extent and severity of infection.^{27,39} However, there is no convincing evidence that a "stepwise" escalation of the dose to the targeted daily dose decreases toxic effects.⁴⁰

Side Effects

Fever and rigors occur in more than 50% of patients upon initial administration of amphotericin B, but tend to subside with continued use. Neonates appear to tolerate amphotericin B side effects better than older children and adults.¹⁸ The mechanism of fever and chills is unknown, but possibly mediated by prostaglandins.⁴¹ These acute

reactions may be blunted by premedication with meperidine, diphenhydramine or hydrocortisone.⁶ Anorexia, nausea, vomiting, headache, and myalgia are common reactions.

Anaphylaxis reactions occur in 1% of courses of amphotericin B and are an absolute contraindication to continued use. Phlebitis can be minimized with the use of central venous catheters and avoidance of amphotericin B concentrations exceeding 0.1 mg/mL.⁴² Some authors report good results when heparin is added to the solution, but no controlled studies have demonstrated its efficacy or safety.⁴³

Nephrotoxicity occurs early in the course of treatment, generally within the first two weeks and usually is reversible in >80%. Renal failure is not common. The drug causes a decline in glomerular filtration rate and renal blood flow and decreases proximal and distal tubular reabsorption of electrolytes.⁶ Manifestations of nephrotoxicity vary from renal tubular acidosis, azotemia, and oliguria to potassium and magnesium wasting. Hypokalemia is common and 90% or more of patients require potassium supplementation.²⁷ Renal toxicity is potentiated by the use of other nephrotoxic agents, particularly the aminoglycosides, cyclosporine, and antineoplastic such as cisplatin⁶ and diuretics⁴⁴ (Table 2). Amphotericin B dosage is usually adjusted when the blood urea nitrogen (BUN) or creatinine level reaches three times pretreatment levels.²⁸ The drug is discontinued first for 24 hours, then resumed at half the previous dose and gradually titrated upward as permitted by the BUN and creatinine. In non-randomized adult studies, a sodium load has been shown to reduce the incidence of renal toxicity.⁴⁵⁻⁴⁶ Administration of saline with close attention to total body weight, electrolyte levels, and cardiopulmonary function may attenuate azotemia.^{6,42} Blood urea nitrogen, creatinine, potassium, sodium and magnesium should be monitored at least two to three times per week while the patient is on amphotericin B and corrected accordingly. Other strategies, including pentozifylline and low-dose dopamine, may be used to control azotemia.⁶

Anemia, usually normocytic normochromic, occurs in more than 75% of patients, with an 18%-35% decrease in hemoglobin^{6,43} and is related to changes in erythropoietin levels.⁴⁷ Treatment with erythropoietin may reverse amphotericin B-induced anemia.^{39,40} The anemia resolves within several months of discontinuing therapy.⁶

Acute pulmonary reactions have been associated with simultaneous transfusion of granulocytes and amphotericin B.⁴⁸ Although some investigators have disputed the causality of amphotericin B to such reactions, a rational approach is to separate the infusions by the longest time possible.⁶

TABLE 2. Potential drug interactions with systemic antifungal drugs.*

| Drug | Amp B | Flucyt. | Keto. | Flucon. | Itracon. |
|--------------------------|-------|---------|-------|---------|----------|
| Corticosteroids | + | | | | |
| Tacrolimus | | | | | + |
| Cyclosporine | + | | + | + | + |
| Leucocyte transfusions | +/- | | | | |
| Oral hypoglycemic drugs | | | | + | + |
| Hydrochlorothiazide | | | | + | |
| Aminoglycosides | + | | | | |
| Pentamidine | + | | | | |
| Cimetadine | | | | + | + |
| Rifampin | | | + | + | + |
| Coumarin-like drugs | | | + | + | + |
| Calcium channel blockers | | | | | + |
| Digitalis glycosides | + | | + | | + |
| Quinidine | | | | | + |
| Phenytoin | | | + | | + |
| Theophylline | | | | + | |
| Terfenadine | | | + | | + |
| Isoniazid | | | + | | + |
| Zidovudine | | | | | |
| Cytosine arabinoside | | + | | | |
| Cisapride | | | + | | |
| Midazolam | | | + | | |
| Triazolam | | | + | | + |
| Flucytosine | + | | | | |
| Amphotericin B | | + | | | |
| Ketoconazole | + | | | | |
| Miconazole | + | | | | |
| Fluconazole | + | | | | |
| Astemizole | | | + | + | + |
| Anti-neoplastic drugs | + | | | | |
| Oral contraceptives | | | | + | |

*Based on FDA-approved leaflet inserts; amp=amphotericin B; flucyt.=flucytosine; keto.=ketoconazole, flucon.=fluconazole; itracon.=itraconazole.

Liposomal Amphotericin B

Encapsulating amphotericin B into liposomal vesicles or binding of amphotericin B to other lipid carriers is reported to result in a significant reduction of toxicity and possibly an increased therapeutic index of the drug.^{25,40} Following promising clinical results with investigational formulations, three industrial compounds have been developed: AmBisome, Amphocil (Amphotericin B

Colloidal Dispersion, ABCD) and Amphotericin B Lipid Complex (ABLC, Abelcet). These three formulations differ significantly in composition and pharmacokinetics. Amphotericin B serum levels, after administration of ABLC and Amphocil, are relatively low when compared to AmBisome. All of the preparations appear to be preferentially accumulated in organs of the reticuloendothelial systems, opposed to the kidney.^{25,26} All three compounds share a considerable reduction of nephrotoxicity. However, the acute reaction rates differ among these compounds, with Amphocil showing the highest and AmBisome the lowest rates.²⁵ Patients with life-threatening mycoses for whom therapy has failed, or who are intolerant to therapy with amphotericin B deoxycholate, have been successfully treated with these formulations.²⁶ Therefore, these compounds are recommended only in cases of intolerance to, or failure of conventional amphotericin B therapy.⁴⁹ Amphotericin B Lipid Complex (ABLC, Abelcet) was approved by the US Food and Drug Administration (FDA) on November 1995 for use in patients with invasive aspergillosis who are refractory to or intolerant of treatment with conventional amphotericin B.²⁶ The optimal therapeutic dosages have not been established, but dosages as low as 1 mg/kg/day should be avoided in the initial treatment of fulminant fungal infections, because efficacy may be inferior to equal doses of conventional amphotericin B,²⁵ and doses as high as 7 mg/kg/day have been well tolerated.²⁶ Liposomal amphotericin B appears to be safe, effective and well-tolerated in very low birthweight infants.¹⁹

Anecdotal reports of the use of amphotericin B mixed with intralipid used for parenteral nutrition are increasing with report of decreased infusion-related toxicity with no effect on renal toxicity.^{5,49} Unfortunately amphotericin does not appear to mix well with fat emulsions.²⁶ In a recent randomized study comparing the use of amphotericin B mixed with intralipid or amphotericin B dissolved in dextrose in treatment of AIDS-associated cryptococcal meningitis, Joly et al. found that intralipid reduced the infusion-related toxicity (fever, chills) without altering its antifungal activity.⁵⁰ However, renal toxicity was higher, suggesting that intralipid/amphotericin B, unlike other lipid formulation of amphotericin B, does not allow larger doses than the conventional amphotericin B/dextrose. Therefore, mixing amphotericin B with intralipid cannot be recommended but should only be considered investigational at this time.

Flucytosine

Flucytosine is a fluorine analogue of cytosine.⁴⁰ Flucytosine is useful in combination with amphotericin B in the treatment of several deep mycoses.⁶ Its spectrum of activity is limited to candidiasis, cryptococcosis and

chromomycosis, and is affected by native resistance, and the development of resistance on therapy.²³

Absorption from the gastrointestinal tract is rapid and complete. The drug is distributed widely in various organs with spinal fluid concentrations up to 74% of serum concentration. The plasma half-life is three to five hours in patients with normal renal function, and 90% is excreted unchanged in urine. It is readily cleared with hemodialysis and peritoneal dialysis. The dose is 50-150 mg/kg/day given orally at six-hour intervals. Hepatic toxicity occurs in 5% of patients, but is usually asymptomatic and reversible. Diarrhea, nausea and vomiting are the most frequent side effects occurring in 6% of patients.⁴⁰

Myelotoxicity including leukopenia and thrombocytopenia appears to be dose-dependent. This occurs more often in patients with renal impairment or patients on amphotericin B. Serum concentrations of flucytosine should be measured for correct adjustment of dosage. This is especially important in patients with impaired renal function. Two-hour post-dose levels are usually maintained at 50-75 µg/mL, as levels above 100 µg/mL are associated with a higher incidence of bone marrow suppression and enterocolitis.⁵²⁻⁵⁷ Francis and Walsh concluded that flucytosine in combination with amphotericin B is well tolerated in myelosuppressed patients when serum flucytosine levels are serially monitored and maintained at 50-75 µg/mL.⁵³ Flucytosine is contraindicated in pregnancy because of its teratogenic effects in rats.³⁹

Azoles

The azole drugs interfere with the biosynthesis of sterols and other membrane lipids that comprise the fungal cell membrane. They inhibit 14- α -demethylase, a cytochrome P-450-dependent enzyme which is responsible for converting lanosterol to ergosterol, which is the primary component of fungal cell membranes, causing an increased permeability and progressive instability. Ergosterol is the primary component of fungal cell membranes.³⁰

Ketoconazole is less well tolerated than either fluconazole or itraconazole and is associated with more clinically important toxic effects, including hepatitis and inhibition of steroid hormone synthesis. However, ketoconazole is less expensive than fluconazole and itraconazole, an especially important consideration for patients receiving long-term therapy. All three drugs are effective alternatives to amphotericin B and flucytosine as therapy for selected systemic mycoses. Ketoconazole and itraconazole are effective in patients with the chronic, indolent forms of the endemic mycoses, including blastomycosis, coccidioidomycosis, and histoplasmosis. Itraconazole is effective in patients with sporotrichosis.

Fluconazole is useful in the common forms of fungal meningitis, namely, coccidioidal and cryptococcal meningitis. In addition, fluconazole is effective for selected patients with serious candida syndromes such as candidemia, and itraconazole is the most effective of the azoles for the treatment of aspergillosis.^{30,54}

While serum concentrations of azoles may be useful in determining absorption of drug, they have not been consistently assessed for relationship to therapeutic efficacy in clinical studies.³⁵

Ketoconazole

Mechanism of Action

Ketoconazole inhibits 14- α -demethylase, a cytochrome P-450-dependent enzyme. Bioavailability is good after oral administration, even though it is only minimally water-soluble. It requires an acidic environment (pH<3) to become water-soluble and allow for absorption. CSF concentration is <10% of the serum. The initial half-life ($t_{1/2}$) is 2 hours with terminal ($t_{1/2}$) of 7-10 hours. It is metabolized in the liver, and excreted as inactive drug in bile and to a small extent in the urine. Elimination of ketoconazole is not affected substantially by hepatic or renal impairment.

Spectrum of Activity

Ketoconazole is effective against most pathogenic fungi, except many isolates of *C. tropicalis* and *Aspergillus* spp. Ketoconazole is effective for treating mucosal candida infections, including oral thrush, candida esophagitis, and chronic mucocutaneous candidiasis, with cure rates ranging from 40% to 85%.³² Clinical response rates and cure rates in immunocompetent hosts have been demonstrated with ketoconazole treatment of histoplasmosis. It is not recommended for cryptococcal disease because of poor penetration into the CSF of noninflamed meninges.³⁰

Dosages

The dose for pediatric patients is 3.3-6.6 mg/kg given as a single daily dose. In adults the usual starting dose is 200 mg, which can be increased to 400 to 600 mg once daily.

Side Effects

Drug interaction: Drugs that induce the cytochrome P450 system, such as rifampin, isoniazid, and phenytoin increase the metabolism of ketoconazole and cause significant decreases in its peak serum levels (Table 2).

Nausea, anorexia, vomiting, and diarrhea occur in approximately 15% of treated patients and can be minimized by administering the medication with food. Itching and allergic rash occur in 10% of patients.

Hepatotoxicity with mild elevations in liver transaminases occurs in approximately 2% to 5% of patients and typically resolves with discontinuation of ketoconazole, however, fulminant hepatitis has been reported in a few instances.

Ketoconazole can interfere with adrenal corticosteroid synthesis, although reports of adrenal insufficiency are rare. Also it may cause gynecomastia, oligospermia, and decreased libido, which are dose-dependent symptoms that result from the lowering of serum testosterone levels with ketoconazole's action upon the cytochrome P450 system.³⁰ This effect typically resolves when therapy is discontinued.

Miconazole

Miconazole is synthetic imidazole with a broad spectrum of activity except for *Aspergillus* species and phycomycetes. It has been replaced by newer agents because of its limited activity and toxicity, which include phlebitis, rash, fever, hepatic toxicity and thrombocytopenia.⁵⁴ It is the drug of choice for pseudoallescheriasis.⁶

Fluconazole

Because of its oral absorption, availability as oral and intravenous preparations, good CNS penetration, high concentrations in urine and relative lack of toxicity, fluconazole is considered as a potential agent of choice for selected cases of cryptococcal meningitis and disseminated candidiasis.^{54,55} In patients with AIDS it is the drug of choice at present for maintenance therapy against cryptococcal meningitis, and is a preferred agent for secondary prophylaxis against candida infections. It is also a favored agent for primary prophylaxis in patients at risk because of neutropenia associated with chemotherapy or bone marrow transplantation.^{23,54,56}

The widespread use of fluconazole to suppress fungal infections has contributed to a significant increase in *C. krusei* infection.⁵⁷ Experimental studies have generally shown *C. krusei* to be less virulent than *C. albicans* in terms of its adherence to both epithelial cells and prosthetic surfaces, proteolytic potential and production of phospholipases.⁵⁸

Mechanism of Action and Pharmacological Properties

Fluconazole, unlike the imidazole derivatives, is water-soluble, available in oral and intravenous forms, and the oral absorption is not altered by gastric pH. The bioavailability following oral administration exceeds 90%, and peak serum levels occur two to four hours after ingestion.³⁰ Unlike other azoles including itraconazole, fluconazole readily penetrates into CSF in inflamed or noninflamed meninges, achieving levels that are 70% to 90% of serum levels.³⁰ Most of the drug (80%) is excreted

via the kidney unchanged. Thus, fluconazole dosages need to be adjusted in patients who have renal impairment with glomerular filtration rate (GFR) <50 mL/min. It is effectively removed during hemodialysis, and to a lesser extent in peritoneal dialysis. It has a longer elimination half-life in adults (30 hours) compared to 17 hours in children, but in the neonate it is prolonged up to 88 hours.^{18,40,59}

Spectrum of Activity and Clinical Use

Fluconazole is active against several of the most common yeasts encountered in immunocompromised patients. Most *Candida* spp., with the exception of *C. krusei*, are susceptible.³⁰ Fluconazole has been used as prophylaxis in bone marrow transplant recipients, with resultant decreased candida colonization and fewer superficial and systemic candida infections. However, this practice has been associated with an increasing incidence of *C. krusei* in some institutions. In addition, AIDS patients on long-term fluconazole have been reported to develop fluconazole-resistant *C. albicans* isolates.

In a recent prospective, randomized, multicenter study of fluconazole versus amphotericin B, Anaissie et al. found that the overall response rates to fluconazole and amphotericin B were similar (66% vs. 64%), and there was no difference in response as related to site of infection, time to defervescence, relapse, or survival rate between the two groups; but the adverse effects were significantly more frequent with amphotericin-treated group ($P < .0001$), and they conclude that fluconazole is as effective as, but better tolerated than amphotericin B in treatment of candida infections including neutropenic patients.⁶⁰ Due to high urine concentrations, fluconazole is effective in the treatment of candida cystitis, avoiding cumbersome therapy via amphotericin bladder washes.

Fluconazole has proven efficacious in the treatment of cryptococcal meningitis in AIDS patients. Fluconazole appears to be superior to amphotericin B for maintenance therapy of patients who have HIV infection.^{38,61}

Fluconazole is not indicated for aspergillosis, mucormycosis or pseudoallescheriasis.³⁹

Dosage

The usual dose ranges from 3 to 6 mg/kg per day orally or intravenously, although some recommend doses as high as 12 mg/kg per day. When fluconazole is used for systemic candidiasis, the initial dose is 400-800 mg (8-12 mg/kg per day), followed by 200 mg per day (4 to 6 mg/kg per day).

Side Effects

The most frequent events are gastrointestinal complaints, headache and skin rash, including rare exfoliative skin reactions. Isolated instances of clinically

overt hepatic dysfunction have occurred in patients with AIDS.^{56,62} Liver function should be monitored during the course of fluconazole therapy in patients with AIDS and underlying liver dysfunction.⁶²

Unlike ketoconazole, fluconazole is affected minimally by administration of histamine H₂-receptor antagonists, and has no apparent effect upon adrenal corticosteroid secretion or testosterone levels.⁶³

Itraconazole

Itraconazole was licensed in 1992 for use in pulmonary and extrapulmonary blastomycosis and histoplasmosis (nonmeningeal). It has proved to be useful as treatment for histoplasmosis in patients infected with human immunodeficiency virus.⁶⁴ One of its greatest advantages is in its activity against aspergillosis, though it is also efficacious against many pathogenic fungi.⁵⁴ Itraconazole appears to be at least as effective as amphotericin B in the treatment of osteoarticular sporotrichosis and pulmonary sporotrichosis in patients infected with human immunodeficiency virus, thus obviating the need for intravenous amphotericin B therapy, with its associated toxic effects.⁶⁵ It acts like other azoles through cytochrome P-450, primarily by impairing the synthesis of ergosterol, resulting in a defective fungal cell membrane with altered permeability and function.⁶⁶

Dosage

The usual dose is 2-5 mg/kg/day, with maximum adult dose of 100-400 mg/day only given orally. Bioavailability is 2-3 times higher when taken with food or with a carbonated beverage.

The bioavailability is increased when it is administered in hydroxypropyl- β -cyclodextrin, a cyclic oligosaccharide carrier molecule that increases the solubility of lipophilic compounds in aqueous solution.^{6,67} Itraconazole is metabolized in the liver. It is not removed by hemodialysis. The tissue concentration is higher than plasma.⁴⁰ It is a lipophilic agent, and tissue concentrations may correlate better with efficacy than plasma levels.⁶⁹ CSF and urine concentrations are low and <1% of plasma.

Most adverse effects have been relatively minor and do not require discontinuation of therapy. These include nausea, vomiting, headache and increased liver transaminase. Hypokalemia has rarely been reported. No endocrine effects have been reported.

Drug Combinations

The toxicity of amphotericin B, the fungistatic nature of the azoles, as well as emerging resistance issues have led to the investigation of combination therapy which may improve efficacy, reduce side effects and decrease duration

of therapy.⁷⁰ Based on limited studies in animal models and with in vitro data, both tetracycline and rifampin showed synergy with amphotericin B against selected organisms,^{39,71,72} however, clinical studies have not been forthcoming.

Studies based on animal models of disseminated candidiasis suggest that amphotericin B combined with 5-flucytosine (5-FC) is more effective than amphotericin B alone against most deep-seated *Candida* infections.⁷³ They are synergistic for cryptococcal meningitis in non-AIDS patients.⁷⁴ Francis and Walsh investigated the safety and tolerability of flucytosine in myelosuppressed patients and conclude that flucytosine in combination with amphotericin B is well tolerated when serum flucytosine levels are serially monitored.⁵³

The combination of amphotericin B plus fluconazole has been reviewed recently by Sugar.⁷⁰ Ramani et al. found that no antagonism between amphotericin B and fluconazole occurs using 50% inhibitory endpoints with *C. albicans*.⁷⁵

In another study investigating the antifungal activity of amphotericin B plus fluconazole against three strains of *C. albicans*, using kill curve methods, Wolfe et al. found the activity of the combination yielded a slightly greater reduction in colony-forming units compared to fluconazole alone.⁷⁶ Sugar et al. found the combination of fluconazole and amphotericin B was not antagonistic in vivo in mice with invasive candidiasis and suggested combination therapy be considered in management of clinical candidiasis.⁷⁷ Walsh et al. reported that in-vitro combinations of amphotericin B and antifungal azoles were synergistic, additive, or indifferent in their interaction against *P. boydii* and antagonism was not observed.⁷⁸ Combinations of antifungal drugs have proven to be the most effective approach for treating cryptococcal meningitis.

Prophylaxis

Fluconazole appears as effective as amphotericin B plus flucytosine in the prevention and early treatment of disseminated candidiasis.^{73,79} With the exception of fluconazole, no antifungal drug or drug combination has been shown to prevent invasive fungal infection (mainly *Candida albicans* infections) in certain high-risk patients.^{13,57,80}

The benefits of fungal prophylaxis with fluconazole in bone marrow transplant patients appear to outweigh the risks of a possible increase in colonization and infection by *C. krusei* or *C. glabrata*. Disseminated fungal infections caused by *C. tropicalis* and *C. albicans* have a high mortality rate, and these infections may be prevented by the prophylactic use of fluconazole. *C. krusei* and *C. glabrata* infections generally do not contribute to increased

mortality, and most patients infected by these organisms recover after appropriate antifungal therapy.

Bodey et al. showed no difference in the fungal infection rates between groups receiving 400 mg/d of fluconazole and those receiving 0.5 mg/kg of amphotericin B three times weekly.⁸¹ However, Goodman et al. demonstrated a significant reduction in colonization as well as systemic infection in patients who received fluconazole compared to those who received a placebo, although there was no difference in overall mortality between the two groups.⁸⁰ One retrospective study found low-dose amphotericin B therapy to be effective in preventing *Candida* infections,⁸² but results from a placebo-controlled, randomized prospective trial with 0.1 mg/kg/day failed to support this claim.^{57,83} Low-dose amphotericin B prophylaxis (0.1-0.25 mg/kg/day) shows promise against aspergillosis, an opportunistic infection associated with high morbidity and mortality.⁵⁷ The literature suggests the possible value of using oral or intravenous fluconazole 200-400 mg/d or intravenous amphotericin B 0.1-0.25 mg/kg/d as antifungal prophylaxis in patients after autologous or allogeneic bone marrow transplant.⁵⁷ These studies described the potential decrease in morbidity and mortality of bone marrow transplant patients with the use of either fluconazole or amphotericin B, but it is not known whether all patients after bone marrow transplant or only those at high risk of fungal infection may benefit from prophylaxis. Clinicians should be aware of the possible increase in colonization by less pathogenic fungal species, such as *C. krusei* and *C. glabrata*, when prescribing fluconazole prophylaxis.⁵⁷ In a recent randomized multicenter trial, adults receiving chemotherapy or bone marrow transplant for hematological malignancies received itraconazole or fluconazole prophylaxis during neutropenia. Both drugs provided effective prophylaxis against candida infection, but itraconazole may have been more effective than fluconazole in preventing fatal aspergillosis.⁸⁴

In a randomized, placebo-controlled multicenter trial, Winston et al. found that fluconazole prevents colonization and superficial infections in *Candida* spp. other than *C. krusei* in patients undergoing chemotherapy for acute leukemia.⁸⁵ In another recent randomized, placebo-controlled study of fluconazole 400 mg/d (8 mg/kg/day) IV/PO as early empirical antifungal therapy in neutropenic patients receiving cancer chemotherapy, Walsh et al. found that there was a significant reduction of fungemia ($P=0.03$) and persistent fever ($P=0.024$) in fluconazole-treated patients.⁷⁹ The most significant responses to early empirical fluconazole were observed in children compared with adults, and in hematologic malignancies compared with solid tumors. Children receiving fluconazole for less than seven days had the greatest benefit with reduction of empirical use of amphotericin B ($P=0.001$) and persistent

fever ($P=0.002$). They conclude that early empirical antifungal therapy with fluconazole reduces candidemia, persistent fever, and the empirical use of amphotericin B in neutropenic patients, particularly children and those with hematologic malignancies.

In summary, antifungal prophylaxis is recommended in selected high-risk patients and fluconazole is well tolerated and usually effective in this regard.

Antifungal Resistance

Clinical resistance can be defined as persistence of clinical lesions despite the treatment prescribed at a dose known to be effective for at least seven days.⁸⁶ Mycological failure (failure of therapy to eradicate the yeast) is hard to interpret because many patients improve despite persistence of the organism.⁸⁶ Others define mycological resistance as a decrease of in-vitro susceptibility compared with the minimum inhibitory concentration (MIC) on isolates easily cleared by the antifungal drug at the usual dose, based on the proposed method M27P of the National Committee for Clinical Laboratory Standards (NCCLS) for antifungal agents' susceptibility, as it will facilitate comparison of MICs between reports.⁸⁷ Amphotericin B is defined in the clinical microbiology laboratory as MIC ≥ 2 $\mu\text{g/mL}$, however, therapeutic failure has been reported with an MIC as low as 0.8 $\mu\text{g/mL}$ in immunocompromised patients.¹⁰

Candida organisms resistant to polyenes and azoles have been increasingly isolated from oncology and HIV-infected patients. Outbreaks of infections due to these less susceptible organisms have been reported in several centers.^{10,86-88} Antifungal resistance has largely been observed among non-*Candida albicans* species, especially *Candida parapsilosis*, *Candida lusitanae*, and *Candida krusei*. However, there has also been an increase in the isolation of resistant *Candida albicans*, the more prevalent and more virulent species of *Candida*, from other patients.^{10,88-90}

Vazquez et al. found that fluconazole prophylaxis did not increase the rate of antifungal resistance in *C. albicans*. There was a significant incidence of azole cross resistance among the non-*C. albicans* isolates, unrelated to fluconazole use.⁹¹

In a recent ten-year review of *C. albicans* isolates obtained from sterile body sites tested against fluconazole, ketoconazole, and miconazole using microdilution antifungal susceptibility testing method, Bodnar et al. found there was a dramatic increase in the number of *C. albicans* isolates from sterile body sites after 1992.⁹² The isolates prior to 1993 were all fluconazole-susceptible. Within three years of widespread azole use, they found emergence of drug resistance to all agents in the class. They conclude that the incidence of serious fungal

infections continues to increase coincident with diminished susceptibility.

Despite the availability of standardized methods, it is not recommended at this point that susceptibility testing be routinely performed for all fungi in each microbiology laboratory; however, it may be useful to evaluate potential emergence of resistance if patient fails therapy despite adequate dosage, compliance, and after looking into drug interaction.

New Developments and Future Directions

In the past 10 years there has been a major expansion in the development of antifungal drugs, but there are still weaknesses in the range and scope of current antifungal chemotherapy. New developments have included the modification of existing drug molecules to eliminate toxicity and improve activity. New triazoles with broad-spectrum antifungal activity, such as saperconazole, are also being assessed, but clinical studies had been discontinued because of saperconazole-associated tumors in laboratory animals.⁵

Voriconazole (VOR) is a novel triazole derivative with potent broad-spectrum antifungal activity against various fungi, including those that are resistant to fluconazole, such as *C. krusei*.⁹³ Early studies suggest VOR is more effective than fluconazole in disrupting candida sterol biosynthesis, consistent with the different antifungal potencies of these compounds.

The mechanism of fungal glucan synthesis and its inhibition currently represent actively pursued areas for antifungal target and drug discovery.⁹⁴ The pneumocandins are potent antifungal agents of the echinocandin class which are under development for use as broad-spectrum antimycotic therapy.^{5,6,94,95} The echinocandin lipopeptides are fungicidal agents with low toxicity, and one member has been tested in the clinic, a semisynthetic analogue of echinocandin B called cilofungin. Newer echinocandins, such as LY303366 and the pneumocandins, have excellent activity against yeasts and *Pneumocystis carinii* infections in animals and show promise as potential clinical antifungal candidates. Chitin synthase inhibitors are limited because of unfavorable pharmacokinetics. The pradimicins show the ability to bind mannan and thus exert an antifungal effect. The mode of action of this class of inhibitors is not fully understood, but their unique action may provide a better understanding of mannan as a target.^{94,95} Vazquez et al. evaluated the activity of a new water-soluble pneumocandin, L-733560, with 107 pathogenic strains of *Candida* and *Torulopsis* species, which included 23 strains with known multi-azole resistance patterns, and they found that the new antifungal agent demonstrated the best activity with the lowest MICs against *C. albicans*, *T.*

glabrata, *C. tropicalis*, and *C. kefyr* and *C. krusei*, less activity against *C. krusei*, *C. lusitanae*, and *C. parapsilosis*, and the least activity against *C. guilliermondii*. Good activity was also demonstrated against the various multi-azole-resistant *Candida* and *T. glabrata* isolates.⁹⁷

Gonzalez et al. have studied the activity of pradimicin, a new dihydrobenzophenanthrone quinone, against subacute disseminated candidiasis and experimental pulmonary aspergillosis in persistently neutropenic rabbits. They conclude that pradimicin is a safe and effective compound in the treatment of these infections in neutropenic rabbits.^{97,98}

Fothergill et al. tested the terbinafine, which is currently used to treat dermatophytic infections in combination with fluconazole and itraconazole against a battery of 70 yeast isolates displaying varying azole-susceptibility patterns.¹⁰⁰ They found that there was a dramatic synergism, suggesting exciting treatment possibilities. Further clinical investigations are warranted to determine whether the in vivo activity of terbinafine-azole combinations correlates with these in vitro data.

Another study investigated the in vitro interactions between terbinafine and amphotericin B, itraconazole and fluconazole, using four isolates of *A. fumigatus*. Ryder et al. found there is antifungal synergy between terbinafine and triazoles in *A. fumigatus*, as might be expected from drugs acting on two different stages of ergosterol biosynthesis.¹⁰¹ The combination of terbinafine and amphotericin B ranged from indifferent to synergistic effects. No antagonism was observed. They concluded that terbinafine alone, or in combination with amphotericin B or triazoles may have potential in the therapy of aspergillosis.

In summary, antifungal therapy has advanced rapidly in the last few years compared to previous years, and recommendations for treatment of fungal infections are likely to be changed in the near future as our understanding of fungal infections improves and new antifungal therapies are discovered.

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