Systemic Antifungal Agents

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Fungal infections are being identified with an ever-increasing frequency in premature infants, immunocompromised children, patients receiving immunosuppressive agents, and in those with Acquired Immuno-Deficiency Syndrome (AIDS).[1]

Fungal infections traditionally have been classified into two distinctive classes: systemic and superficial. Consequently, antifungal agents are classified under two major headings, systemic and topical agents. In this review, only systemic antifungal agents will be discussed. There are only a few systemic antifungal drugs available for use and these are polyenes (Amphotericin B), pyrimidines (flucytosine) and azoles (*ketoconazole*, fluconazole and itraconazole), and Griseofulvin.

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Amphotericin B (AMB)

Amphotericin B was originally discovered in 1955 by Gold and coworkers[2] from an aerobic actinomycete, *Streptomyces nodosus* obtained from the Orinoco River Valley of Venezuela. It is the standard treatment for more deep-seated mycosis since the early 1960s despite its adverse effects.

Amphotericin B is a member of the polyene macrolide class of antibiotics and derives its name from the amphoteric behavior of its molecule: the presence of a carboxyl group on the main ring and a primary aminogroup on mycosamine confers acqueous solubility at both extremes of pH. Amphotericin B exerts its fungicidal effect by irreversible binding to ergosterol, asterol present in the fungal cell membrane. This interaction alters fungal membrane permeability, causing leakage of cytosolic content and death.[3] Its antifungal property is augmented by its immunomodulatory effect on macrophages and formation of oxidative metabolites or free radicals that may increase membrane permeability.

Amphotericin B has a higher affinity for ergosterol than for cholesterol, the major sterol in mammalian cells. Other potential mechanisms of action include oxidative damage and immunomodulation.

Preparation

The original AMB is insoluble in water, but was formulated for intravenous infusion by complexing it with bile salt deoxycholate and marketed as a buffered lyophilized powder (FUNGIZONE) in vials of 50 mg each. The amphotericin B-deoxycholate complex (DOC) forms a colloid in water, with particles largely below 0.4 ug in diameter. So, filters in intravenous infusion lines that filter out particles above 0.2 micron pore size are incompatible. The powder should be reconstituted in 5% dextrose solutions. The addition of electrolyte to infusion solutions causes the colloid to aggregate. The infusion bottles need not be covered from light, as was once recommended. Toxcity has been a major problem with amphotericin B deoxycholate.

Pharmacologic Properties

Amphotericin B is delivered, after a test-dose, through a central venous catheter in a concentration of 0.5 mg/ml of 5% dextrose or through a peripheral venous catheter in a concentration of 0.1 mg/ml in a single daily dose. Recent data demonstrate that an infusion time of 1 hour does not increase toxicity.[4] Theoretically, the shortened infusion time enhances drug delivery by increasing the blood-to-tissue gradient (high peak and trough levels).

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Absorption of amphotericin B from gastrointestinal tract is negligible. Following intravenous infusion, amphotericin B is released from its complex with deoxycholate in the blood stream, and is more than 90% bound to proteins, largely B-lipoprotein.

Amphotericin B is eliminated by a renal mechanism mainly in an active form for weeks after cessation of therapy. No adjustment of dosage is required for neonates, or patients undergoing dialysis. If renal impairment is due to the amphotericin B, the daily total dose can be decreased by 50% or the dose can be given every other day. Hepatic or biliary disease has no known effect on metabolism of the drug. Extensive penetrations, with highest concentrations are found in liver and spleen, with lesser amounts in kidney and lung. Penetration into Cerebrospinal Fluid (CSF), vitreous humor or amniotic fluid is poor. The half life is 15 days.

The usual target dosing is 0.5 to 0.6 mg/ kg/ day or 1.0 to 1.2 mg/ kg (or 50 mg) every other day, and up to 1.5 mg/kg in aspergillosis and mucormycosis (Table 1). Patients are commonly pre-medicated with aspirin or diphenythydramine or co-infused with hydrocortisone for the anticipated infusion-related toxicity. Slow infusion also reduces the occurrence of these toxicities.

The optimal dose of amphotericin B is unknown. *Candida albicans* species usually respond to 0.5 mg/ kg/ day, with non-albicans species sometimes requiring higher doses. Treatment of aspergillus spp, or mucorceae may require 1.5 mg/ kg/ day. Cumulative doses of 15 mg/ kg may be adequate for treatment of transient candidemia. However, larger doses of 15-40 mg/ kg are required for more sustained cases of systemic candidiasis.[1]

Amphotericin B can also be administered intrathecally in fungal meningitis. It can be injected into the CSF of the lumbar spine, cisterna magna, or lateral cerebral ventricle. Regardless of the site of injection, the initial dose in infants should be 0.01 mg and may be increased gradually over 5-7 days to 0.1 mg given either every other or third day. Amphotericin B should be diluted in sterile water in a concentration that should not exceed 0.25 mg/ ml. Further dilution with CSF is recommended. Fever and headache are common reactions and may be decreased by intrathecal administration of hydrocortisone. Other complications include pleocytosis (arachnoiditis), transient radiculitis and sensory loss.

Intraocular injections of AMB have been used successfully for fungal endophthalmitis. Bladder irrigation with 50 ug/ ml amphotericin B in sterile water is effective for candida cystitis. However, relapse is common if the catheter remains in the bladder, or if there is significant postvoiding residual urine.

Antimicrobial Activity and Therapeutic Uses:

Amphotericin B is active against most species of fungi that cause human infections. *Candida albicans* is usually susceptible, whereas other candida species can have reduced susceptibility. *Candida lusitaniae, Pseudallescheria boydii* and fusarium spp have primary resistance to amphotericin B.

Amphotericin B is indicated for treatment of systemic fungal diseases caused by candida spp, aspengilli, *Cryptococcus neoformans*, the mucormycoses and other deep fungal infections. It is also used as an empirical treatment in the febrile neutropenic patient with persistent fever unresponding to broad spectrum antibiotics.

The true incidence of amphotericin B resistance is unknown. Resistance can be caused by altered access of amphotericin B to ergosterol, or a decrease in fungal ergosterol content.[5,6] Fortunately for most clinicians, resistance to amphotericin B among the fungi has not been a great problem. Also, resistance in *C. albicans* is a relatively rare event, probably because this yeast is diploid and lacks a haploid stage.

Drug Interactions

There is antagonistic effect between amphotericin B, which binds to ergosterol, and azole antifungal agents, which inhibit synthesis of ergosterol.[7] Amphotericin B may enhance the nephrotoxcity of other nephrotoxic agents such as aminoglycosides and cyclosporine. Potentiation of digitalis toxicity due to hypokalemia induced by amphotericin B may happen. There has been association between the development of respiratory distress and the concurrent administration of amphotericin B and leukocyte transfusions.[8]

Table 1: Dosing of Amphotericin B: By Total Dose or Duration of Therapy.

Infection	Total Dose/Duration	Remarks
Candidiasis		Therapy should be individualized on the basis of: -the type of infection, clinical response, and presence or absence of neutropenia. -patients at high risk for morbidity and mortality should be treated for a prolonged period and until all signs and symptoms of infection have resolved (e.g. neutropenic patients or others whose immune status is markedly compromised).
Catheter-related sepsis CAPD –related Peritonitis	0.3 to 0.5 gm 10-15 mg/kg/day	Until cultures have been negative for 7 to 14 days. Catheter removal is advisable.
Non-life-threatening	0.5 to 1.0 gm	10-20 mg/kg (children)
*Life-threatening endocarditis	2 to 4 gm (alternate day 0.8 mg/kg in endocarditis)	Definitive treatment requires resection of the valve.
Neonatal disseminated candidiasis	25-30 mg/kg	
Hepatosplenic candidiasis	until all lesions disappear or calcify	
Blastomycosis (severe)	1.5-2 gm	Children with CNS infections should receive amphotericin B (30-40 mg/kg) given during 4 to 6 week course. Treatment should be longer with higher total doses if clinical response is not optimal.
Coccidioidomycosis	2 to 2.5 gm	40-60 mg/kg (in children)
*Cryptoc. Meningitis	For 4-6 weeks; follows with suppression Rx in AIDS patients with flucon/itracon.	
Histoplasmosis (severe)	2 to 4 gm, follow with suppression Rx (fllucon/itracon)	Immunocompetent children with symptomatic histoplasmosis rarely require antifungal Rx. Except in children with AIDS, most patients with progressive, disseminated histoplamosis are cured after 4 weeks of Rx. Measurement of urine antigen excretion twice weekly is recommended.
Mucormycosis	2 to 4 gm	In children, the total duration of antifungal therapy has not been defined. The mainstay of Rx is a combination of surgical excision of infected tissue, drainage of fungal abscesses and administration of Ampho-B Immunosuppressive medications should be reduced or discontinued if possible.
Aspergillosis (may use with Rifampin or 5Fc)	2 to 4 gm	Surgical intervention can be an important therapeutic adjunct to antifungal chemotherapy of invasive aspergillosis.
Sporotrichosis (disseminated)	1.5 to 2 gm	Surgical debridment is an important adjunct to antifungal therapy in patients with osteoarticular disease.

**with 5Fc*

Adverse Reactions

The most common side effects of amphotericin B treatment are infusion-related reactions and nephrotoxcity. The major acute infusion-related reactions are fever and chills. Sometimes, tachypnea that typically occurs 30-45 minutes after beginning the first infusion and may last for 2-4 hours. The use of oral acetaminophen, hydrocortisone (25-50 mg given intravenously or mixed with amphotericin B infusion solution), diphenylhydramine (50 mg given orally or rectally) and intravenous meperidine can diminish the frequency and severity of these reactions. Sometimes respiratory stridor or modest hypotention may occur, but true bronchospasm or anaphylaxis is rare. The mechanism of the febrile reaction is thought to be mediated by the release of interleukin-1 and tumor necrosis factor from monocytes and macrophages.

Azotemia is another major adverse effect, which occurs in 80% of patients who receive amphotericin B. This toxcity is a dose-dependent and transient, although permanent histologic damage to renal tubules has been demonstrated even with short courses. Nephrotoxcity is increased by concurrent administration of other nephrotoxic agents, such as aminoglycosides or cyclosporine. Renal Tubular Acidosis (RTA) and renal wasting of potassium and magnesium also may be seen during and up to several weeks after therapy. The mechanism of nephrotoxcity is a result of a direct vasoconstrictive effect on the afferent renal arterioles, reducing glomerular and renal tubular blood flow. Correction of dehydration, discontinuation of diuretics and loading with saline to increase effective circulating volume could reduce the nephrotoxcity of amphotericin B, but can exacerbate hypokalemia.[9]

Other amphotericin B toxicities include: nausea, anorexia and vomiting. Also, it inhibits erythropoietin production which results in normochromic, normocytic anemia (with hematocrit rarely falling below 20% to 25%), thrombocytopenia and leukopenia. Hepatotoxcity, neurotoxcity consisting of psychotic behavior, convulsions, blurring of vision, loss of hearing and encephalopathy have been described. Thrombophlebitis is common. Cardiac arrythmias have been reported with overdose of amphotericin B.

Nephrotoxcity, and bone marrow suppression should be monitored closely by serum creatinine, potassium and magnesium every other day and complete blood count once a week.

Other Drug Formulation (See Table 2):

In view of difficulties in administration and high toxicity of amphotericin B, new liposomal preparations of amphotericin B have been developed, which retain its therapeutic efficacy but are tolerated better. The administration of such liposomal forms modifies the pharmacologic and toxicologic properties of amphotericin B deoxycholate.

These have advantages over the conventional amphotericin B, namely, up to 10-fold increase of daily dose, high tissue concentrations, decrease in infusion-related side effects, and decrease in renal toxicity. However, optimal daily or total dose has not been established. The lipid formulation is very expensive comparing to the original amphotericin B.

The first of these is amphotericin B colloidal dispersion (ABCD, amphotec), which contains roughly equimolar amounts of amphotericin B and cholesteryl sulfate.

The second formulation is liposomal amphotericin B (Ambisome), is a small unilamellar liposme about 55-75 nm in diameter, made up of bilayer membrane of hydrogenated soy phosphatidyl choline and distearoyl phosphatidylglycerol stabilized by cholesterol and combined with amphotericin B in 2:0,8 : 1:0,4 ratio.

The third formulation is amphotericin B lipid complex (ABLC, Abelcet), which is a ribbon like structure of a bilayered membrane formed by combining a 7:3 mixture of dimyristoyl-phosphatidyl glycerol with amphotericin B (drug/lipid ratio of 1:1).

The antifungal activities of these new liposomal preparations of amphotercin B *in vitro* are comparable to those of standard amphotericin B. However, serum levels of the liposomal amphotericin B are higher than those achieved with standard amphotericin B. Serum levels of amphotericin B colloidal dispersion and amphotericin B lipid complex are similar to amphotericin B deoxycholate.

These new liposomal preparations of amphotericin B can be used as an empirical treatment for presumed fungal infections refractory intolerant to amphotericin B desoxycholate including infections caused by zygomycetes, fusarium, and other invasive moulds such as aspergillus. These forms of amphotericin B are also indicated as an empiric therapy for patients with febrile neutropenia. In patients with pre-existing renal insufficiency, the lipid form of amphotericin B may be favored to AMB deoxycholate. Dosages of lipid form of amphotericin B range from 3 to 5 mg/ kg/ day.

Azoles

Azoles antifungal agents have added greatly to the treatment of fungal infections. These agents have a broad spectrum of antimycotic activity, are available in oral formulations, and have less major toxicities. The azole family of antifungal includes two broad classes: the imidazoles (clotrimazole, ketoconazole, miconazole) and the triazoles (fluconazole and itraconazole) according to whether they contain two or three nitrogen atoms, respectively in the five-membered azole ring. Imidazoles are still widely used for the treatment of superficial mycoses and vaginal candidiasis. Since the introduction of triazoles (fluconazole in 1990 and itraconazole in 1992) the role of ketoconazole in the treatment of systemic fungal infections has decreased. The systemic triazoles are more slowly metabolized and have less effect on human sterol synthesis than do imidazoles, hence, they are preferred for systemic therapy.

Mechanism of Action

All azoles have a common mechanism of action, namely, interference with the synthesis and permeability of fungal cell membranes. Azoles inhibit sterol 14-α-demethylase, an enzyme system of the cytochrome p450 group, impairing the biosythesis of ergosterol, the major sterol of fungal cell membrane cytoplasmic membrane resulting in accumulation 14-α-methylsterols. Azoles have a greater affinity for fungal p450 enzymes than for those in mammalian cells. These methylsterols disrupt the close packing of the membrane phospholipids and thereby interfere with the membrane bound enzyme like ATPase or the electron transport chain[10] and thus inhibiting growth of the fungi. Other effects on fungal cells include inhibition of endogenous respiration and hyphal transformation.[11]

Spectrum of Activity

Both imidazoles and triazoles are active against C. ablicans, Cryptococcus neoformans, and the common dimorphic fungi such as Coccidioides immitis, Histoplasma capsultatum, Blastomyces dermatitidis, Paracoccidioides brasiliensis, and Sporothrix schenckii.[12] However, there is lack of activity of miconazole against B. dermatitidis. In addition, the azoles are less active against non-albicans species of candida, including C. krusei and Torulopsis glabrata. Itraconazole is more effective than other azole drugs against aspergillus species.[13]

Mechanisms of Resistance

There has been a widespread use of these antifungal agents as prophylactic and therapeutic agents in immunocompromised patients including AIDS, bone marrow suppression or solid organ transplants. As expected, the reporting resistance to these drugs has coincided with their widespread use. A special consideration regarding antifungal susceptibility testing of these agents is the lack of correlation between *in vitro* testing results and *in vivo* clinical response: *i.e.* that is the MICs of most common fungi seen to be quite resistant, yet there is a good clinical response.[14] This effect is most likely a result of the use of different end points for susceptibility testing. So, there is no accepted definition of resistance and susceptibility.

Adverse Effects (See Table 4):

Azoles are much better tolerated than the older antifungal drugs. The side effects of the azoles are generally mild. Dose-related gastrointestinal symptoms including nausea, anorexia, and vomiting are the most common side effects, but rarely necessitate the discontinuation of therapy in patients receiving up to 400mg daily.[11] Headache, dizziness, rash, and pruritis have also been reported. All azoles can cause significant elevations in plasma aminotransferase concentrations (estimates of toxicity

range from 1 in every 10,000 to 50,000 patients after a mean of 4 weeks of therapy).

Although most patients with azole-induced liver dysfunction are asymptomatic, ketoconazole, and rarely the triazoles may cause symptomatic liver dysfunction and even fatal hepatitis.[15] Monitoring of liver function, especially aminotransferase should be conducted before initiation of treatment and periodically thereafter, particularly in the first few months of treatment. Azole therapy should always be discontinued in patients who have symptomatic liver dysfunction or laboratory evidence of progressive or persistent liver impairment. Enzyme elevations are reversible but may take long time to normalize. Ketoconazole can reversibly inhibit steroidogenesis when given in daily doses exceeding 400mg/day and may cause gynecomastia, adrenal insufficiency, and decreased libido. By contrast, fluconazole and itraconazole, when given in recommended doses, do not inhibit steroidogenesis. Itraconazole at dosages greater than 400mg/day can cause hypertension, hypokalemia, and pedal edema.

Drug interaction can occur because of the inhibition of cytochrome p450 pathway. So, coadministration of drugs that interact with hepatic microsomal enzymes may cause alteration in the drug levels resulting either subtherapeutic level or systemic toxicity. So, plasma concentrations of both azole and the interacting drug should be monitored. Also, drug interaction can occur by the inhibition of absorption of the azole, leading to decreased bioavailability. Table (5) reveals the drug interactions with azoles.

Ketoconazole

Ketoconazole is the only imidazole effective in systemic fungal infections. It has broad therapeutic potential for the treatment of candidiasis, dermatophytoses, and various deep mycoses. However, because of the slow response to therapy, variable bioavailability, and adverse effects, itraconazole has replaced ketoconazole for all its major indications.

Pharmacologic Properties (See Table 4):

Ketoconazole is administered orally. Absorption is decreased as pH of the gastric contents increases. So, bioavailability is markedly depressed in patients taking H_2-blockers or antacids. Ingestion of food, however, does not have a major impact. It has good tissue distribution but it crosses the blood-brain barrier poorly and its levels in its eye are minimal.

Ketoconazole is partially metabolized in the liver. Ketoconazole should be avoided in patients with severe hepatic insufficiency. Its metabolism is not affected by azotemia, hemodialysis, or peritoneal dialysis.

Drug Interactions (See Table 5):

Ketoconazole is metabolized by the cytochrome p450 enzyme CYP3A4. So, the list of drug interaction is long: rifampin and phenytoin reduce ketoconazole level while it increases cyclosporine and warfarin levels. Ketoconazole increases terfenadine and astemizole blood levels, which can lead to a decrease in cardiac contraction and prolong QT interval.[16]

Adverse Effects (See Table 3):

The adverse effects are dose-dependent and gastrointestinal side effects are most common: nausea, anorexia and vomiting occur in about 20% of patients receiving 400 mg daily. The significant adverse effects are related to the inhibition of steroid biosynthesis which leads to menstrual irregularities, gynecomastia and azospermia. Mild, asymptomatic elevation of liver enzymes is common, occurring in 5-10% of patients. Hypertension and fluid retention have also been documented. Ketoconazole is teratogenic in animals, so its use in pregnancy is not recommended.[10]

Antimicrobial Activity and Therapeutic Uses:

Ketoconazole is considered as an alternative agent to itraconazole for the treatment of systemic fungal infections with exception of candidiasis where it is used as an alternative to fluconazole. The indications are for: histoplasmosis in normal host with non-meningeal disease; blastomycosis in normal host with non-meningeal and non-genitourinary disease; non-systemic candidiasis, limited to oropharyngeal, esophageal, vaginal and mucocutaneous disease; coccidiomycosis with disseminated non-meningeal disease, and paracoccidioidomycosis.

Dosages used in those conditions range from 600 to 800 mg a day orally. Duration of treatment usually is for 6 to 12 months.

Fluconazole

Fluconazole is the first of synthetic triazole antifungal agents. It is a fluorinated bistriazole. Its structure has several advantages over other systemic antifungal agents. These include good oral absorption, high CSF and urinary concentration, minimal protein binding and few side effects.[17]

Pharmacologic Properties (See also Table 4):

Fluconazole is almost completely absorbed with oral bioavailability fo more than 90%. Oral absorption is not altered by food or gastric acidity. It is highly water soluble, has low affinity for plasma protein and is metabolically stable. Over 90% of drug is eliminated by renal excretion; hence, offers a therapeutic advantage in renal involvement of systemic mycoses. It is extensively and evenly distributed into body fluids, including CSF,[18] sputum, saliva, nails and peritoneal fluid. An elimination half-life of approximately 30 hours allows once-daily dosing.

Dosage and Administration

Because fluconazole is almost completely absorbed orally, the daily dose is the same for oral and intravenous administration. However, to obtain steady-state levels earlier, an initial doubling dose is used. Appropriate adjustments in dosage should be made in patients with renal impairment: administer usual load, then adjust daily doses by administering 50% of recommended daily doses or administer every 48 hours in patients with creatinine clearances of 11-50 ml/minute.

During the first 2 weeks of life, especially for premature neonates, administer the same dose as older children and give every 72 hours. For children, a once-daily dosing is recommended. Doses and duration should be determined by the type of infection. For example, systemic candidiasis in children requires 6-12 mg/kg/day for at least 28 days, cryptococcal meningitis requires 12 mg/kg on first day, and then 6-12 mg/ kg for at least 10-12 weeks after CSF culture becomes negative.

In Adults, treatment of systemic candidiasis requires 400mg on the first day, then 200 mg/day for at least 28 days, while cryptococcal meningitis requires 400mg, then 200mg/ day for at least 10-12 weeks after CSF culture becomes negative.

Drug Interactions (See Table 5):

The potential for drug interactions with fluconazole is particularly important,[19] because many patients taking fluconazole are seriously ill and are likely to be taking other drugs as well. Fluconazole increases plasma concentration/activity of warfarin, phenytoin, cyclosporins and oral hypogclycemics. Rifampin decreases the fluconazole's Area Under the Curve (AUC) by about 25%. Thiazide diuretics decrease renal clearance and increases serum concentration of fluconazole.

Adverse Effects (See Table 3):

Fluconazole is generally well tolerated and is infrequently associated with adverse side effects or laboratory abnormalities. The most commonly observed clinical adverse events are nausea in 3.7%, headache 1.9%, skin rash 1.8%, vomiting 1.7%, abdominal pain 1.7%, diarrhea 1.5%, and transient enzymes in <5%. Serious hepatic toxicity is rare.[20] Fluconazole has been well tolerated by the pediatric population.

Antimicrobial Activity and Therapeutic Uses:

Most species of candida are susceptible to fluconazole but with variable sensitivity. MIC 90 ranges from 0.25-6.4 mg/L for *C. albicans*, ≤2mg/L for *C. tropicalis*, and ≥50mg/L for *C. krusei*. *C. parapsillosis, C. glabrata* and *C. grillermondii* fall between the two extremes i.e *C. albicans* and *C. krusei*.[20]

Fluconazole has been extensively and effectively used against candidiasis, including systemic infections, esophageal, or other deep organs. Treatment of mucosal candidiasis with fluconazole was significantly superior to ketoconazole and other polyenes in immunocompromised patients. It may not be an effective treatment of deep candidiasis in profoundly neutropenic patients. However, it has been effectively used for prophylaxis in oncology and ICU settings.

Fluconazole is the regimen of choice in suppressing relapse of cryptococcal meningitis in AIDS-associated cryptococcal meningitis after primary therapy with AMB and flucytosine.[21]

Fluconazole has activity against coccidioidomycosis, histoplasmosis, blastomycosis, sporotrichosis and ring worm. Fluconazole does not have activity against preventing or treating aspergillosis. Also, there is no activity against *C. Krusei* and mucormycosis.

Itraconazole

Itraconazole, a triazole, is closely related to ketoconazole, however, it has a wider antifungal activity and fewer adverse effects than does ketoconazle.

Pharmacologic Properties (See Table 4):

Itraconazole inhibits fungal cytochrome p450-dependent enzymes, blocking synthesis of a fungal cell membrane sterol, namely ergosterol.[22]

Plasma concentrations reach a peak approximately 4 hours after oral intake. Itraconazole is administered orally. Absorption requires gastric acidity.[23] Capsule is better absorbed with food, while solution is better absorbed on an empty stomach. Absorption of both products is significantly increased when taken with a cola beverage.

Itraconazole is metabolized primarily in the liver, and is concentrated 2 to 20 fold more in lipophilic tissues such as fat, liver, kidney, and skin than in plasma.

Dosing adjustment in hepatic impairment may be necessary, but specific guidelines are not available. However, it is not necessary to adjust dose in renal impairment. Itraconazole is 99.9% bound to serum proteins and its metabolite hydroxy-itraconazole is 99.5% bound to plasma proteins.

Extensive binding to tissues also occurs. Penetration into CSF is poor, and little or no intact drug appears in urine.

Drug Interactions (See Table 5):

Drug interactions are possible with all co-administered drugs that are metabolized by the liver cytochrome p 450 system. Itraconazole concentrations are decreased by concomitant therapy with rifampin, phenytoin, carbamazapine, didanosine, isoniazid, phenobarbital, and H_2-blockers. Itraconazole increases the concentrations of drugs metabolized through cytochrome p450 CYP3A4 including digoxin[24], cyclosporine, phenytoin, warfarine, and oral hypoglycemic agents. Co-administration of terfenadine and astemizole, are absolutely contraindicated due to secondary cardiotoxcity of increased drug level.[25] Itraconazole may increase levels of cispride, midazolam, triazolam, simvastatin, and lavastatin. So, concomitant administration of these medications are contraindicated.[26]

Adverse Effects (See Table 3):

Adverse effects are seen only occasionally with itraconazole. These include nausea, vomiting, abdominal pain, and diarrhea. Also, hypertension, edema, hypertriglyceridemia, hepatotoxcity, hypokalemia, and rash have been reported.

Antimicrobial Activity and Therapeutic Uses:

Itraconazole has activity against aspergillus, candida, sporothrix, histoplasma, coccidioides, cryptococcus, and mycetoma forming fungi. Considerable spectral advantages over fluconazole include greater activity against aspergillosis, blastomycosis, histoplasmosis, and sporatrichiosis. [27] Oral solution (not capsules) is marketed for oral and esophageal candidiasis. It is useful in superficial mycoses including dermatophytoses (e.g, tinea capites), pityriasis versicolor, seborheic dermatitis, vaginal and chronic mucocutaneous candidiasis and systemic mycoses. Intravenous solution is indicated in the treatment of blastomycosis, histoplasmosis (non meningeal), and aspergillosis (in patients intolerant or refractory to amphotericin B therapy).

Table 2: Liposomal Formulation of Amphotericin B.

Amphotericin B Lipid Formulation	*Indications*	*Dosages*	*FDA Approval*	*Daily Cost*
Amphotericin B Lipid Complex (ABLC) (Abelcet)	Invasive fungal infections in patients refractory or intolerant to amphotericin B deoxycholate	5 mg/kg/day as single infusion	1995	$776
Amphotericin B cholesterol sulfate complex colloidal dispersion (ABCD) (Amphotec)	Treatment of patients who either failed or are intolerant to amphotericin B deoxycholate	3-4mg/kg/day (up to 6 mg/kg/day)	1996	$480
Liposomal amphotericin B L-AMB (Ambisome)	Empirical therapy for presumed fungal infection in febrile neutropenic patients. Treatment of patients with Aspergillus species, candida species, and/or cryptococcus species infection refractory to amphotericin B deoxycholate, or in patients when renal impairment or toxicity precludes the use of amphotericin B deoxycholate.	3-5 mg/kg/day or single infugus	1997	$942

Table 3: Adverse Effects of Azoles.

Organ or System	*Ketoconazole*	*Fluconazole*	*Itraconazole*
Gastrointestinal Tract	Nausea & Vomiting (20%)	Nausea & Vomiting <5%	Nausea & Vomiting <10%
Skin	Rash (8.6%), pruritis (2%)	Rash (2%) Steven-Johnson Syndrome (rare)	Rash
Liver:			
Transient increase of liver enzymes	2-10%	<1%	<1-5%
Hepatitis		rare	rare
Endocrine System	Adrenal insufficiency rare Decreased Libido (1.2%) Impotence Gynecomastia Menstrual irregularities (10%)	-	Hypokalemia (6%) Edema Impotence (rare)
Other	Headache, fever & chills Photophobia	Headache, seizures	Headache & dizziness. Alopecia
Pregnancy Risk Factor	*C	*C	*C

**FDA use-in-pregnancy rating for drugs.*

Category C: Risk cannot be ruled out: Human studies are lacking and animal studies are either positive for fetal risk or lacking as well. However, potential benefits may justify the potential risk.

Table 4: Pharmacologic Properties of Azoles

Factor	*Ketoconazole*	*Fluconazole*	*Itraconazole*
Formulation	200 mg tablets	Tablets: 50, 150,200 mg Oral suspension 10 or 40 mg/ml Intravenous: 2 mg/ml	100 mg capsules 10 mg/ml oral suspension
Oral bioavailability (%)	75	>90	>70
Absorption decreased by H_2-blocking agents or antacids	Yes	No	Yes
Peak plasma concentration (ug/ml)	1.5-3	10.0	0.2-0.4
Time to peak plasma concentration (hr)	1-4	2-4	4-5
Protein binding (%)	99	11	>99
Half-life	7-10*	25-30	24-42*
Clearance	Hepatic	Renal	Hepatic
Dose adjustment in renal failure**	None	Yes	None
Unchanged drug in urine (%)	2-4	80	<1
CSF/serum concentration (%)	<10	>60	<1

* *Ketoconazole and itraconazole exhibit dose-dependent elimination, so higher doses may result in prolonged terminal elimination half-life.*

** *Dose adjustment also required in neonates.*

Source of data – reference # 22 & 27.

Table 5: Drug Interactions with Azoles Anti-fungal Agents.

Outcome	*Ketoconazole*	*Fluconazole*	*Itraconazole*
Decreased absorption of the azole:			
Antacids	+	-	+
H2-receptor blockers	+	-	+
Omeprazole	+	-	+
Decreased serum levels of the azole:			
Rifampin*	+	+	+
Isoniazid	+	-	+
Phenytoin	+	-	+
Didanosine	+	-	+
Sucralfate	+	-	-
Phenobarbital	-	-	+
Carbamazepine	-	+	+
Increased plasma concentration of co-administered drug:			
Cycosporine	+	+	+
Phenytoin	+	+	+
Warfarin	+	+	+
Methyl prednisolone	+	-	-
Cispride	+	-	+
Sulfonylureas	-	+	+
Digoxin	+	-	+
Increased serum level of the co-administered drug & life threatening arrhythmias:			
Terfenadine	+	-	+
Astemizole	+	-	+
Loratadine	+	-	-

**Ketoconazole and itraconazole levels might be significantly decreased. So, they should not be administered concomitantly with rifampin.*

Fluocytosine (5-Flucytosine OR 5-FC):

Flucytosine (5-FC, ancobon) is a fluorinated pyrimidine related to fluorouracil and floxuridine. It is the only pyrimidine approved as an antifungal agent. It is an oral anti fungal agent originally developed in 1957 as antimetabolite for leukemia. It has a limited use because of its narrow spectrum of activity, its potential for toxic effects, and emerging resistance that develop if it is used as a single agent.

Mechanism of Action:

Following penetration of the fungal cell wall.[27] 5-flucytosine is deaminated to 5-fluorouracil (5-fu), a potent inhibitor of DNA and RNA synthesis by cytosine deaminase. Mammalian cell do not convert flucytosine to fluorouracil, and this allows selective effects on fungal cells. Combination therapy with AMB and flucytosine results in altered permeability of fungal cell membrane allowing increased uptake of 5-Fc by these fungi.

Antimicrobial Activity and Therapeutic Uses:

Flucytosine has clinically useful activity against a narrow spectrum of fungi, namely candida, cryptococcus, and the agents of chromomycosis. Most strains of aspergillus spp are moderately or highly resistant to 5-fc. Dimorphic fungal pathogens such as *Blastomyces dermatiditis, Paracoccidioides brasillensis, Sporothrix schencki, Histoplasma capsulatum, Coccidioides immitis*, the causes of mucormycosis, and most dermatophytes are generally considered resistant to 5-fc.

Clinically, the principal use of flucytosine is as adjunctive therapy with amphotericin B in the treatment of candidal or cryptococcal diseases.[5]

Resistance to flucytosine (5-fluorocytosine) is common, wide-spread, and well known. Because of this, flucytosine cannot be used as a single agent in the treatment of most fungal agents. The National Committee on Laboratory Standards (NCCLS) has created standards to improve *in vitro* testing and make it more useful. An overall rate of primary resistance of *C. albicans* to 5-fc is 5-10%. Non-albicans species of candida are generally more resistant to 5-fc than *C. albicans*.[28] 1% to 4% of cryptococci are resistant to flucytosine.

The emerging of secondary resistance of candida species and cryptococci in patients on flucytosine as single agent is common. Up to 67% of yeast isolates from patients receiving flucytosine have developed resistance during treatment. Hence, flucytosine should be used only in combination with amphotericin B, and serum levels greater than 25 ug/mL should be maintained to prevent the development of flucytosine resistance during combination treatment.[29] The majority of resistant strains of *C. albicans* to flucytosine have mutations that inhibit the production of uridine 5-phosphate pyrophosphate phosphoribosyl transferase and so prevent the incorporation of flucytosine into RNA. Other defects affecting transport into the cell have been reported in laboratory strains.

Pharmacokinetics:

Flucytosine is well absorbed when taken by mouth in up to 90% but absorption can be delayed if taken with food and antiacids. Peak level in serum reaches a good therapeutic level 1 to 2 hours after a single oral dose of 150 mg in a patient with normal renal function.

5-fc is widely distributed into CSF, aqueous humor, joints, peritoneal fluid, and bronchial secretions. This is partly due to a low degree of protein binding (approximately 4%). Up to 96% of the total dose of 5-fc is eliminated as unchanged drug in urine, primarily by glomerular filtration. The elimination half-life of 5-fc ranges from 3-8 hours. 5-fc is removed by hemo- and peritoneal dialysis. In renal insufficiency, modification of dosage needs to be made.

Dosing and Administration:

The usual dose of 5-Fc in children and adults ranges from 50-150 mg/kg/day and administered orally. To minimize toxicity and maintain concentration within the therapeutic range (25-100 ug/mL), monitoring of serum levels of 5-fc is highly recommended,[29] particularly in all patients who receive high doses of 75 mg/kg/day or more for prolonged periods of time (>1 week), pediatric patients, and those with renal impairment. If serum 5-fc levels are not routinely available, regular monitoring of complete blood counts (2-3 times/ week) provides an indirect method of screening for excessive dosing.

Dosing Interval in Renal Impairment:

This is summarized below:

Creatinine Clearance	Suggested Dose
20-50 mL/min	½ normal dose (12.5 mg/kg Q6h or 25 mg/kg Q12h)
<20 mL/min	¼ (25 mg/kg once daily)
Hemodialysis	½ normal dose or supplement at end of dialysis
Peritoneal dialysis (adults)	0.5-1.0 g Q24hr/

Drug Interactions:

Flucytosine efficacy and toxicity increase with concurrent use of amphotericin B administration. Cytosine arabinoside may inactivate flucytosine activity by competitive inhibition.

Adverse Reactions:

Gastrointestinal toxicity (nausea, vomiting, and diarrhea) and bone marrow suppression (leukopenia and thrombocytopenia) that is usually reversible are the major adverse reactions. Most of the hematologic toxicity associated with 5-fc is thought to result from the vivo conversion of 5-fc to 5-fu. In 5% of the cases, there may be reversible elevations in serum aminotransferases or alkaline phosphate.

Griseofulvin:

Griseofulvin is derived from penicillium. It is fungistatic *in vitro* for various species of dermatophytes like the trichophytons, microsporum, and Epidermophyton. Griseofulvin has no effect on bacteria, candida, or other fungi causing deep mycoses. It is useful for the oral treatment of tinea capitis and tinea unguinum, both of which are usually resistant to treatment with topical agents.

Griseofulvin causes disruption of the mitotic spindle by interacting with polymerized microtubules. The oral administration of griseofulvin results in variable blood levels. Oral absorption is improved by decreasing the size of the crystals and the administration of the drug with a fatty meal.

Griseofulvin has a serum half-life of 20 hours, and approximately 50% of the oral dose can be detected in the urine within 5 days. It is metabolized in the liver; thus no need to adjust the dosage in patients with renal impairment. Barbiturates decrease the oral absorption of griseofulvin.

Griseofulvin is available as microsize crystals in a 250-mg capsule, 500-mg tablet, and suspension containing 125 mg/5mL. The usual dose for children is 15-20 mg/kg/day of the microcrystalline preparation, up to a maximum of 1 g/day, in divided doses. Griseofulvin ultramicrosize crystals are better absorbed, permitting a lower dose of 7.25 to 10 mg/kg/day for equivalent efficacy. The drug (in either form) is effective for the treatment of tinea capaitis and should be continued for 6 to 8 weeks.[30]

The adverse effects are infrequent but include headache, hypersensitivity rash, unticaria, nausea, vomiting, diarrhea, fatigue, and rarely bone marrow suppression, and mild reversible nephrotoxcity. Routine testing of blood counts and liver function is not recommended in patients not receiving hepatotoxic drugs and without a history of liver disease.[31]

Summary

Clinical Indications of Antifungal Agents:

Table (6) summarizes the primary indications of antifungal agents in deep fungal infections.

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Table 6: Treatment of Specific Deep Fungal Infection.

Type of Infection	*Drug of Choice*	*Alternatives*
Candidiasis		
Candidemia	Amphotericin B∀ flucytosine or fluconazole	
Invasive	Amphotericin B∀ flucytosine or fluconazole	
Aspergillosis		
Invasive pulmonary/disseminated	Amphotericin B	Itraconazole
Histoplasmosis		
Mild to moderate	Itraconazole	Ketoconazole/fluconazole
Severe or meningeal	Amphotericin B	
AIDS: initial	Itraconazole/amphotericin B if severe	Fluconazole
Maintenance	Itraconazole	Amphotericin B/fluconazole
Cryptococcisis		
Meningeal	Amphoterin B∀ flycocytosine	Amphotericin B∀ flucocytosine followed by fluconazole
Other deep-seated	Fluconazole/Amphotericin B∀ flucytosine if severe	
AIDS:		
Initial	Amphotericin B∀ flucytosine followed by fluconazole	Amphotericin B∀ flucytosine followed by itraconazole
Maintenance	Fluconazole	Itraconazole/Amphotericin B
Coccidioidomycosis		
Meningeal	Fluconazole	Amphotericin B (intravenous + intrathecal)
Other deep-seated	Fluconazole or itraconazole	Ketoconazole
AIDS:		
Initial	Fluconazole	Amphotericin B
Maintenance	Fluconazole	Amphotericin B
Blastomycosis		
Mild or Moderate	Itraconazole	Ketoconazole/high dose fluconazole
Severe, meningeal, or genitourinary	Amphotericin B	
Zygomycosis	Amphotericin B	
Sporotrichosis		
Lymphocutaneous	Itraconazole	Potassium iodide/fluconazole
Deep-seated	Itraconazole/Amphotericin B if severe	Fluconazole/high dose ketoconazole
Pseudallescheriasis	Ketoconazole/itraconazole	
Paracoccidioidomycosis	Itraconazole/Amphotericin B	Ketoconazole/fluconazole

Source of data – reference # 22 & 27.

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تصوير الرنين المغناطيسي للقنوات المرارية و البنكرياس في المرضى الذين عمل لهم استئصال المرارة عن طريق المنظار

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الملخص :

الهدف: تحديد الائدة و الأداء التشخيصي للتصوير المغناطيسي للقنوات المرارية و البنكرياسية بالإضافة إلى الرنين المغناطيسي للجزء العلوي للبطن في المرضى الذين تم استئصال المرارة لهم عن طريق المنظار و مقارنة النتائج مع التصوير الملون للقنوات المرارية و البنكرياسية عن طريق المنظار.

الطرق: هذه الدراسة عملت على 113 مريض (30 ذكر و83 أنثى) الذين عمل لهم استئصال المرارة عن طريق المنظار و كانوا يعانون من ألم في البطن واصفرار أو ارتفاع في وظائف الكبد وقد عمل لهم تصوير مغناطيسي للقنوات المرارية و البنكرياسية و تصوير مغناطيسي لأعلى البطن وتم مقارنتها بالتصوير الملون للقنوات المرارية والبنكرياسية عن طريق المنظار و التصوير التلفزيوني ومتابعتهم سريرياً.

النتائج: تصوير الرنين المغناطيسي للقنوات المرارية و البنكرياسية كانت واضحة في جميع المرضى، 50 مريض (47%) منهم كانت الصور طبيعية و 60 مريض (53%) كان هناك توسع في القنوات المرارية مع وجود حصى في 19 مريض (17%) و تضيق في 26 مريض (23%) ولم يوجد سبب لتوسع القنوات المرارية في 15 مريض (13%) إن التصوير المغناطيسي للقنوات المرارية والبنكرياسية حساسية 93% ، و خاصية 99% ، ودقة تشخيص 97% .

الخلاصة: إن التصوير المغناطيسي للقنوات المرارية و البنكرياسية يقدم طريقة غير تداخلية ذات فعالية تشخيصية عالية لتقييم المرضى الذين يعانون من اضطرابات صفراوية بعد استئصال المرارة.