Opportunistic Fungal Infections

Patients at Increased Risk of Fungal Infection

Compromised Hosts
Long-term corticosteroid use
Cancer patients (receiving antineoplastics and/or radiation)
Extended-spectrum antibiotic use
Granulocytopenic patients (T-cell defects)
Transplant recipients
AIDS Patients
Diabetics
Patients with chronic obstructive pulmonary disease (COPD)
Patients with prosthetic heart valves
Patients receiving TPN
IV drug abusers
Genetic predisposition

Table 40. Major Opportunistic Fungi in U.S.

<table>
<thead>
<tr>
<th>Fungi</th>
<th>Major Disease Sites</th>
<th>External Factors</th>
<th>Internal Factors</th>
<th>Neutrophils</th>
<th>Mononuclear phagocytes</th>
<th>Humoral immunity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Candida sp.</td>
<td>oral cavity, vagina, UTI, disseminated</td>
<td>IV and Bladder catheters</td>
<td>Normal flora altered by antibiotics</td>
<td>+++</td>
<td>+++</td>
<td>+ ?</td>
</tr>
<tr>
<td>Aspergillus sp.</td>
<td>lung, bladder</td>
<td>Dust, soil</td>
<td>altered immunity</td>
<td>+++</td>
<td>++</td>
<td>+ ?</td>
</tr>
<tr>
<td>Mucor sp.</td>
<td>lung, sinuses, brain</td>
<td>Dust, soil</td>
<td>Normal flora altered immunity</td>
<td>+++</td>
<td>++</td>
<td>+ ?</td>
</tr>
<tr>
<td>Cryptococcus neoformans</td>
<td>lung, brain (meningitis)</td>
<td>Pigeon feces, soil</td>
<td>Dissemination to CNS by reactivation</td>
<td>– ?</td>
<td>+++</td>
<td>+ ?</td>
</tr>
<tr>
<td>Histoplasma capsulatum</td>
<td>lung</td>
<td>Soil in Ohio and Mississippi River valleys, Southern U.S., Caribbean</td>
<td>COPD patients, Dissemination, often by reactivation</td>
<td>– ?</td>
<td>+++</td>
<td>+ ?</td>
</tr>
<tr>
<td>Blastomyces dermatitidis</td>
<td>lung</td>
<td>Dogs, soil in Ohio &amp; Mississippi River valleys, Great Lakes</td>
<td>Dissemination, often by reactivation</td>
<td>– ?</td>
<td>+++</td>
<td>+ ?</td>
</tr>
</tbody>
</table>

### Systemic Antifungal Agents

**Polyenes - Amphotericin B and Nystatin**

![Chemical structure of Amphotericin B](image)

#### I. HISTORY AND STRUCTURAL CHARACTERISTICS

Amphotericin B is one of the polyene macrolide antibiotics. Amphotericin B is used systemically and nystatin is more commonly used topically. Amphotericin B is produced in _Streptomyces nodosus_. The structure was completely solved in 1971 and consists of 7 conjugated double bonds (polyene), a lactone (macrolide), a free carboxyl, and a glycosidic side chain with a primary amino group. The drug is amphoteric but has limited water solubility. Commercial preparations consist of a complex with desoxycholate, a bile salt, injected as a suspension or as a liposomal delivery system.

#### II. MECHANISM OF ACTION

a.) Combination with cytoplasmic membrane sterols. Interaction is highest with ergosterol, a sterol that is in high concn. in fungal membranes. Results in leaky membranes.

b.) Pore formation - interaction with the lipid component of cell membranes.

c.) Fungistatic at low concentrations, fungicidal at higher concentrations.

#### III. SPECTRUM AND USES

Amphotericin B has a broad spectrum of activity versus a variety of fungal pathogens. Amphotericin is toxic and should only be used in patients with progressive and potentially fatal fungal infections. Some of the most important fungi that cause opportunistic infections in humans are listed below:

a.) _Candida albicans_ and other _Candida sp._ – thrush, esophagitis, disseminated infection

b.) _Cryptococcus neoformans_ – meningitis

c.) _Aspergillus_ – usually lung also sinus, liver, brain

d.) _Coccidioides immitis_ – pneumonia, meningitis
e.) *Histoplasma capsulatum* – pneumonia

f.) *Blastomyces* – lung

g.) other fungal pathogens - *Torulopsis glabrata, Mucor, Rhizopus, Sporothrix, Paracoccidioides*

IV. RESISTANCE

Resistance may occur via a lowered production of membrane sterols.

V. DISPOSITION, METABOLISM, AND EXCRETION

**Distribution** – >95% bound to cholesterol in lipoproteins. Vd = 4L/kg but is quite variable. Penetrates poorly into CNS, peritoneal cavity, and into bronchial secretions. Highest concentrations in liver > spleen, kidneys > lungs > heart, muscles > bone

**Pharmacokinetics** – Terminal elimination half-life is 15 days. Distributional half-life is 1-2 d

**Excretion** – excreted in both bile and urine. Urinary excretion is low (≤10% of the dose/day). Output over 7 days (~40% of dose infused). Excretion into urine is prolonged and AmB levels in urine are measurable for as long as 7 weeks.

VI. ADVERSE EFFECTS

a.) Generalized toxic reactions upon infusion – headache, fever and chills, anorexia, malaise, muscle and joint pains, hypotension

b.) Renal toxicity - chronic renal toxicity in up to 30% of patients. May result in permanent damage with large doses (> 5g). Should determine BUN or serum creatine weekly during therapy. If BUN is > 40 mg/dl or is serum creatinine is > 3 mg/dl, discontinue drug or reduce dosage until renal function improves.

c.) GI problems - nausea, vomiting, epigastric pain, diarrhea, cramping

d.) Hematologic toxicity - normochromic, normocytic anemia (18-35% in Hct), hypokalemia due to renal tubular acidosis, hypomagnesemia

e.) Phlebitis and thrombophlebitis at injection site

f.) Rare adverse reactions – cardiac arrhythmias; convulsions, peripheral neuropathy, vertigo, hearing loss, tinnitus, visual disturbances, rash, anaphylactoid reactions.

Note: to prevent some of the febrile reactions other drugs may be coadministered e.g. aspirin, acetaminophen, or meperidine; antihistamines; antiemetics; small doses of corticosteroids such as dexamethasone; dantrolene. Heparin added to infusion (500 -2000 units), rotation of infusion sites, and use of large veins may decrease incidence of thrombophlebitis.

VII. PRODUCTS AND DOSING
Dosing: Administer a test dose of 1 mg over 6 hours at a concentration of 0.1 mg/ml. Monitor for adverse reactions. If OK, then usually start with 0.25 mg/kg and gradually increase as tolerance permits. Total daily dosage may be up to 1 mg/kg. Do not exceed 1.5 mg/kg. For many fungal infections, several months of therapy may be needed.

**Amphotericin B** - Fungizone® (Bristol-Myers Squibb). 50 mg per vial as sterile lyophilized cake. Reconstitute by rapid injection of 10 ml sterile water for injection, USP. Shake until colloidal solution is clear. May further dilute (1:50 with 5% dextrose). Do not reconstitute with saline or with a bacteriostatic agent. Protect from light if not used within 8 hours.

**Amphotericin B Lipid Complex** - Abelcet® (The Liposome Company). 5 mg amphotericin B, 3.4 mg L-α-dimyristoylphosphatidylcholine, 1.5 mg L-α-dimyristoyl-phosphatidylglycerol per ml in 20 ml single dose vials.

**Liposomal Amphotericin B** - Ambisome® (Fujisawa/Nextar) appears to be as or more effective (direct membrane transfer ?) and less toxic than Fungizone. 100 mg/20ml suspension in single dose vials. Recommended daily dose is 5 mg/kg infused at 2.5 mg/kg/hour.

**Amphotericin B cholesteryl** – Amphotec® (Sequus Pharmaceuticals). 50 mg and 100 mg powder for injection in 20 mL vials. A test dose is advisable (10 mL – 1.6 to 8.3 mg) infused over 15-30 min. Recommended dose is 3-4 mg/kg/day infused at 1 mg/kg/hr. Do not use inline filter.

Note: Abelcet, Amphotec, and Ambisome are very expensive. (~10-20X more than Fungizone)

**Oral Suspension** – Fungizone® (Bristol Meyers-Squibb) 100 mg amphotericin B/ml. In 24 ml with dropper. Dose: 1 ml four times daily.

*Indication:* Treatment of oral candidiasis

**Capsofungin Acetate (Cancidas®)**

I. **STRUC**

**URAL CHARACTE**

**RISTICS**

Capsofungin is a synthetic lipopeptide in the echinocandin class of antifungal compounds. It is synthesized from the fermentation product of *Glarea lozoyensis.* It was approved in 2001 for the treatment of resistant *Aspergillus* infections.

II. **MECHANISM OF ACTION**
Caspofungin acetate inhibits the biosynthesis of β(1,3)-D-glucan, an essential component of the cell wall of filamentous fungi. β(1,3)-D-glucan is not present in mammalian cells. Capsofungin appears to inhibit the active cell growth of the hyphae of *Aspergillus fumigatus*.

III. SPECTRUM AND USES

Echinocandins like capsofungin have broad activity versus a variety of filamentous fungi. Capsofungin has in vitro activity vs. *A. fumigatus, A. flavus, and A. terreus*. The drug is only approved for the treatment of invasive aspergillosis in patients who are refractory to or intolerant of other therapies (i.e. Amphotericin B, lipid formulations of amphotericin B, and/or itraconazole). It has not been studied for the initial therapy of invasive aspergillosis. There is no antagonism with Amp. B.

IV. DISPOSITION, METABOLISM, AND EXCRETION

Capsofungin appears to have a long half-life and large volume of distribution. After a loading dose of 70 mg, there is a short α phase, followed by a β-phase of 9-11 h (log linear decline from 6-48h). A very long terminal elimination phase (redistribution from tissue binding sites) of 40-50h also occurs. The compound is slowly metabolized by hydrolysis and N-acetylation. It also undergoes spontaneous chemical degradation to a ring-opened compound. After 27 d, 35% of radiolabelled capsofungin was excreted in feces and 41% of the dose in urine. Only as small amount is excreted unchanged in urine (1.4%). Total clearance is low (12 mL/min).

V. ADVERSE EFFECTS

Fairly well tolerated if slowly infused. Some reports of histamine-mediated symptoms (rash, facial swelling, itching, sensation of warmth. One case of anaphylaxis in 623 patients. Other adverse effects are low (2-3% incidence). Drug interaction potential is low, but cyclosporin increase capsofungin AUC by 35% and tacrolimus concentrations were reduced by 20% by capsofungin.

VI. DOSING AND PRODUCT

Capsofungin acetate (Cancidas®-Merck) - white to off-white powder in either 70mg or 50 mg vials. Reconstitute with 10.5 mL of 0.9% NaCl which may be stored for up to 1 hr at room temp. Add to 250 ml IV bag or bottle containing 0.9% NaCl

Loading dose: 70mg infused slowly over 1 hr
Maintenance dose: 50 mg daily infused slowly over 1 hr

**Flucytosine (5-Fluorocytosine)**

![Flucytosine](image)

I. MECHANISM OF ACTION
Flucytosine was synthesized in 1957 as potential antitumor agent, but was found to be inactive. However, fungi are able to deaminate flucytosine to 5-fluorouracil (5-FU). 5-FU is converted through several steps to 5-fluorodeoxyuracil monophosphate, a non-competitive inhibitor of thymidylate synthetase. 5-FU is also incorporated into RNA. This inhibits fungal DNA synthesis.

II. SPECTRUM AND USES

Flucytosine is synergistic in combination with Amphotericin B. When used alone resistance develops rapidly. This allows a reduction of the dose of AmB from 0.4 mg/kg/day to 0.3 mg/kg/day resulting in less nephrotoxicity.

a.) *Candida albicans* (in combo with AmB) - septicemia, UTIs, endocarditis.

b.) Cryptococcal meningitis (with AmB) and pulmonary infections. Excellent for UTIs.

c.) Chromoblastomycosis - drug of choice

d.) *Aspergillus* - synergistic effect is somewhat controversial but there appears to an additive effect.

e.) Chromomycosis, *Torulopsis glabrata*

III. DISPOSITION, METABOLISM, AND EXCRETION

**Absorption** - well absorbed after oral dosing. Peak levels reached within 2 hours

**Distribution** – Well distributed. reaches joints, peritoneal fluid, aqueous humor. CSF levels are 65-90% of serum levels.

**Pharmacokinetics** - Half-life = 2-5 hours with normal renal function. $V_d = 0.6-0.9$ L/kg. Toxicity is observed at concentrations $>100 \mu g/ml$. Should monitor levels periodically, esp. since AmB decreases GFR.

**Elimination** - 80-90% excreted unchanged in urine. $\leq 10\%$ in feces. Half-life is dependent upon renal function and may be $\geq 72$ hrs in anuric patients.

IV. ADVERSE EFFECTS - toxic side effects most commonly observed at 100-125 $\mu g/ml$

a.) GI upset - common side effect - nausea, vomiting, abdominal pain, diarrhea, GI hemorrhage, ulcers. GI upset may be reduced by taking capsules a few at a time over 15 min.

b.) Hepatic dysfunction - $\sim 5\%$ of patients have transaminase levels.

c.) Hematologic – anemia, leukopenia, thrombocytopenia. Give with extreme caution to patients with bone marrow depression or if they are undergoing radiation treatment or chemotherapy.

d.) Hypersensitivity - rash, itching, photosensitivity
e.) Avoid in pregnancy. Not recommended for children.

V. PRODUCTS AND DOSING

Dosing: 50-150 mg/kg/day in divided doses at 6 hr intervals. If BUN or serum creatinine is elevated, reduce dosage.

Flucytosine - Ancobon® (Roche) - 250 and 500 mg capsules.

Drug Interactions:
- Synergistic with AmB. Also increased toxicity.
- Cytosine is antagonistic
- Flucytosine interferes with creatinine determinations with the dry-slide enzymatic method (Kodak Ektachem analyzer). Use Jaffe method instead.
Imidazoles and Triazoles

I. STRUCTURAL CHARACTERISTICS AND MECHANISM OF ACTION

The imidazole/triazole class of antifungal agents has been an important addition to the treatment of systemic fungal infections. The first imidazoles developed, clotrimazole and miconazole, were not useful for oral therapy. Miconazole is effective when used IV, but has been largely supplanted by fluconazole which is much less toxic. Ketoconazole, introduced in 1984, provided the first effective oral therapy for candidal infections. Ketoconazole and miconazole are imidazoles. Fluconazole, itraconazole, and the new second generation agent, voriconazole, are triazoles that have improved activity.

**Mechanism of Action** - bind to the heme of fungal cytochrome P450s primarily inhibiting the 14-demethylation of lanosterol to ergosterol, an essential sterol component of fungal and yeast membranes. Also inhibit other oxidative P450s involved in sterol biosynthesis.

**Resistance** - resistance occurs either by alteration of lanosterol 14-demethylase or by active efflux (in *Candida* sp.) of the imidazoles. The latter mechanism appears to be particularly important for candidal resistance to fluconazole in AIDS patients

II. SPECTRUM AND USES

**Ketoconazole** - fairly broad spectrum of activity. Less effective than AmB for serious systemic fungal infections. Indicated for candidiasis, chronic mucocutaneous candidiasis, oral thrush, candidal esophagitis, blastomycosis, coccidiomycosis, histoplasmosis, chromomycosis, and paracoccidioidomycosis. Not very effective vs. cryptococcal meningitis. Useful for prophylactic treatment of fungal infections in persons with neutropenia or AIDS. Other uses - investigational for prostate cancer (400 mg q 8 h), Cushing's syndrome (800-1200 mg/day)

**Fluconazole** - available oral and IV. Useful for treatment of thrush, *Candida* esophagitis, and *Cryptococcus*. Appears to be effective for initial treatment of cryptocoecal meningitis. Also used to prevent relapse of cryptocoecal meningitis in AIDS. Recently approved as a single treatment for vaginal candidiasis. $$$$

**Itraconazole** - introduced in 1992. Indicated only for treatment of blastomycosis (pulmonary and extrapulmonary) and histoplasmosis in normal and immunocompromised patients. Drug of choice for *Sporotrich schenckii*. Itraconazole has an expanded spectrum of antifungal activity that includes *Aspergillus*. Recently approved for onchomycosis (toenail infections) Further studies will be necessary to determine if it will be a replacement for the more toxic AmB. $$$$

**Voriconazole** – approved in October 2001. A second-generationazole with enhanced activity for fluconazole-resistant *Candida krusei* and *C. glabrata*. Voriconazole is fungicidal against all *Aspergillus sp.*, and has good activity vs. molds such as *Scedosporium sp.* and *Fusarium sp.* The major use of this agent will be for invasive aspergillosis, empirical treatment of presumed fungal infections in patients with persistent fever and neutropenia, serious *Candida* infections, and infections due to emerging pathogens including *Scedosporium sp.* and *Fusarium sp.* $$$$$
Ketoconazole

Itraconazole

Fluconazole

Miconazole

Econazole

Oxiconazole

Sulconazole

Tioconazole
III. DISPOSITION, METABOLISM, AND EXCRETION

Absorption

Ketoconazole (weak base, pKa ~ 5) requires acidic pH to dissolve. In patients with achlorhydria or hypochlorhydria (AIDS, elderly), dissolve KC tablets in 4 ml of 0.2N HCl and drink through glass or plastic straw. Follow with a glass of water or citrus juice. Avoid antacids, H2 blockers, or omeprazole.

Itraconazole is absorbed better when taken with food. Food increases AUC by 75%.

Voriconazole is well absorbed. Ideal for IV-to-oral switch therapy. High-fat meals reduce absorption by 25-35%.

Distribution

Ketoconazole and Itraconazole are highly protein bound and very lipophilic. Tissue concentrations in fat, liver, kidney, and skin are 2-20x higher than in serum.

Fluconazole achieves adequate CSF concentrations and is probably better for meningitis. However, both KC and Itra have been effective for some meningeal infections.

Voriconazole has a large volume of distribution. CSF concentration may be adequate.

Elimination

Fluconazole is excreted largely unchanged in urine. Adjust dose in renal failure.

Ketoconazole is excreted primarily through the bile (80-90% in feces). It is extensively metabolized to a variety of oxidative metabolites. No need to adjust dose in renal failure.

Itraconazole is almost entirely metabolized. It has an active metabolite, hydroxyitraconazole, that is present in plasma at higher concentrations than the parent drug.

Voriconazole is almost completely metabolized. Metabolism is saturable. CYP2C19 poor metabolizers (15-20% of Asians, 2-4% of Caucasians and Blacks) display about 4-fold higher levels of voriconazole compared to extensive metabolizers.

**TABLE 41. PHARMACOKINETIC PARAMETERS OF IMIDAZOLE/TRIAZOLE ANTIFUNGALS**

<table>
<thead>
<tr>
<th>DRUG</th>
<th>Bioavailability</th>
<th>Half-life (hrs)</th>
<th>% bound</th>
<th>Cmax (µg/ml)</th>
<th>Tmax (hrs)</th>
<th>V_d L/kg</th>
<th>CSF (µg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ketoconazole</td>
<td>50% pH dep.</td>
<td>6-10</td>
<td>2-4%</td>
<td>1.6-6.9</td>
<td>95-99%</td>
<td>&lt;1</td>
<td></td>
</tr>
<tr>
<td>Fluconazole</td>
<td>&gt;90%</td>
<td>30</td>
<td>80%</td>
<td>4-8</td>
<td>1-2</td>
<td>0.5-0.9</td>
<td></td>
</tr>
<tr>
<td>Itraconazole</td>
<td>50-80% pH dep.</td>
<td>64</td>
<td>0.03%</td>
<td>0.25</td>
<td>4.5</td>
<td>99.8%</td>
<td>negligibl e</td>
</tr>
<tr>
<td>Drug</td>
<td>56</td>
<td>3-5 %</td>
<td>0.40</td>
<td>5.1</td>
<td>99.5%</td>
<td>NA</td>
<td>negligibl e</td>
</tr>
<tr>
<td>-------------------</td>
<td>----</td>
<td>-------</td>
<td>------</td>
<td>-----</td>
<td>-------</td>
<td>----</td>
<td>-------------</td>
</tr>
<tr>
<td>Hydroxyitraconazole</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Voriconazole*</td>
<td>96%</td>
<td>Dose-dependent</td>
<td>&lt;2%</td>
<td>1.6</td>
<td>1-2</td>
<td>58%</td>
<td>4.6</td>
</tr>
</tbody>
</table>

* displays non-linear kinetics in the 200-400 mg dose range
V. ADVERSE EFFECTS AND DRUG INTERACTIONS

Ketoconazole

a.) Hepatotoxicity - mild elevation of transaminases in ~10%. Severe hepatotoxicity (usually fatal) in 1:10,000 persons. Appears to be allergic component.

b.) GI upset - nausea/vomiting (3-10%), anorexia - more prevalent with higher doses.

c.) Hormonal effects - KC lowers serum testosterone by inhibition of steroidal P450s. Testosterone levels are lowered at 800 mg/day & nearly abolished at 1600 mg/day. Also decreases adrenal corticosteroid levels. Side effects - gynecomastia, oligospermia at higher doses, decreased libido, menstrual problems.

d.) Hypersensivity - rare, itching (1.5%).

Fluconazole – 16% of patients, 1.5% discontinued due to adverse effects, 1.3% lab values

a.) GI upset - Nausea (3.7%), Vomiting (1.7%), abdominal pain (1.5%), diarrhea (1.5%).

b.) Hypersensitivity - skin rash (1.8%) - may be higher in AIDS

c.) Hepatotoxicity - elevated transaminases (1% showed 8-fold in ALT). 2 cases of severe hepatotoxicity in trials (>4000 patients).

Itraconazole - adverse effects reported for U.S. trials - less problems in foreign studies.

a.) GI - Nausea (10.6%), Vomiting (5.1%), Diarrhea (3.3%), Anorexia (1.2%).

b.) Dermatologic - rash (8.6%), itching (2.5%) - higher in AIDS

c.) Hepatic - 2.7% elevated transaminases. 3 cases of severe hepatotoxicity (>2500 persons).

d.) Others - edema (3.5%), fatigue (2.8%), headache (3.8%), hypertension (3.2%).

Voriconazole – adverse effects reported in clinical trials

a.) GI – Nausea (15.3%), Vomiting (17.3%), Diarrhea (14.4%)

b.) Dermatologic – rash (18.0%)

c.) Visual disturbances – (24%) – altered visual perception, blurred vision, color vision changes, and photophobia – effects are reversible. Discontinuation in only 0.5%.

d.) Acute renal failure – 1.3%

e.) Elevated liver function tests = 1.1%

f.) Others – edema (11.8%), sepsis (11.7%), headache (12.8%)
Drug Interactions

**Ketoconazole** – potent inhibitor of several P450 isozymes, especially CYP3A4. Most severe interactions are listed below:

Astemizole - serum levels - has resulted in fatal cardiovascular toxicity

Carbamazepine - serum levels - ataxia

Cisapride - serum levels (8x in AUC) - prolonged QT

Cyclosporin - serum levels - May result in nephrotoxicity. Has been used to reduce cyclosporin dosage to save $.  

Phenytoin - serum levels

Rifampin - serum levels.

Terfenadine - serum levels - has resulted in fatal cardiac dysrhythmias

Warfarin - serum levels. prothrombin time, bleeding.

Rifampin induces KC metabolism, resulting in lower blood levels. Decreased KC absorption with agents that elevate stomach pH - antacids, ranitidine.

**Fluconazole** - less potent of a P450 inhibitor than KC. Appears to be relatively selective as an inhibitor of CYP2C9. No effect on testosterone metabolism. Minor effect on cyclosporin, although some people may require dosage adjustment.

Phenytoin - 75% increase in AUC in healthy volunteers.

Sulfonylureas - Significant increases in AUC and $C_{max}$ of tolbutamide, glyburide, and glipizide. In glyburide study, several volunteers required oral glucose.

Warfarin - 12% increase in PT time

Hydrochlorothiazide has been shown to increase fluconazole AUC by ~40%. Rifampin caused a 25% decrease in AUC of fluconazole, 20% in half-life.

**Itraconazole** - triazole - less potent of an inhibitor of P450 than KC

Astemizole - serum levels - has resulted in fatal cardiac dysrhythmias

Cyclosporin- reduce cyclosporin dose by 50% when itraconazole doses are >100 mg/day.

Digoxin - serum levels

Sulfonylureas - hypoglycemia may occur.
Terfenadine - serum levels - has resulted in fatal cardiac dysrhythmias

Warfarin - increase in PT time.

Phenytoin and Rifampin appear to decrease Itraconazole levels (enzyme induction). Isoniazid, antacids, and H₂ antagonists may lower levels also.

**Voriconazole** – triazole – high affinity for CYP3A4 (100X greater than CYP2C9 & CYP2C19)

Sirolimus – large increase in AUC

Rifampin, carbamazepine, phenytoin, and St. John’s wort are expected to induce voriconazole metabolism.

VI. PRODUCTS AND DOSING

**Ketoconazole** - Nizoral® (Janssen) - 200 mg tablets

- Adults: 200 mg/day. For serious infections - 400 mg/day. Minimum treatment for candidiasis is 1-2 weeks. Other deep systemic mycoses, 400 to 800 mg/day - 6-12 mos. Chronic mucocutaneous candidiasis - maintenance therapy at 200 mg/day.

**Fluconazole** - Diflucan® (Roerig) - 50, 100, 150, and 200 mg trapezoidal tablets.
- Powder for oral suspension: 10 mg/ml and 40 mg/ml when reconstituted (orange flavor)
- Injection - 200 mg/100 ml and 400 mg/100 ml - infuse at maximum rate of 200 mg/hr.

*Oropharyngeal and Esophageal candidiasis* – 200 mg first day, then 100 mg per day.
Continue treatment for at least 2 weeks after resolution of symptoms. May be used as maintenance therapy for recurrent oral thrush.

*Systemic candidiasis* - 400 mg first day, then 200 mg once daily. Treat for a minimum of 4 weeks and for at least 2 weeks after resolution of symptoms.

*Vaginal candidiasis* - 150 mg as a single oral dose

*Cryptococcal meninitis* - 400 mg first day, then 200-400 mg daily. Treat for 10-12 weeks after CSF culture becomes negative. In AIDS patients, maintenance dose is 200 mg/day.

**Itraconazole** - Sporanox® (Janssen) - 100 mg capsules & 100 mg/10 ml oral solution

- Dose: 200 mg once daily. May be increased by 100 mg up to 400 mg daily. Take with food. For life threatening situations - loading dose of 200 mg t.i.d. (600 mg/day) for 3 days.

*Onchomycosis* - 200 mg once daily for 12 weeks.
Pulse dosing: 200 mg BID x 1 week/month x 3 months
In AIDS patients and some cancer patients, itraconazole is absorbed poorly due to achlorhydria. The oral solution of itraconazole dissolved in hydroxypropyl β-cyclodextrin appears to be much better absorbed.

**Voriconazole – Vfend® (Pfizer) – 50 and 200 mg tablets.**
IV formulation: 200 mg voriconazole in 30 mL vial, when reconstituted 10 mg/mL.
Solubilized with sulfobutylether-β-cyclodextrin (160 mg/mL).

Dose: Loading dose of two 400 mg doses taken 12 hrs apart, Maintenance dose - 200 mg BID

IV dosing for serious *Candida* infections:
Loading dose 6 mg/kg 12 hr apart, followed by 3 mg/kg every 12 hrs.
IV dosing for invasive aspergillosis/*Scedosporium*, and *Fusarium* infections.
Loading dose 6 mg/kg 12 h apart, followed by 4 mg/kg every 12 hrs.
Terbinafine

I. MECHANISM OF ACTION

Terbinafine is a synthetic allylamine. Terbinafine interferes with sterol biosynthesis by inhibiting the enzyme squalene 2,3-epoxidase. This decreases the amount of ergosterol and causes squalene accumulation in fungi. Allylamines are fungicidal against a broad spectrum of fungi. Fungistatic versus C. albicans. Approved in December 1996 for systemic use.

II. USES

a) Terbinafine is approved for oral treatment of onchomycosis of the toenail or fingernail

b) Unlabeled uses include treatment for systemic candidiasis & pityriasis (tinea) versicolor

III. DISPOSITION, METABOLISM, AND EXCRETION

Terbinafine is >70% absorbed, but is subject to relatively high first pass metabolism (F=0.6). An increase in the AUC of about 20% is observed with food. Peak plasma concentrations are approximately 1 µg/ml after 250 mg single dose. The drug is very highly protein bound (>99%) and is widely distributed. The effective systemic half-life is approximately 36 hours, but the terminal half-life is 200-400 hours representing slow release from the skin and fat. It is extensively metabolized to inactive metabolites, 70% of which are recovered in the urine.

IV. ADVERSE EFFECTS

a.) Diarrhea (5.6% versus 2.9% in placebo)

b.) Skin rash (5.6% versus 2.2% in placebo); anaphylaxis has been reported (rare)

c.) Visual changes in the ocular lens and retina have been reported

d.) Elevation in liver enzymes (~3.3% vs. 1.4% in placebo). Cholestatic hepatitis is rare.

e.) Neutropenia - a few isolated cases in the clinical trials were reported

f.) Taste disturbances - loss of taste reported in 2.8% of patients

V. DRUG INTERACTIONS

Terbinafine is partially metabolized by CYP3A4, the major P450 enzyme in liver. It may have a small inductive effect on this enzyme as evidenced by its interaction with cyclosporin.

<table>
<thead>
<tr>
<th>Precipitant Drug</th>
<th>Object Drug</th>
<th>Description of Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cimetidine</td>
<td>Terbinafine</td>
<td>Terbinafine Cl ↓ by 33%</td>
</tr>
<tr>
<td>Rifampin</td>
<td>Terbinafine</td>
<td>Terbinafine Cl ↓ by 100%</td>
</tr>
<tr>
<td>Terbinafine</td>
<td>Caffeine</td>
<td>IV Caffeine Cl ↓ by 19%</td>
</tr>
<tr>
<td>Terbinafine</td>
<td>Cyclosporine</td>
<td>Cyclosporine Cl/F ↓ by 15%</td>
</tr>
</tbody>
</table>

VI. PRODUCTS AND DOSING

Lamisil® (Novartis) - 250 mg biconvex tablets. Also available as a topical 1% cream.
For fingernail infections, 250 mg/day for 6 weeks. For toenail infections treat for 12 weeks

**Griseofulvin**

---

**I. HISTORY AND MECHANISM OF ACTION**

Isolated in 1939 from *Penicillium griseofulvium*. Not evaluated for antifungal purposes until 1957. Griseofulvin binds to fungal RNA and interferes with microtubule formation. Microtubules transport material through the cytoplasm to the cell wall. In fungi, cell wall synthesis is impaired at the growing tips of fungi. It is only effective against growing organisms. Fungistatic.

**II. USES**

a.) Dermatophytic infections (tinea) except for tinea versicolor. Drug of choice for tinea barbae and tinea capitis (scalp infections).

b.) Fungal infections of the nail and toenails - onchomycosis

**III. DISPOSITION, METABOLISM, AND EXCRETION**

Absorption is poor. Dissolution is a problem. To increase surface area for dissolution, it is produced in microsized and ultramicrocrystalline forms. Absorption of ultramicrocrystalline form is about 1.5 times that of microsized form.

Griseofulvin is widely distributed especially in liver, fat, and muscle. Concentrated in keratin precursor cells, so the new keratin that is formed is resistant to infection. It does not affect previously formed keratin, which must be shed for complete remission. This may take several months.

Metabolized by O-dealkylation. Less than 1% is excreted unchanged in urine.

**IV. ADVERSE EFFECTS**

a.) Hypersensitivity - rashes, urticaria, angioneurotic anemia. Photosensitivity.

b.) Headache, dizziness, mental confusion, impairment of performance

c.) GI upset, nausea, vomiting

d.) Lupus erythematosus - may exacerbate condition in patients with SLE

e.) Carcinogenic in animals - avoid in pregnancy.

**IV. PRODUCTS**
Griseofulvin Microsize - Fulvicin® U/F (Schering), Grifulvin® V (Ortho) - 250 & 500 mg tablets. Grisactin® (Wyeth-Ayerst) – 250 and 500 mg capsules. Grifulvin® V Oral Suspension 125 mg/5ml.

Griseofulvin Ultramicrsize - Fulvic P/G® (Schering), Grisactin Ultra® (Wyeth-Ayerst), Gris-PEG® (Allergan Herbert) - 125 mg, 165 mg, 250 mg, and 330 mg tablets.
Topical Antifungal Agents

Polyenes

Nystatin is commonly used for topical treatment of Candidal infections. See Polyene section in Systemic Antifungal agents for details on structure and mechanism of action.

I. USES

Nystatin - topical infections due to *Candida albicans*

a.) Thrush - in neutropenic patients undergoing chemotherapy, organ transplant recipients. Common initial symptom of AIDS and - swish and swallow of oral suspension, or as troches, or nystatin popsicles.

b.) Intestinal candidiasis - oral tablets or vaginal tablets taken orally

c.) vaginal candidiasis - nystatin vaginal tablets

II. PRODUCTS and DOSING

**Amphotericin B** - Fungizone (Apothecon) - 3% Cream, Lotion, or ointment - for treatment of cutaneous or mucocutaneous candidiasis.

**Nystatin** - Mycostatin® Pastilles (B-M Squibb) - Licorice flavored troches - 200,000 units - one or two troches 4 or 5 times daily. Do not chew or swallow.

Oral Suspension: Mycostatin® (Squibb), Nilstat® (Lederle) – 100,000 units per ml. Dose: 400,000 - 600,000 units q.i.d. Place one half of dose in each side of mouth, retaining the drug as long as possible before swallowing.

Nystatin Powder for Extemporaneous Preparation of Oral Suspension (Paddock), Nilstat® (Lederle) - 50,000,000 units - 5,000,000,000 units. Used to prepare nystatin popsicles containing 250,000 - 500,000 units.

500,000 unit Oral Tablets - Mycostatin® (Squibb) give 1-2 tablets t.i.d. for intestinal candidiasis.

Vaginal Tablets: Mycostatin® (Squibb), Nilstat® (Lederle) 100,000 units - Insert 1 tablet vaginally daily for 2 weeks

Oral/Vaginal Therapy Pack O-V Statin (Squibb) - 42 oral tablets (500,000 units) and 14 vaginal tablets (100,000 units) with applicator.
Imidazole Antifungals (Topical)

I. USES

a.) Topical treatment of dermal infections due to *Trichophyton rubrum*, *T. mentagrophytes*, and *Epidermophyton floccosum*.

i. Athlete's foot (Tinea pedis)

ii. Jock itch (Tinea cruris)

iii. Ringworm (Tinea corporis)

b.) Vaginal candidiasis

c.) Cutaneous candidiasis (moniliasis) & pityriasis (tinea versicolor) due to *Malassezia furfur* - Rx only

d.) Dandruff due to *Pityrosporum ovale* - Ketoconazole only. Reduction in *P. ovale* in scalp was greater than with selenium sulfide (Selsun Blue®).

e.) Seborrheic dermatitis - Ketoconazole only - also due to *Pityrosporum ovale*

II. PRODUCTS

**Butoconazole nitrate** – Femstat® (Procter Syntex) - 2% vaginal cream with applicator. 1 applicatorful (~5 g) h.s. for 3 days. May be extended to 6 days (esp. if pregnant). FemStat One® (2% butaconazole) was approved as a Rx single-day treatment for candidal vaginitis in 1997.

**Clotrimazole** – Lotrimin® (Schering), Mycelex® (Bayer) - 1% cream, 1% lotion, 1% solution. as otc products - Lotrimin AF® (Schering-Plough), Mycelex OTC® (Miles) 1% cream, 1% solution.

Vaginal cream - FemCare® (Schering-Plough), Gyne-Lotrimin® cream (Schering Plough), Mycelex-G® (Miles) - 45 g of 1% cream (7 day supply) with applicator. One applicatorful (5 g) h.s. for 7-14 days.

Vaginal tablets - Gyne-Lotrimin® and Mycelex-G® tablets 100mg are otc. 500 mg vaginal tablets are Rx. Insert one 100 mg tablet h.s. for 7 nights or 2 100 mg tablets hs. for 3 nights or Insert one 500 mg h.s. one time only.

**Econazole nitrate** – Spectazole® (Ortho) - 1% cream

**Ketoconazole** – Nizoral (Janssen) -2% cream, 2% shampoo for dandruff. For tinea infection apply twice daily for 2 weeks. For seborrheic dermatitis - apply for 4 weeks.

**Miconazole nitrate** – Micatin® (Ortho) - 2% cream, 2% powder, 2% spray
Vaginal suppositories - Monistat 3® (Ortho) - 200 mg suppositories. Insert one suppository vaginally one daily h.s. for 3 days. Monistat 7® - 100 mg suppositories. Insert 1 daily h.s. for 7 days.

Vaginal cream - Monistat 7® (Ortho) - 2% cream, 45 g. One applicatorful cream for 7 days h.s.

**Oxiconazole nitrate** – Oxistat® (Glaxo) - 1% cream and 1% lotion

**Sulconazole nitrate** – Exelderm® (Westwood Squibb) 1% cream and 1% lotion

**Tioconazole** – Vagistat-1® (Bristol-Myers Squibb) - 6.5% vaginal ointment. OTC status 1997. Insert one applicatorful (~ 4.6 g) intravaginally h.s. as a single dose.

**Terconazole** – Vaginal Cream - Terazol 7® (Ortho) - 0.4% vaginal cream, 45 g. Insert one applicatorful (5 g) h.s. for 7 days. Terazol 3® (Ortho) - 0.8% vaginal cream, 80 mg vaginal suppositories Insert one applicatorful (5 g) or one suppository intravaginally h.s. for 3 days.

**Tolnaftate**

I. USES

   a.) Topical treatment of dermal infections due to *Trichophyton rubrum*, *T. mentagrophytes*, *Epidermophyton floccosum*, *Malassezia furfur*, *Microsporum canis*

      i. Athlete's foot (Tinea pedis)

      ii. jock itch (Tinea cruris)

      iii. Ringworm (Tinea corporis)

      iv. Pityriasis (Tinea versicolor)

II. PRODUCTS

   1% cream - NP.27® (Thompson Medical), Tinactin® (Schering-Plough)
   1% Solution - NP.27® (Thompson Medical), Tinactin® (Schering-Plough)
   1% Gel - Aftate® (Schering-Plough)
   1% Powder - Absorbine® (W.F Young), Aftate® (Schering-Plough), NP.27® (Thompson)
   1% Spray Powder – Aftate® & Tinactin® (Schering-Plough), NP.27 (Thompson Medical)
   1% Spray Liquid - Aftate® (Schering-Plough), Desenex® (Fisons)

**Undecylenic acid**

I. USES
Athlete's foot (Tinea pedis) - Desenex® (Ciba Consumer)
Jock itch (Tinea cruris) - Cruex® (Ciba Consumer)

II. PRODUCTS
10, 15%, or 19% powder - Cruex® (Ciba Consumer), Desenex® (Ciba Consumer)
20% Cream - Cruex® (Ciba Consumer), Desenex® (Ciba Consumer)
10% Foam - Desenex® (Ciba Consumer) - contains 35.2% isopropyl alcohol
22% Ointment - Desenex® (Ciba Consumer)
Soap – Desenex® (Ciba Consumer)
Note: Ointments, Creams, and Liquids are better for primary therapy. Powders are used as adjunctive therapy.
**Cicloprox olamine**

I. MECHANISM OF ACTION

This broad spectrum agent blocks transmembrane transport of amino acids into the fungal cell. At higher concentrations, the fungal cell membrane is altered allowing leakage of intracellular material.

II. USES

a.) Tinea pedis, Tinea cruris, Tinea corporis due to *T. rubrum, T. mentagrophytes, E. floccosum, and M. canis.*

b.) Candidiasis (moniliasis) due to *C. albicans*

c.) Tinea versicolor due to *M. furfur*

d.) Onychomycosis (nail infections) – 8% topical solution

III. PRODUCTS

Ciclopirox olamine - Loprox® (Hoechst-Marion-Roussel) - 1% cream and 1% ointment
Ciclopirox – Penlac Nail Liqueur (Dermik) – 8% topical solution (Rx only)

**Haloprinig**

II. USES

a.) Tinea pedis, Tinea cruris, Tinea corporis, Tinea manuum due to *T. rubrum, T. mentagrophytes, T. tonsurans, E. floccosum, and M. canis.*

b.) Candidiasis (moniliasis) due to *C. albicans*

c.) Tinea versicolor due to *M. furfur*

III. PRODUCTS

Haloprinig - Halotex (Westwood Squibb) - 1% cream and 1% solution

**Naftifine and Terbinafine**

I. MECHANISM OF ACTION

Naftifine and terbinafine are synthetic allylamines. They interfere with sterol biosynthesis by inhibiting the enzyme squalene 2,3-epoxidase. This decreases the amount of ergosterol and causes squalene accumulation in fungi. Allylamines are fungicidal against a broad spectrum of fungi. Fungistatic versus *C. albicans.*

II. USES
a.) Tinea pedis, Tinea cruris, Tinea corporis, Tinea manuum due to \textit{T. rubrum, T. mentagrophytes, T. tonsurans, E. floccosum, and M. canis}.

b) Terbinafine is approved for oral treatment of onchomycosis of the toenail or fingernail

### III. PRODUCTS

- **Naftifine** - Naftin® (Allergan Herbert) - 1% cream, 1% gel
- **Terbinafine** - Lamisil® (Novartis) - 1% cream

Systemic absorption of naftifine was 6% with cream, ≤4.2% with gel. ~3.5% with terbinafine cream.

### Butenafine:

#### I. MECHANISM OF ACTION

Butenafine is a benzylamine analog with a mechanism of action similar to naftifine and terbinafine, the allylamine antifungals. It is also an inhibitor of squalene epoxidase, a key enzyme in the synthesis of ergosterol. For some fungal species, the drug is fungicidal.

#### II. USES

Approved for the topical treatment of athlete's foot due to \textit{Epidermophyton floccosum, Trichophyton mentagrophytes, or T. rubrum}

#### III. PRODUCTS

Mentax® (Penederm) - 1% cream in 2, 15, and 30 g tubes

### Triacetin (Glyceryl triacetate)

#### I. USES -

Very broad spectrum antifungal and antimicrobial agent. Kills both fungi (including \textit{Aspergillus, Candida, Rhizopus}) and yeasts. Has gram positive and gram negative spectrum as well

a.) Onychomycosis (nail fungus)

b.) Monilial impetigo and dermatitis due to \textit{Candida} sp.

c.) Tinea pedis, Tinea cruris, Tinea corporis, Tinea manuum due to \textit{T. rubrum, T. mentagrophytes, T. tonsurans, E. floccosum, and M. canis}.

#### II. PRODUCTS

Fungoid® (Pedinol) - Tincture (for nails), Solution, Cream
Ony-Clear Nail® - Aerosol Spray