

ANTIFUNGAL DRUGS

Fungal infections (mycoses) can be both **superficial** and **systemic**.

Susceptibility: Broad-spectrum antimicrobial agents, AIDS, Immunosuppressant drugs, Cancer chemotherapy.

Systemic infections (Candidiasis, Cryptococcal meningitis, Aspergillosis, Blastomycosis). Pulmonary aspergillosis is a leading cause of death in immune-compromised patients.

Superficial infections (Oral and vulvovaginal candidiasis, Tinea pedis, Tinea corporis, ringworm, etc.)

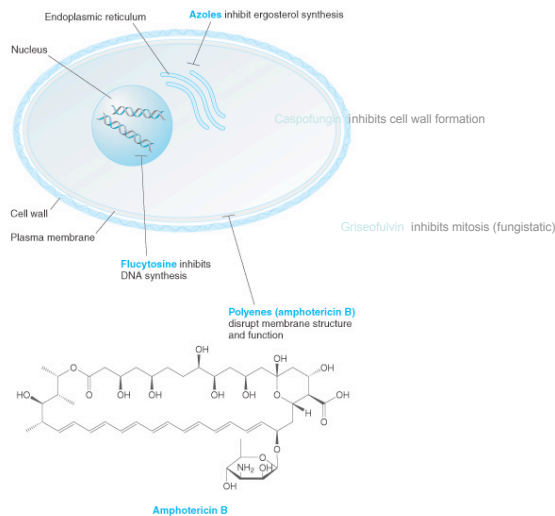


Figure 36-1. **Cellular Targets of Antifungal Agents.** Currently available antifungal agents target three cellular components of fungi. Fungi synthesize ergosterol, a membrane sterol not present in mammalian cells. Azoles inhibit the synthesis of ergosterol in the endoplasmic reticulum of the fungal cell. Polyenes such as amphotericin B bind to ergosterol in the fungal membrane, causing disruption of membrane structure and function. Flucytosine is converted within the fungal cell to 5-fluorouracil, which inhibits DNA synthesis.

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Topical and Systemic antifungal drugs

Amphotericin B: Used for treating systemic fungal disease by slow intravenous injection. This drug is also used topically (mycotic corneal ulcers and keratitis can be cured with topical drops).

Nystatin: It is very similar in structure to Amphotericin B but is used only as a topical drug because it is too toxic for systemic administration. Not absorbed from skin and oral membranes.

Ketoconazole: Used both as topical agent in lotion/shampoo and given orally for systemic fungal infections.

Clotrimazole: Topical agent used in lotions and oral troches.

Griseofulvin: Fungistatic drug used only in the systemic treatment of dermatophytosis.

Flucytosine: Synthetic antifungal drug given orally for systemic infections.

Amphotericin-B and Nystatin

Mechanism

Fungal cells, unlike mammalian cells and bacteria, contain large amount of ergosterol in the plasma membrane. Polyene antibiotics bind to ergosterol, act as ionophores, and cause leakage of potassium ions.

Azoles---Synthetic fungistatic agents

Mechanism

Azoles inhibit ergosterol synthesis by blocking lanosterine 14 α -demethylase, which converts lanosterol to ergosterol. This leads to increase membrane fluidity and permeability and inhibition of fungal cell growth and replication.

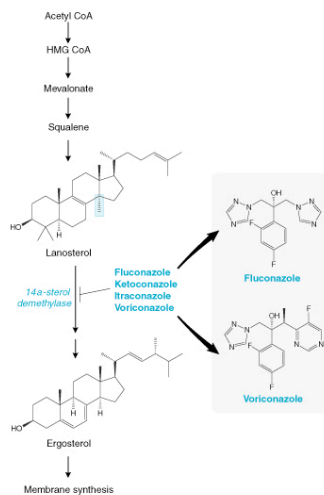


Figure 36-2 **Mechanism of Action of Azoles.** Ergosterol is synthesized within fungal cells from acetyl CoA building blocks. (Note the similarity between this pathway and the biosynthetic pathway leading to cholesterol synthesis in mammalian cells, depicted in Fig. 22-7.) Azoles act by inhibiting the cytochrome P450 enzyme 14 α -sterol demethylase, an enzyme not expressed in mammalian cells. Inhibition of this enzyme prevents the synthesis of ergosterol, which is the principal sterol in fungal membranes.

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Ketoconazole

Broad-spectrum antifungal agent, given orally, and requires acidity for dissolution. Toxic. Inhibits steroid and testosterone synthesis at high dose, resulting in gynecomastia in some male patients.

Contraindications: Histamine H2-receptor antagonists, Antacids

Miconazole

Broad-spectrum agent, applied topically and intravenously. Superior drug for systemic infections.

Itraconazole

Requires low pH for absorption, does not penetrate CSF. Does not inhibit steroidogenesis.

Fluconazole

Does not require low gastric pH for absorption. Fungicidal. CSF concentration is 70% that of plasma. Does not inhibit steroidogenesis. Fungal meningitis.

Clotrimazole (Gyne-Lotrimin)

Broad-spectrum fungistatic agent. Topical drug for vaginal and oral candidiasis.

Flucytosine

Synthetic fluorinated pyrimidine. Fungistatic agent well absorbed after oral administration. Its concentration in CSF is 50-90% that in plasma. Less toxic than amphotericin-B. Combination is treatment choice for Cryptococcal meningitis.

Mechanism: Flucytosine is converted to the antimetabolite 5-fluorouracil (5-FU) in fungal cells. 5-FU inhibits thymidylate synthetase and DNA synthesis. Mammals lack cytosine deaminase.

Griseofulvin

Mechanism

Acts as a fungistatic agent by binding to microtubules causing inhibition of mitosis. Induces cytochrome 450 and causes important drug interactions.

Echinocandins (Caspofungin)

Natural product antibiotic, blocks cell wall formation

Useful vs. cryptic Aspergillus (invasive aspergillosis) and Candida (esophageal candiditis), especially in azole resistance or amphotericin B intolerance

Not absorbed from GI tract; administered by iv infusion once daily

Candidiasis Treatment: Topical vs. Systemic Drugs

Topical antifungals are usually the drug of choice for uncomplicated, localized candidiasis in patients with normal immune function.

Systemic antifungals are usually indicated in cases of disseminated disease and/or in immunocompromised patients.

Duration of therapy: Medication should be continued for at least 48 hours after the disappearance of clinical signs of candidiasis along with complete healing and the absence of mucosal erythema. Some sources recommend drug therapy should be continued for 10–14 days regardless of the disappearance of clinical signs of candidiasis.

Suggested Medications for the Treatment of Pseudomembranous Candidiasis:

Topical antifungal medications:

1. Rx:
Nystatin oral suspension 100,000 units/ml
Disp: 300 ml (14+ day supply)
Sig: Rinse with 1 teaspoonful (5 ml) for two minutes, use q.i.d. (after meals, and at bedtime) and spit out. NPO 1/2 hour. (Patient can be directed to rinse and swallow if there is pharyngeal involvement).
2. Rx:
Clotrimazole troches, 10 mg
Disp: 70 troches
Sig: Let 1 troche dissolve in mouth 5 times per day for 14 days. Do not chew. NPO 1/2 hour.

• Systemic antifungal medications:

1. Rx:
Ketoconazole tablets, 200 mg
Disp: 14 tablets
Sig: Take 1 tab q.d. with a meal or orange juice for 14 days
2. Rx:
Fluconazole tablets, 100 mg
Disp: 15 tablets
Sig: Take 2 tablets stat, then 1 tablet q.d. for 14 days
3. Rx:
Itraconazole tablets, 100 mg
Disp: 28 tablets
Sig: Take 1 tablet b.i.d. with a meal or orange juice for 14 days