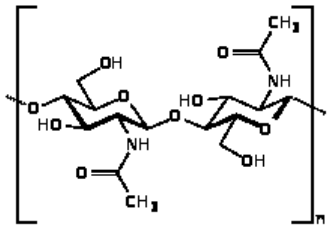
Antifungal Drugs

Pharmacology 3

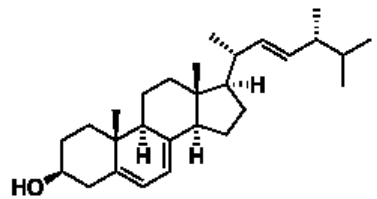
Dr. Heba Khader

Fungi

- Eukaryotic organisms
- Have rigid cell wall contain chitin (derivative of glucose) and polysaccharides
- Cell membrane composed of ergosterol

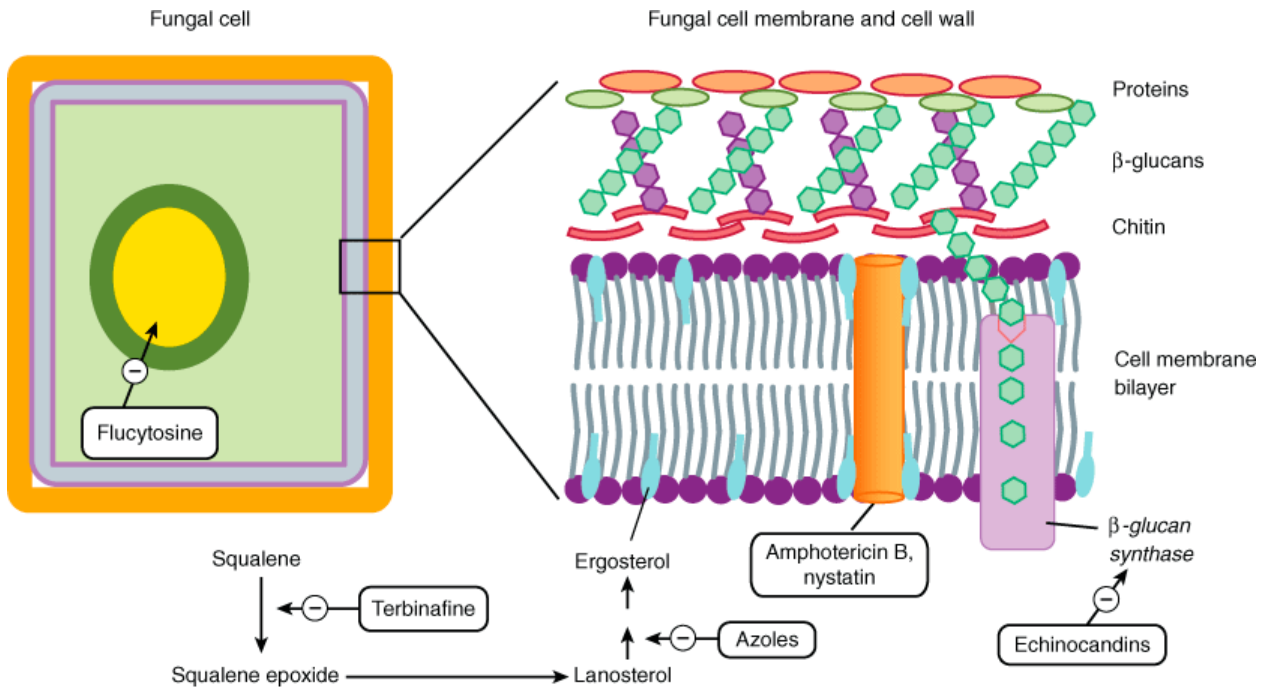


Structure of the chitin molecule



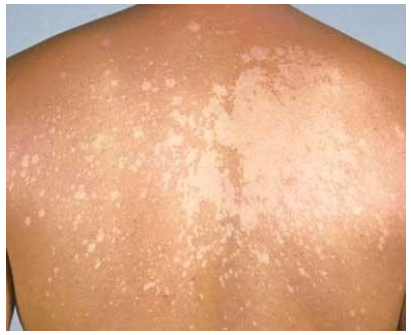
Ergosterol

Fungal cell wall and membrane

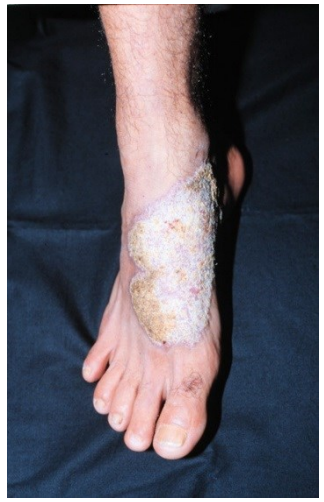


Source: Katzung BG, Masters SB, Trevor AJ: *Basic & Clinical Pharmacology, 11th Edition:* http://www.accessmedicine.com

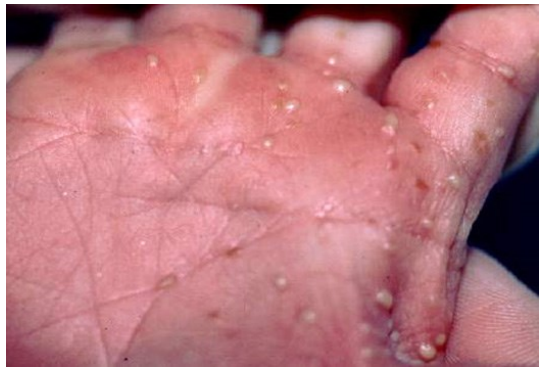
- Infectious diseases caused by fungi called mycoses
- Many common mycotic infection are superficial and only involve the skin, but fungi may also penetrate the skin causing subcutaneous, cutaneous, and systemic infections



Superficial



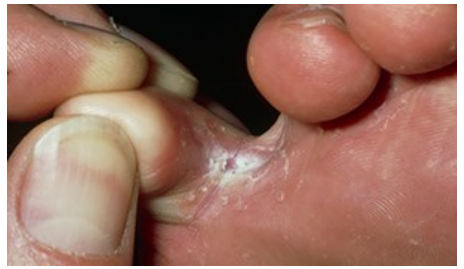
Subcutaneous
Chromoblastomycosis



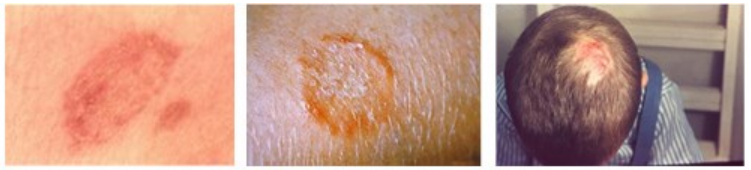
Cutaneous

Common fungal infections

- Athlete's foot



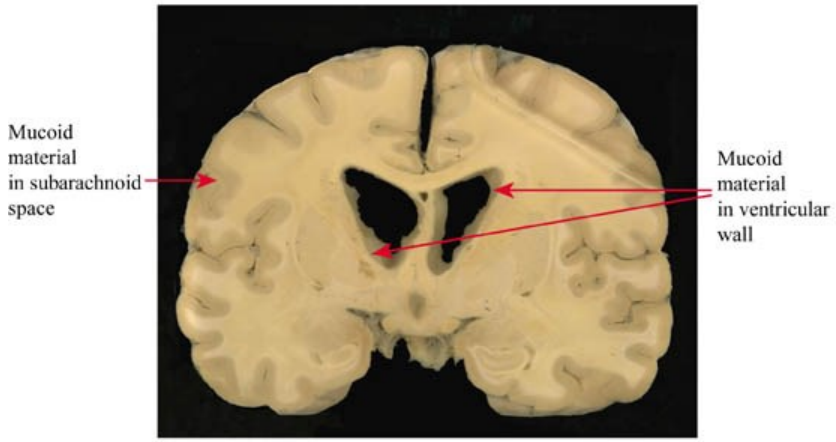
- Ringworm



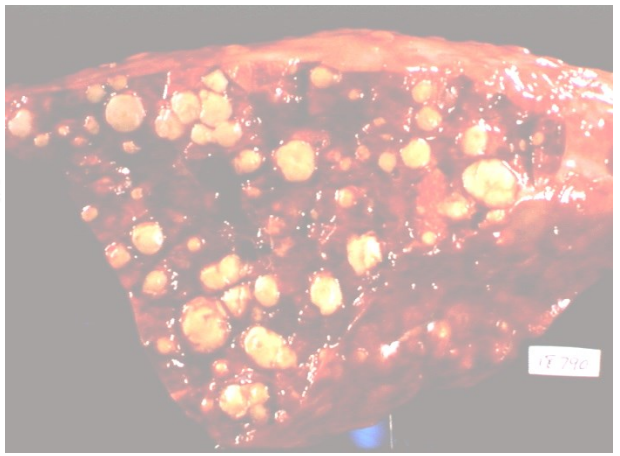
Ringworm on the back | Ringworm on the arm | Ringworm on the scalp

- Yeast diaper rash
- Candidiasis
  - in the mouth or throat is called "thrush" or oropharyngeal candidiasis.
  - in the vagina is commonly referred to as a "yeast infection." It occurs when there is overgrowth of the normal yeast in the vagina.
  - Invasive candidiasis occurs when *Candida* species enter the bloodstream and spread throughout the body.

- Fungi are opportunistic organism that cause systemic infection in immunosuppressed individuals (cancer, transplant patients, those debilitated by AIDS, tuberculosis)
- Opportunistic fungi: cryptococcal meningitis or aspergillosis

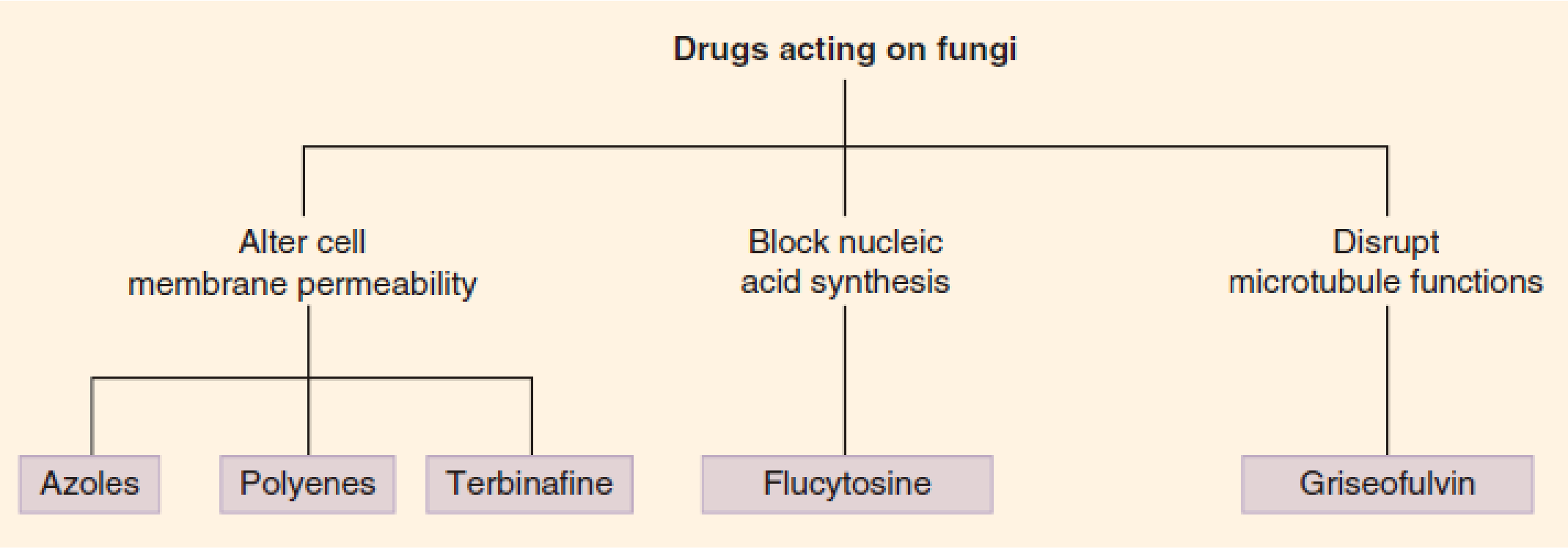


Cryptococcal meningitis - A coronal section of the brain



Aspergillus pneumonia in lung of deer

Antifungal Drugs

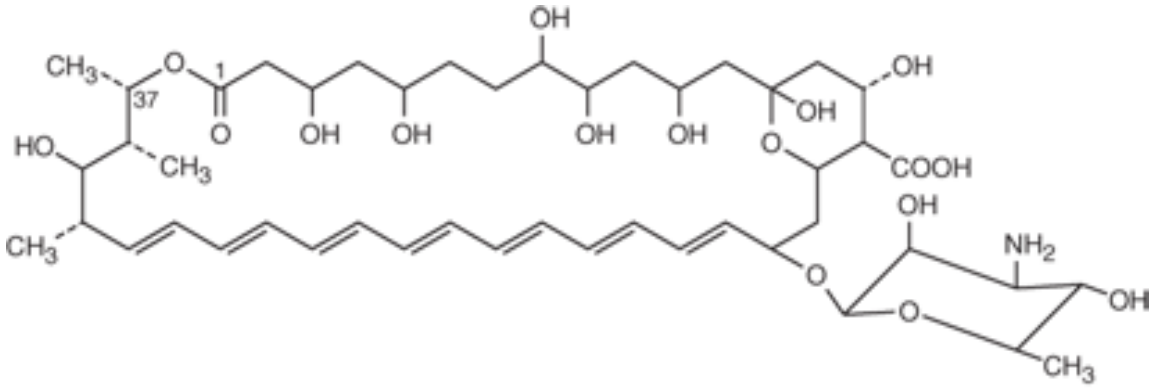


Antifungal Drugs

- The antifungal drugs presently available fall into the following categories:
  - ✓Systemic drugs (oral or parenteral) for systemic infections
    - ✓Amphotericin B
    - ✓Flucytosine
    - ✓Azole antifungals
    - ✓Echinocandins
  - ✓Oral systemic drugs for mucocutaneous infections
    - ✓Griseofulvin
    - ✓Terbinafine
  - ✓Topical drugs for mucocutaneous infections.
    - ✓Nystatin
    - ✓Topical azoles
    - ✓Terbinafine

Amphotericin B

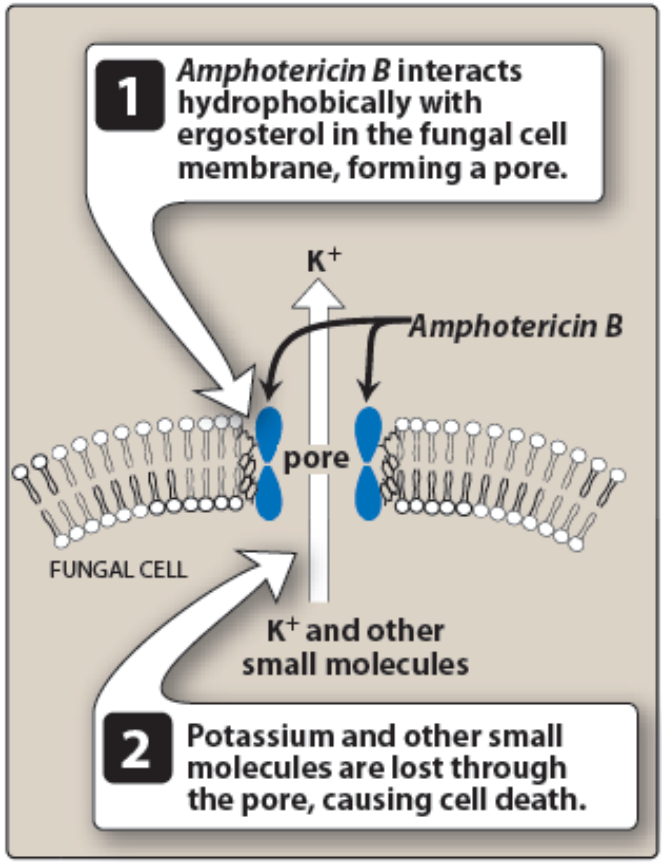
- Naturally occurring polyene macrolide antibiotic.
- **Amphotericin B** was the only efficacious antifungal drug available for systemic use. While highly effective in many serious infections, it is also quite toxic.
- In the last several decades, the relatively nontoxic **azole** drugs (both oral and parenteral formulations) and the **echinocandins** (only available for parenteral administration) have been introduced.



Amphotericin B

Amphotericin B

- **Mechanism of action:**
- The antifungal action of amphotericin B is due to its effects on the permeability and transport properties of fungal membranes.
- Polyenes are molecules with both hydrophilic and lipophilic characteristics (ie, they are amphipathic). They bind to **ergosterol,** a sterol specific to fungal cell membranes, and cause the formation of artificial pores.
- The pores disrupt membrane function, allowing electrolytes (particularly potassium) and small molecules to leak from the cell, resulting in cell death.
- Some binding to human membrane sterols does occur, probably accounting for the drug's prominent toxicity.



Amphotericin B

- **Pharmacokinetics:**
- Amphotericin is poorly absorbed from the gastrointestinal tract and is usually administered **intravenously** (slow intravenous infusion).

- Oral amphotericin B is thus effective only on fungi within the lumen of the tract and cannot be used for treatment of systemic disease.

- The drug is widely distributed in most tissues, but only 2–3% of the blood level is reached in cerebrospinal fluid, thus occasionally necessitating intrathecal therapy for certain types of fungal meningitis.

Amphotericin B

- **Clinical uses:**
- Amphotericin B is one of the most important drugs available for the treatment of systemic mycoses and is often used for initial induction regimens to rapidly reduce fungal burden and then replaced by one of the newer azole drugs for chronic therapy or prevention of relapse.

- Amphotericin B is usually given by **slow intravenous infusion** at a dosage of 0.5–1 mg/kg/d, but in fungal meningitis intrathecal administration, though dangerous, has been used.

- **Local administration** of the drug, with minimal toxicity, has been used in treatment of mycotic corneal ulcers and keratitis.

Amphotericin B

- **Adverse Effects:**

1. **Infusion-related reactions** are nearly universal and consist of fever, chills, muscle spasms, vomiting, headache, and hypotension.

- They can be ameliorated by slowing the infusion rate or decreasing the daily dose.
- Premedication with antipyretics, antihistamines, meperidine (pethidine), or corticosteroids can be helpful.
- When starting therapy, many clinicians administer a test dose of 1 mg intravenously to scale the severity of the reaction. This can serve as a guide to an initial dosing regimen and premedication strategy.
- **Hypotension:** A shock-like fall in blood pressure accompanied by hypokalemia may occur, requiring potassium supplementation. Care must be exercised in patients taking *digoxin* and other drugs that can cause potassium fluctuations.

Amphotericin B

2. Nephrotoxicity

- Renal damage is the most significant toxic reaction. Renal function usually returns with discontinuation of the drug, but residual damage is likely at high doses.
- Anemia may result from decreases in the renal formation of erythropoietin.
- It is common practice to administer normal saline infusions with the daily doses of amphotericin B to reduce renal damage.
- Dose reduction (with lowered toxicity) is possible in some infections when amphotericin B is used with flucytosine.

3. Neurotoxicity

- Intrathecal administration of amphotericin B may cause seizures and neurologic damage.

Lipid Formulation of Amphotericin B

Therapy with amphotericin B is often limited by toxicity, especially drug-induced renal impairment. This has led to the development of lipid drug formulations on the assumption that lipid-packaged drug binds to the mammalian membrane less readily, permitting the use of effective doses of the drug with lower toxicity. Liposomal amphotericin preparations package the active drug in lipid delivery vehicles, in contrast to the colloidal suspensions, which were previously the only available forms. Amphotericin binds to the lipids in these vehicles with an affinity between that for fungal ergosterol and that for human cholesterol. The lipid vehicle then serves as an amphotericin reservoir, reducing nonspecific binding to human cell membranes. This preferential binding allows for a reduction of toxicity without sacrificing efficacy and permits use of larger doses. Furthermore, some fungi contain lipases that may liberate free amphotericin B directly at the site of infection.

Three such formulations are now available and have differing pharmacologic properties as summarized in Table 48–1. Although clinical trials have demonstrated different renal and infusion-related toxicities for these preparations compared with regular amphotericin B, there are no trials comparing the different formulations with each other. Limited studies have suggested at best a moderate improvement in the clinical efficacy of the lipid formulations compared with conventional amphotericin B. Because the lipid preparations are much more expensive, their use is usually restricted to patients intolerant to, or not responding to, conventional amphotericin treatment.

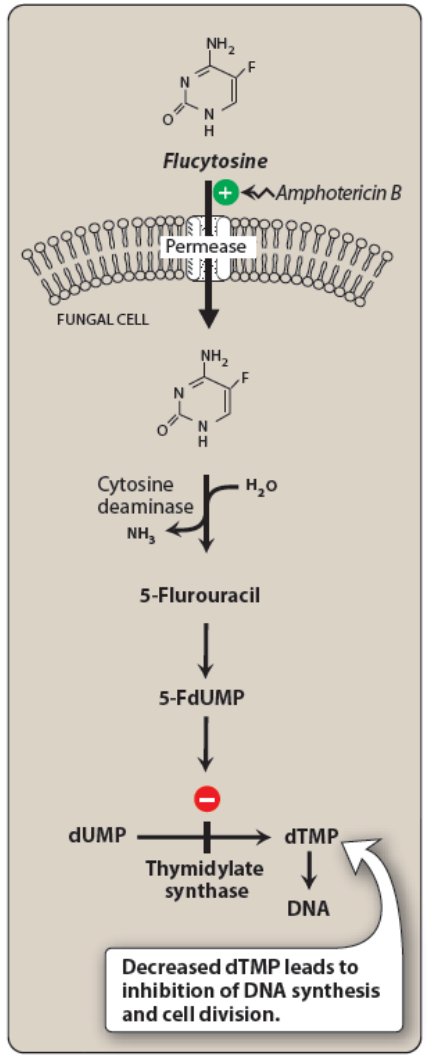
TABLE 48–1 Properties of conventional amphotericin B and some lipid formulations.[1]

Drug	Physical Form	Dosing (mg/kg/d)	C_{max}	Clearance	Nephrotoxicity	Infusional Toxicity	Daily Cost ($)
Conventional formulation							
Fungizone	Micelles	1	—	—	—	—	24
Lipid formulations							
AmBisome	Spheres	3–5	↑	↓	↓	↓	1300
Amphotec	Disks	5	↓	↑	↓	↑(?)	660
Abelcet	Ribbons	5	↓	↑	↓	↓(?)	570

[1]Changes in C_{max} (peak plasma concentration), clearance, nephrotoxicity, and infusional toxicity are relative to conventional amphotericin B.

Flucytosine (5-FC)

- 5-FC is a synthetic pyrimidine often used with amphotericin B for the treatment of systemic mycoses and meningitis caused by *Cryptococcus neoformans* and *Candida albicans.*
- **Mechanism of action:**
- 5-FC enters fungal cells **by cytosine permease**.
- Once inside, it is converted **to 5-fluorouracil (5-FU)** by the enzyme **cytosine deaminase**.
- Selective toxicity occurs because mammalian cells lack cytosine deaminase.
- Note: Amphotericin B increases cell permeability, allowing more 5-FC to penetrate the cell. Thus, 5-FC and amphotericin B are synergistic.



Flucytosine (5-FC)

1. 5-FU is converted into 5-fluorouridine monophosphate(FUMP),

   which is phosphorylated further to **FUTP.**

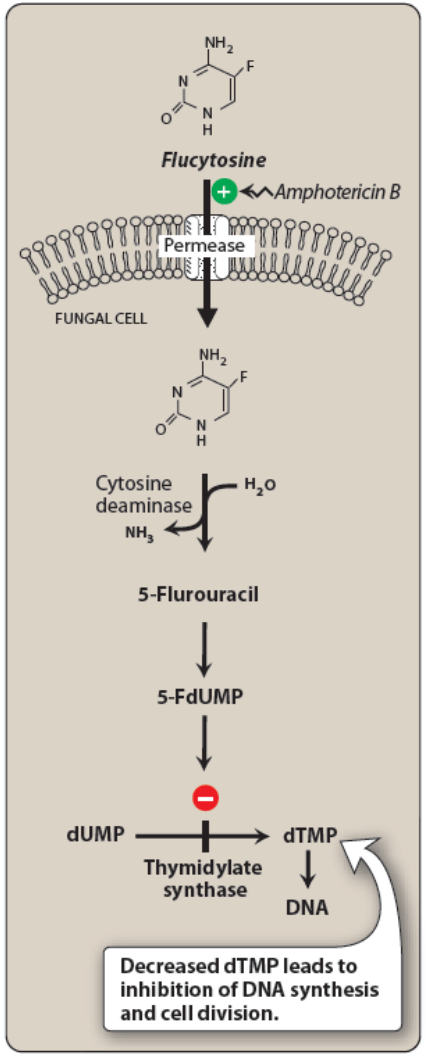
   - This is **incorporated into RNA, resulting in disruption of protein synthesis**.

2. 5-FU is also converted to 5-fluorodeoxyuridine monophosphate

   (**fdUMP**)

   - fdUMP is a potent **inhibitor of thymidylate synthase**, thereby depriving the fungi of thymidylic acid, an essential DNA component.

- **Resistance:**
- Resistance can occur rapidly if flucytosine is used alone and involves decreased activity of the fungal permeases or deaminases.



Flucytosine

Clinical uses:

- The antifungal spectrum of 5-FC is narrow; its clinical use at present is confined to:

1. combination therapy with amphotericin B for cryptococcal meningitis
2. combination therapy with itraconazole for chromoblastomycosis (subcutaneous infection).

Adverse effects:

- The adverse effects of flucytosine result from metabolism (possibly by intestinal flora) to the toxic antineoplastic compound fluorouracil.
- Bone marrow toxicity with anemia, leukopenia, and thrombocytopenia are the most common adverse effects.

Azole Antifungal Agents

- The azoles used for systemic mycoses include **ketoconazole,** an imidazole, and the triazoles **fluconazole, itraconazole, voriconazole,** and **posaconazole.**
- **Miconazole**, and **clotrimazole** (an imidazoles) are used only in **topical therapy**.
- **Fluconazole, itraconazole** and **voriconazole** are available in both oral and intravenous formulations.

TABLE 48–2 Pharmacologic properties of five systemic azole drugs.

	Water Solubility	Absorption	CSF: Serum Concentration Ratio	$t_{1/2}$ (hours)	Elimination	Formulations
Ketoconazole	Low	Variable	< 0.1	7–10	Hepatic	Oral
Itraconazole	Low	Variable	< 0.01	24–42	Hepatic	Oral, IV
Fluconazole	High	High	> 0.7	22–31	Renal	Oral, IV
Voriconazole	High	High	...	6	Hepatic	Oral, IV
Posaconazole	Low	High	...	25	Hepatic	Oral

Azole Antifungal Agents

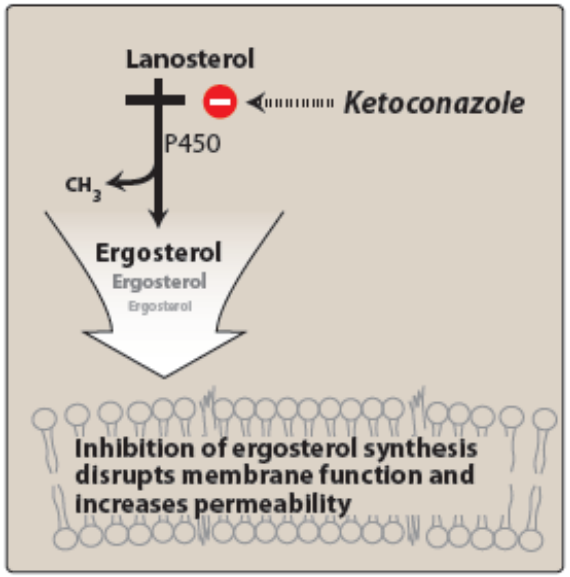
- The drugs are distributed to most body tissues, however, drug levels achieved in the CNS are very low (except **fluconazole**).
- Liver metabolism is responsible for the elimination of azole antifungals except **fluconazole** (which is eliminated by the kidneys, largely in unchanged form).

TABLE 48–2 Pharmacologic properties of five systemic azole drugs.

	Water Solubility	Absorption	CSF: Serum Concentration Ratio	$t_{1/2}$ (hours)	Elimination	Formulations
Ketoconazole	Low	Variable	< 0.1	7–10	Hepatic	Oral
Itraconazole	Low	Variable	< 0.01	24–42	Hepatic	Oral, IV
Fluconazole	High	High	> 0.7	22–31	Renal	Oral, IV
Voriconazole	High	High	...	6	Hepatic	Oral, IV
Posaconazole	Low	High	...	25	Hepatic	Oral

Azole Antifungal Agents

- **Mechanism of action**
- The azoles interfere with fungal cell membrane permeability by inhibiting the synthesis of ergosterol.
- These drugs act at the step of 14α-demethylation of lanosterol to ergosterol, which is catalyzed by a fungal cytochrome P450 isozyme.



- **Resistance:**
- With increasing use of azole antifungals, especially for long-term prophylaxis in immunocompromised and neutropenic patients, resistance is occurring.

Azole Antifungal Agents

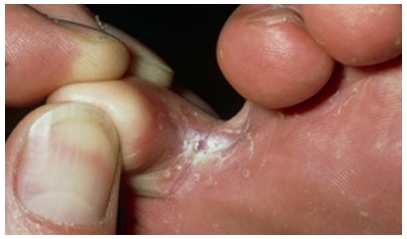
- **Pharmacokinetics:**
- When ketoconazole or itraconazole are administered orally, they requires gastric acid for dissolution and is absorbed through the intestinal mucosa.
- Drugs that raise gastric pH, such as antacids, or that interfere with gastric acid secretion, such as H2-histamine– receptor blockers and proton-pump inhibitors, impair absorption.
- Administering acidifying agents, such as cola drinks, before taking the drug can improve absorption in patients with achlorhydria.

Azole Antifungal Agents

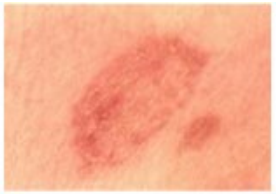
- **Clinical uses**

a. Ketoconazole

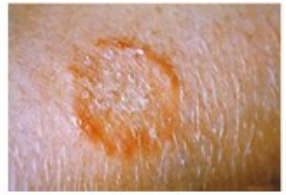
- Ketoconazole was the first oral azole introduced into clinical use. It is distinguished from triazoles by its greater propensity to inhibit mammalian cytochrome P450 enzymes; that is, it is less selective for fungal P450 than are the newer azoles. As a result, <u>systemic ketoconazole use only is only restricted to cases where effective antifungals not available or not tolerated and potential benefits of oral ketoconazole outweigh potential risks.</u>



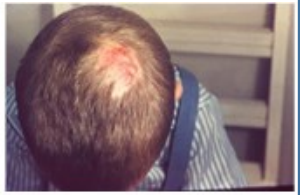
- However, ketoconazole continues to be used for chronic **mucocutaneous candidiasis** and is also effective against dermatophytes (cause **athlete's foot** and **ringworms).**
- It is also used topically in the treatment of
- **seborrheic dermatitis** and **dandruff**.



Ringworm on the back



Ringworm on the arm



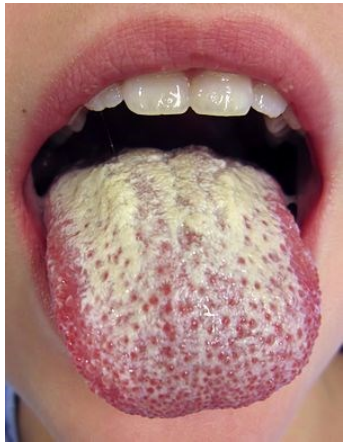
Ringworm on the scalp

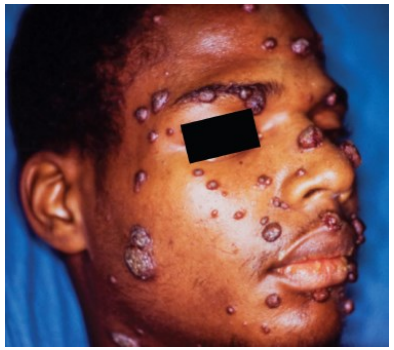
Azole Antifungal Agents

- **Clinical uses**

b. Fluconazole

- Fluconazole is a drug of choice in **esophageal and oropharyngeal candidiasis** and for most infections caused by ***Coccidioides.***
- A single oral dose usually eradicates **vaginal candidiasis.**
- Fluconazole is the drug of choice (with amphotericin B) in treatment of active disease due to ***Cryptococcus neoformans.***
- The drug is also equivalent to amphotericin B in **candidemia**.





Coccidioides

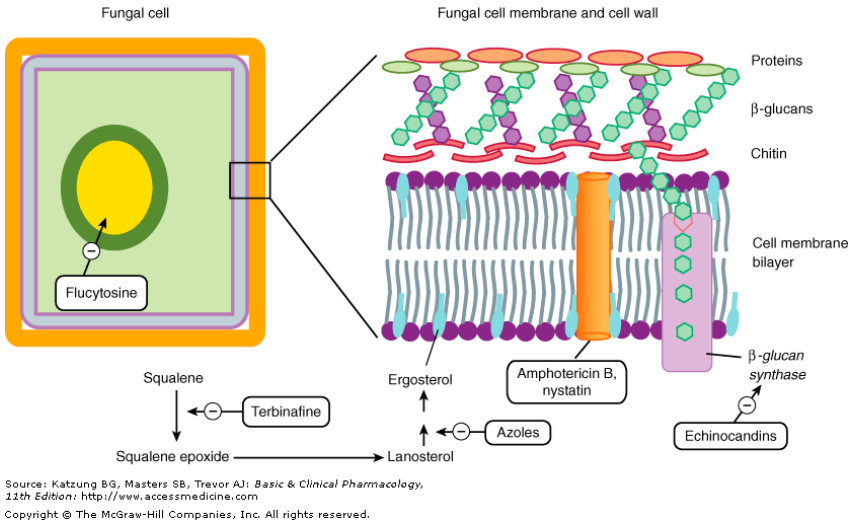
Azole Antifungal Agents

- **Adverse Effects:**
- Adverse effects of the azoles include vomiting, diarrhea, rash, and sometimes hepatotoxicity, especially in patients with preexisting liver dysfunction.

- **Ketoconazole** is a notorious inhibitor of hepatic cytochrome P450 isozymes and may increase the plasma levels of many other drugs, including cyclosporine, oral hypoglycemics, phenytoin, and warfarin.
- Inhibition of cytochrome P450 isoforms by ketoconazole interferes with the synthesis of adrenal and gonadal steroids and may lead to gynecomastia, menstrual irregularities, and infertility.
- The other azoles are more selective inhibitors of fungal cytochrome P450. Although they are less likely than ketoconazole to cause endocrine dysfunction, their inhibitory effects on liver drug-metabolizing enzymes have resulted in drug interactions.

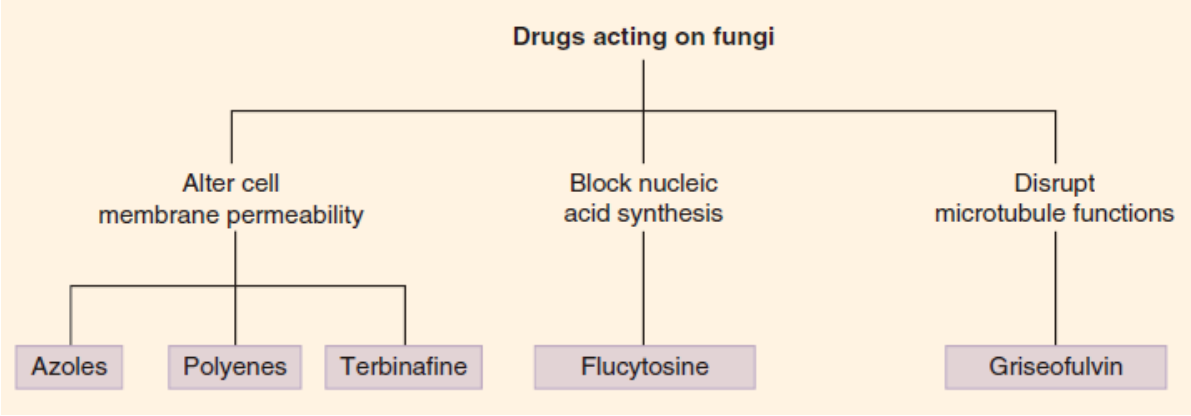
Echinocandins

- Echinocandins (**Caspofungin, micafungin,** and **anidulafungin)** are the newest class of antifungal agents to be developed.
- Echinocandins are available <u>only in intravenous formulations</u>.
- Echinocandins interfere with the synthesis of the fungal cell wall by inhibiting the synthesis of β(1,3)-glucan, leading to lysis and cell death.
- Echinocandin agents are extremely well tolerated, with minor gastrointestinal side effects and flushing reported infrequently.



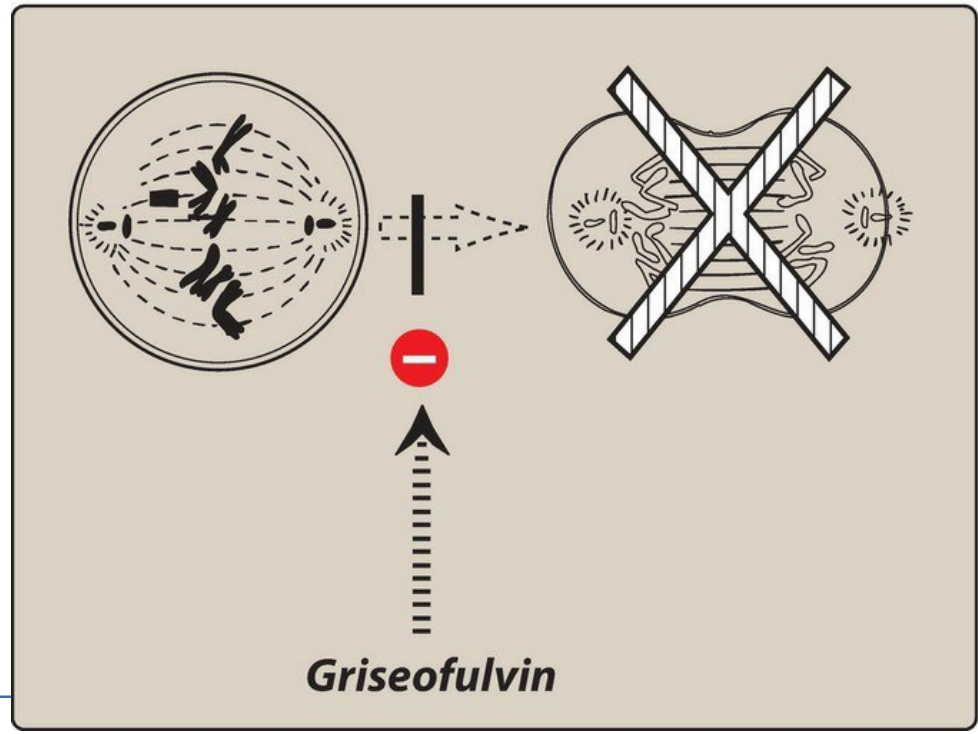
Antifungal Drugs

- The antifungal drugs presently available fall into the following categories:
  - ✓ Systemic drugs (oral or parenteral) for systemic infections
    - ✓ Amphotericin B
    - ✓ Flucytosine
    - ✓ Azole antifungals
    - ✓ Echinocandins
  - ✓ Oral systemic drugs for mucocutaneous infections
    - ✓ Griseofulvin
    - ✓ Terbenafine
  - ✓ Topical drugs for mucocutaneous infections.
    - ✓ Nystatin
    - ✓ Topical azoles
    - ✓ Terbinafine



Griseofulvin

- Griseofulvin is used in the systemic treatment of dermatophytosis of the scalp and hair.
- It is administered in a microcrystalline form at a dosage of 1 g/d. Absorption is improved when it is given with fatty foods.
- Griseofulvin causes disruption of the mitotic spindle and inhibition of fungal mitosis
- It is deposited in newly forming skin where it binds to keratin, protecting the skin from new infection.



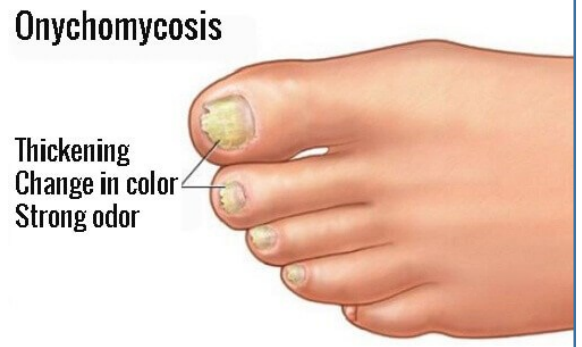
Griseofulvin

- Because its action is to prevent infection of these new skin structures, griseofulvin must be administered for 2–6 weeks for skin and hair infections to allow the replacement of infected keratin by the resistant structures.
- Nail infections may require therapy for months to allow regrowth of the new protected nail and is often followed by relapse. It has been largely replaced by oral terbinafine for the treatment of onychomycosis.

- Griseofulvin induces hepatic CYP450 activity, which increases the rate of metabolism of a number of drugs, including anticoagulants.
- The use of griseofulvin is contraindicated in pregnancy.

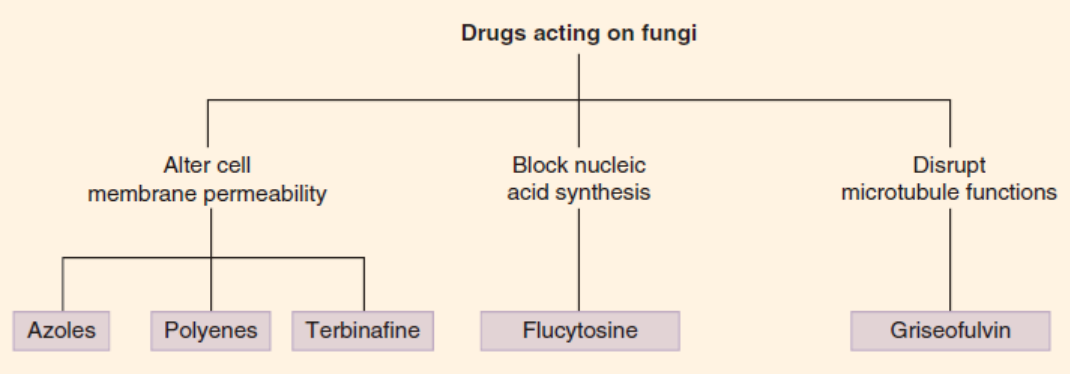
Terbinafine

- Terbinafine is used in the treatment of dermatophytoses, especially onychomycosis.
- Like griseofulvin, terbinafine is a keratophilic medication.
- Like the azole drugs, it interferes with ergosterol biosynthesis, but rather than interacting with the P450 system, terbinafine inhibits the fungal enzyme squalene epoxidase. This leads to the accumulation of the sterol squalene, which is toxic to the organism.
- One tablet given daily for 12 weeks achieves a cure rate of up to 90% for onychomycosis and is more effective than griseofulvin or itraconazole.
- Adverse effects are rare, consisting primarily of gastrointestinal upset and headache.
- Terbinafine does not seem to affect the P450 system and has demonstrated no significant drug interactions to date.



Antifungal Drugs

- The antifungal drugs presently available fall into the following categories:
  - ✓Systemic drugs (oral or parenteral) for systemic infections
    - ✓Amphotericin B
    - ✓Flucytosine
    - ✓Azole antifungals
    - ✓Echinocandins
  - ✓Oral systemic drugs for mucocutaneous infections
    - ✓Griseofulvin
    - ✓Terbenafine
  - ✓Topical drugs for mucocutaneous infections.
    - ✓Nystatin
    - ✓Topical azoles
    - ✓Terbinafine



Nystatin

- **Nystatin** is a polyene macrolide much like amphotericin B. It is too toxic for parenteral administration and is only used topically.
- Nystatin is currently available in creams, ointments, suppositories, and other forms for application to skin and mucous membranes.
- It is not absorbed to a significant degree from skin, mucous membranes, or the gastrointestinal tract. As a result, nystatin has little toxicity, although oral use is often limited by the unpleasant taste.
- Nystatin is active against most *Candida* sp and is most commonly used for suppression of local candidal infections.
- Some common indications include oropharyngeal thrush,

vaginal candidiasis, and intertriginous candidal infections.

  - In medicine, an **intertriginous** area is where two skin areas may touch or rub together.

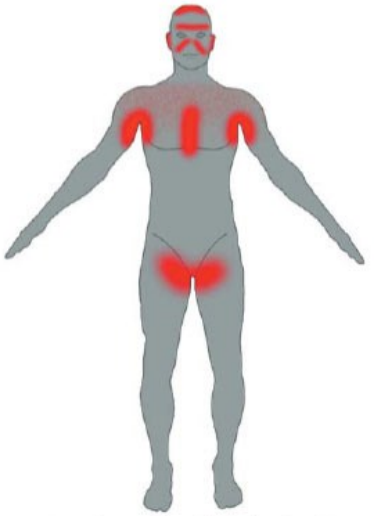


Figure 3: Body sites affected by seborrheic dermatitis

Topical azoles

- The two azoles most commonly used topically are **clotrimazole** and **miconazole**.
- Both are available over-the-counter and are often used for vulvovaginal candidiasis.
- Oral clotrimazole troches are available for treatment of oral thrush and are a pleasant-tasting alternative to nystatin.
- In cream form, both agents are useful for dermatophytic infections. Absorption is negligible, and adverse effects are rare.
- Topical and shampoo forms of **ketoconazole** are also available and useful in the treatment of seborrheic dermatitis.

Topical terbinafine

- Topical terbinafine (1% cream, gel or solution) is used to treat tinea pedis (athlete foot), tinea corporis (ringworm), and tinea cruris (infection of the groin).

- Duration of treatment is usually 1 week.

The End