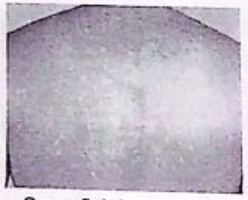
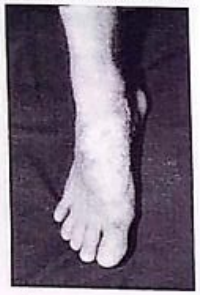
- Infectious diseases cased by fungi called mycoses
- Many common mycotic infection are superficial and only involve the skin, but fungi may also penetrate the skin causing subcutaneous, cutaneous, and systemic infections



Superficial

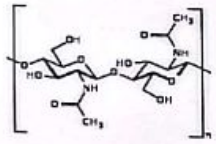


Subcutaneous
Chromoblastomycosis

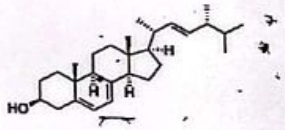
Cutaneous

Fungi

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



Structure of the chitin molecule

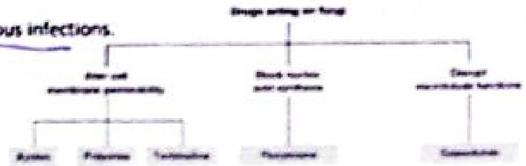


Ergosterol

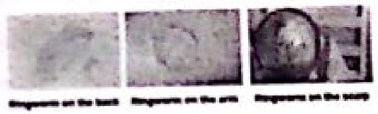
Antifungal Drugs

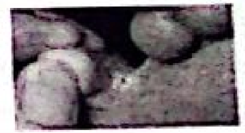
سؤال ✓✓

- 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



Common fungal infections





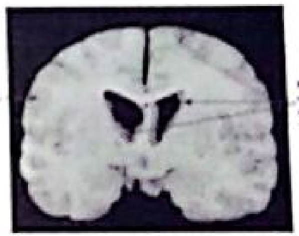
1. Athlete's foot
2. Ringworm
3. Yeast diaper rash
4. Candidiasis
   - in the mouth or throat is called "thrush" or oropharyngeal candidiasis.
   - in the vagina is commonly referred to as a "yeast infection." It occurs when there is overgrowth of the normal yeast in the vagina.
   - Invasive candidiasis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

Amphotericin B → oral + IV + intrathecal + Local

- Naturally occurring polyene macrolide antibiotic (polyene = containing many double bonds; macrolide = containing a large lactone ring of 12 or more atoms).
- For many years, **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.

oral, IV ← azole ← Amphotericin B بدائل ال *
IV ← echinocandins
بسبب سميتة

- Fungi is opportunistic organism which make 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

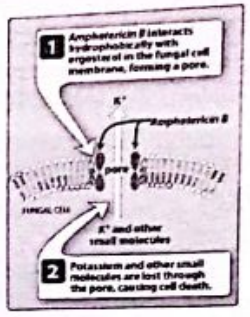
Aspergillus pneumonia in lung of deer

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.
- Elimination is mainly via hepatic metabolism; the half-life is approximately 2 wk.
- A small fraction of the drug is excreted in the urine; dosage modification is necessary only in extreme renal dysfunction.

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.



human membrane sterols

* سبب سميته انه يرتبط بـ

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.
- It has the widest antifungal spectrum of any agent and remains the **drug of choice, or codrug of choice, for most systemic infections** caused by *Aspergillus, Blastomyces, Candida albicans, Cryptococcus, Histoplasma,* and *Mucor.*
- 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.

للعين

Systemic mycosis: large h stoplasmosis abscesses involving the lung

Amphotericin B

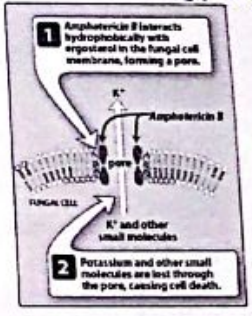
↓ ergosterol.

↓ affinity for the drug.

- **Resistance:**
- Resistance to amphotericin B occurs if ergosterol binding is impaired, either by:
- decreasing the membrane concentration of ergosterol

or

- by modifying the sterol target molecule to reduce its affinity for the drug.



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.
   - Amphotericin B decreases the glomerular filtration rate and causes renal tubular acidosis with magnesium and potassium wasting.
   - 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.

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:

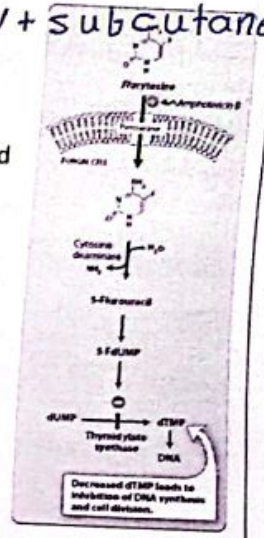
- The adverse effects of flucytosine result from metabolism (possibly by intestinal flora) to the toxic antineoplastic compound fluorouracil.
- Bone marrow toxicity with anemia, leukopenia, and thrombocytopenia are the most common adverse effects.

* 5 FU + amphotericin B = cryptococcal meningitis

* 5 FU + itraconazole = chromoblastomycosis (subcutaneous)

Flucytosine (5-FC) → combination → oral + IV + subcutaneous

- 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.
- Fungi lacking cytosine deaminase are resistant to 5-FC.
- Note: Amphotericin B increases cell permeability, allowing more 5-FC to penetrate the cell. Thus, 5-FC and amphotericin B are synergistic.



Azole Antifungal Agents azole آخره

- 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.**
- Oral bioavailability is variable (normal gastric acidity is required).
- **Fluconazole, itraconazole** and **voriconazole** are available in both oral and intravenous formulations.
- The drugs are distributed to most body tissues, however, drug levels achieved in the CNS are very low (except **fluconazole**). → fungal meningitis الدواء الوحيد المستخدم لل
- Liver metabolism is responsible for the elimination of azole antifungals except **fluconazole** (which is eliminated by the kidneys, largely in unchanged form).

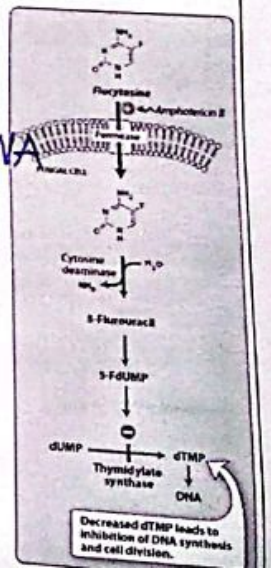
TABLE 48–2 Pharmacologic properties of five systemic azole drugs.

	Water Solubility	Absorption	CSF:Serum Concentration Ratio	$t_{1/2}$ (hours)	Elimination	Formulations
Ketoconazole	Low	Variable	< 0.1	7–19	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

Flucytosine (5-FC)

1. 5-FU is converted into 5-fluorouridine monophosphate(FUMP), which is phosphorylated further to **FUTP.** → inhibit mRNA
   - 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.



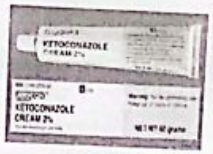
Azole Antifungal Agents

selectivity mammalian cytochrom P450 > selectivity fungal P450

- **Clinical uses**

a. Ketoconazole → oral + topical

- 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, 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.

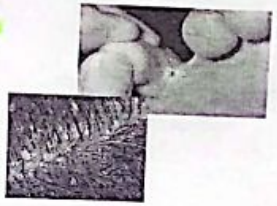


- However, ketoconazole continues to be used for chronic **mucocutaneous candidiasis** and is also effective against dermatophytes (**cause athlete's foot** and **ringworms**).
- It is also used topically in the treatment of **seborrheic dermatitis** and **dandruff**.


Ringworm on the back

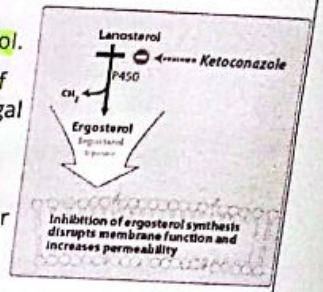
Ringworm on the arm

Ringworm on the scalp



Azole Antifungal Agents

- **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.



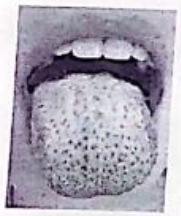
- **Resistance:**
- With increasing use of azole antifungals, especially for long-term prophylaxis in immunocompromised and neutropenic patients, resistance is occurring.
- Identified mechanisms of resistance include:
  1. Mutations in the C-14 α-demethylase gene, which cause decreased azole binding.
  2. Additionally, some strains of fungi have developed the ability to pump the azole out of the cell.

Azole Antifungal Agents

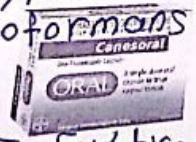
- **Clinical uses**

b. Fluconazole → oral + IV

- Fluconazole is a drug of choice in **esophageal and oropharyngeal candidiasis** and for most infections caused by ***Coccidioides.***
- A single oral dose usually eradicates for **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



x Fluconazole + Amphotericin B = cryptococcus neoformans

* fluconazole = amphotericin = for treat candidemia

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.

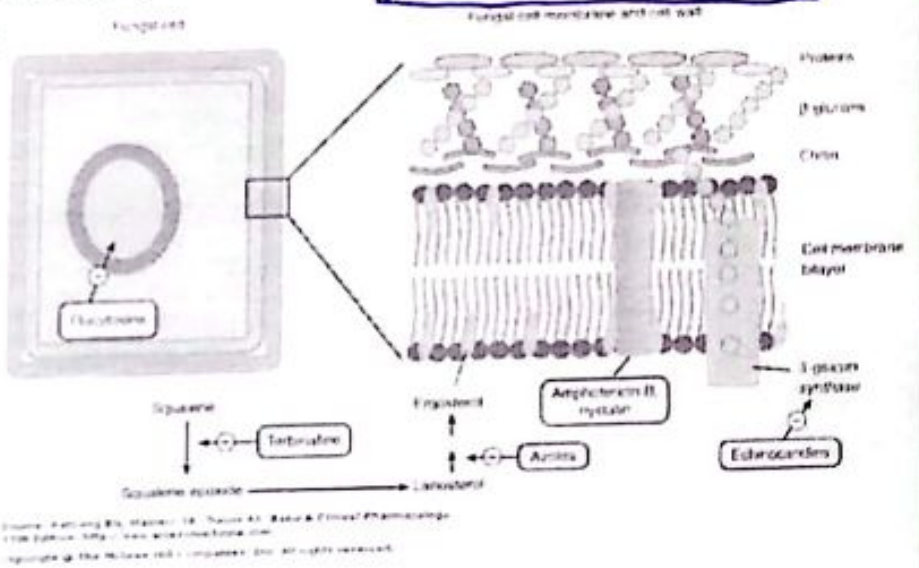
Azole Antifungal Agents

سؤال

- **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

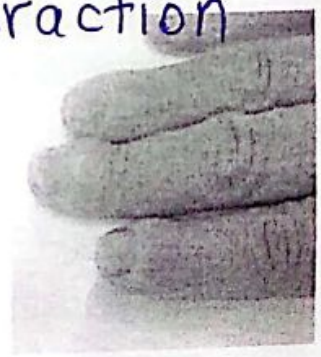
- Echinocandins (**Caspofungin, micafungin,** and **anidulafungin)** are the newest class of antifungal agents to be developed.
- Echinocandins are available only in intravenous formulations.
- Echinocandins interfere with the synthesis of the fungal cell wall by inhibiting the synthesis of β(1,3)-glucan, leading to lysis and cell death.
- These agents are active against *Candida* and *Aspergillus,* but not *C neoformans* or mucormycosis.
- Echinocandin agents are extremely well tolerated, with minor gastrointestinal side effects and flushing reported infrequently.



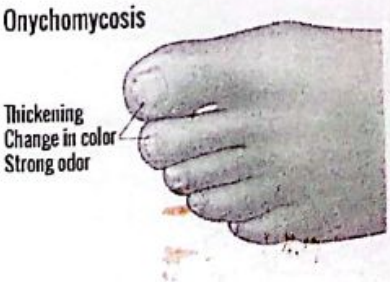
Griseofulvin

- Griseofulvin is only use is in the systemic treatment of dermatophytosis.
- 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's mechanism of action at the cellular level is unclear, but it is deposited in newly forming skin where it binds to keratin, protecting the skin from new infection.
- 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.
- Griseofulvin has been largely replaced by newer antifungal medications such as itraconazole and terbinafine.

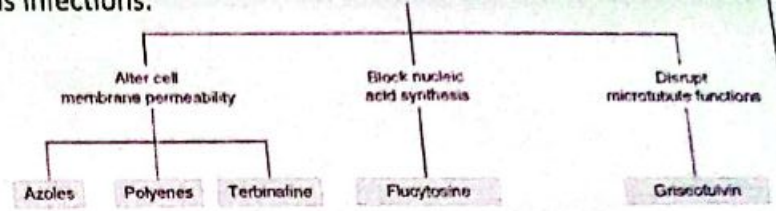
Terbinafine not have drug-drug interaction *



- Terbinafine is available in an oral formulation and is used at a dosage of 250 mg/d. It 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.



- ✓ Topical drugs for mucocutaneous infections:
  - ✓ Nystatin
  - ✓ Topical azoles
  - ✓ Terbinafine



allow the rep
infections ma
protected na

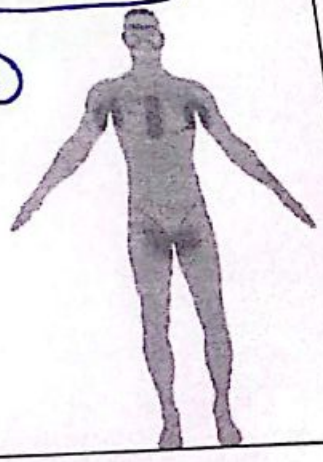
- Griseofulvin
- itraconazol

Nystatin → topical

- **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, (1) vaginal candidiasis, (2) and intertriginous candidal infections.

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



Terb

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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.