بسم الله الرحمن الرحيم

Antifungal part 2

Antifungal Drugs

Pharmacology 3

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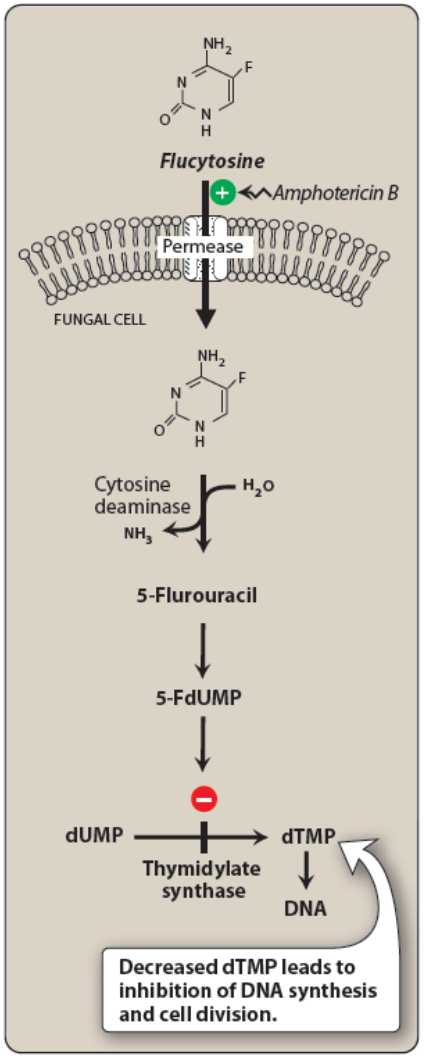
antifungal مع ادوية combination عادة يستخدم
resistance لانه لحاله بصير عليه infection

Flucytosine (5-FC) 5- fluorocytosine

- 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.



طيب هسا التركيز هون مطلوب بشكل كبير جدا جدا لانه حيصير في اختصارات للكلمات وفي تعقيديات بال mechanism فركزوا رجاءا
ال mechanism of action لل 5flucytosine (5-Fc) الي بين قوسين اختصاره واحفظوه وركزوا فيه , ال FC-5 عشان يدخل الخلية بحاجة انزايم اسمه cytosine permease
مجرد ما فات الدواء للخلية بيتحول ل fluorouracil-5 واختصاره (FU-5) بواسطة انزايم اسمه Cytosine deaminase , من الخصائص الي كويسة فيه انه الانزايم هاض مش موجود بال mammalian cells والدواء عامل selective toxicity اله(يعني بس نوخذه امورنا طيبة من هالناحية)
لكن المشكلة انه اذا ال fungai ما عندها هاض الانزايم، هاي ال fungai حتكون عاملة resistance لل FC-5
ال FU-5 وال amphotericin B بعطوا synergistic effect ، كيف؟

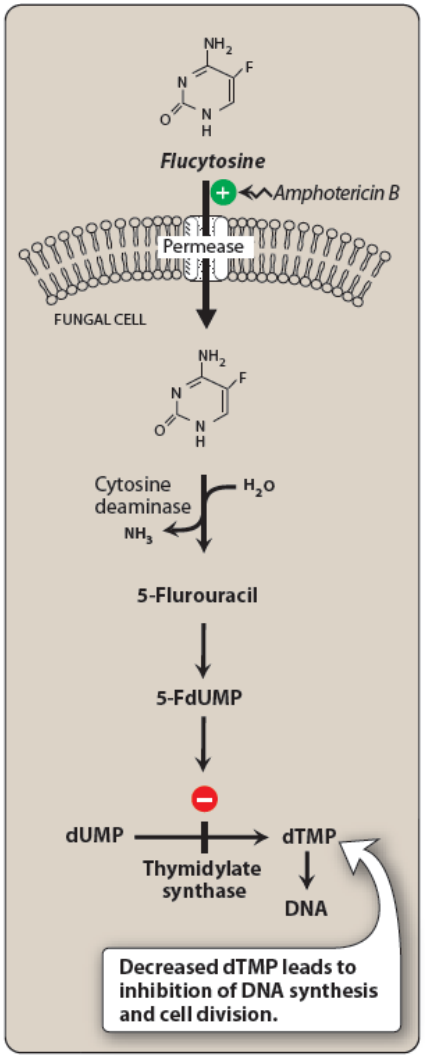
ذاكرين كيف بشتغل ال amphotericin b? كيف انه بعمل pore بال cell membrane وبخرب عند ال cell integrity لما يصير هاض الحكي حيسهل عندي دخول FC-5 لداخل الخلية

----------> لسا في تكملة للقصة هاي عشان هيك بقلكم ركزوا وعيدوا الحكي عشان يثبت.

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.



ال 5FU امامه خيارين
١- انه يتحول ل 5-(fluorouridine monophosphate (FUMP والي بدور بصيرله Phosphorylated to FUTP بصير TRI بدل MONO بندمج مع ال RNA وبعملي Disruption of protein synthesis

٢- انه يتحول 5-(flourodeoxyuridine monophosphate (fdUMP والي بدوره بعملي INHIBTION لل Thymidylate synthesis والي هو essential DNA component

كيف بصير للدواء resistance
هسا زي ما حكيت الدواء بحتاج 2 enzymes واحد عشان يقدر يدخل للخلية وواحد عشان يتحول ل 5 FU
ال fungai بتقلل عدد هذول ال enzymes وبتعملي resistance.

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

اخره zole

- 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**).
- Liver metabolism is responsible for the elimination of azole antifungals except **fluconazole** (which is eliminated by the kidneys, largely in unchanged form).

عشان هيك يمكن نلاقي ال fluconazole هو الدواء الوحيد المستخدم لل Fangal meningitis

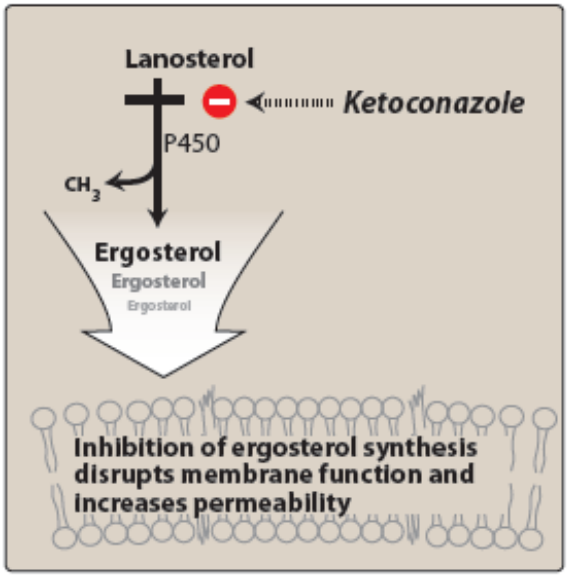
TABLE 48–2 Pharmacologic properties of five systemic azole drugs.

	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

بشتغل بآخر step لما يجي
يتحول ال lanosterol ل
ergosterol وال
conversion هاض يعتبر
demethylatiob

- **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.



خلل بالانزايم قلل من ارتباط الدواء بال
ergosterol

الخلية تطورت وقدرت تطرد ال azole
لبراتها

Azole Antifungal Agents

بده وسط حمضي عشان يتحلل ويمتص من خلال ال intestinal mucosa

- **Pharmacokinetics:**
- When ketoconazole or itraconazole are administered orally, they requires gastric acid for dissolution and is absorbed through the intestinal mucosa.

هاي الاشياء الي بتقلل من حموضة المعدة مش لازم اوخذها مع الدوا لانها بتعملي impair absorbtion

- 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.

الاشياء ال acidifying agent زي الكولا يعني بتخلي الوسط عندي حمضي او بتزيد الحمضية اني اوخذ قبل ما اوخذ الدواء بتزيد عندي ال absorption عند مرضى ال achlorhydria هضول مرضى المعدة عندهم ما بتصنع HCl المعدة عندهم ما بتكون acidic.

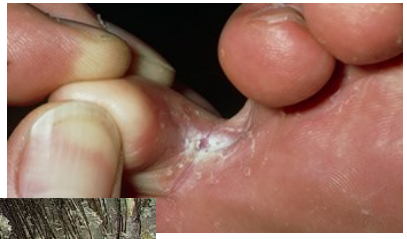
Azole Antifungal Agents

- **Clinical uses**
  selectivity mammalian cytochrome p450>>>selectivity fungal p450

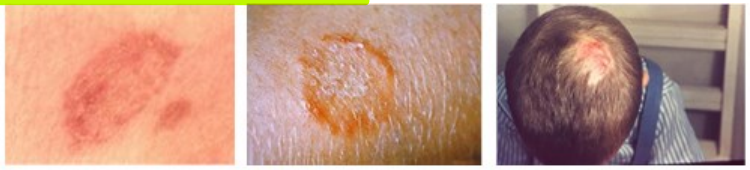
a. Ketoconazole

- 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, 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**.



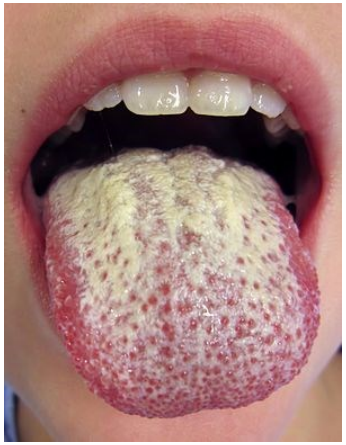
Ringworm on the back Ringworm on the arm Ringworm on the scalp

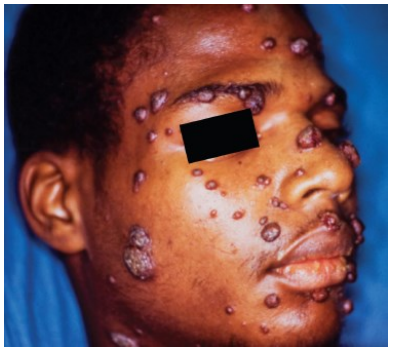
Azole Antifungal Agents

- **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.*** meningitis موجودة باول سلايد
- The drug is also equivalent to amphotericin B in **candidemia**.





Coccidioides

Azole Antifungal Agents

- **Clinical uses** ما حكت عنها الدكتورة غير انه اقرأوها🙂

c. Itraconazole

- This azole is currently the drug of choice for systemic infections caused by *Blastomyces* and *Sporothrix* and for subcutaneous chromoblastomycosis.
- Itraconazole is an alternative agent in the treatment of infections caused by *Aspergillus, Coccidioides, Cryptococcus,* and *Histoplasma.*
- In esophageal candidiasis, the drug is active against some strains resistant to fluconazole.
- Itraconazole is also used extensively in the treatment of dermatophytoses.

d. Voriconazole

- Voriconazole has an even wider spectrum of fungal activity than itraconazole.
- It is a codrug of choice for treatment of invasive aspergillosis; some studies report greater efficacy than amphotericin B.
- Voriconzole is an alternative drug in candidemia with activity against some fluconazole-resistant organisms.

Azole Antifungal Agents

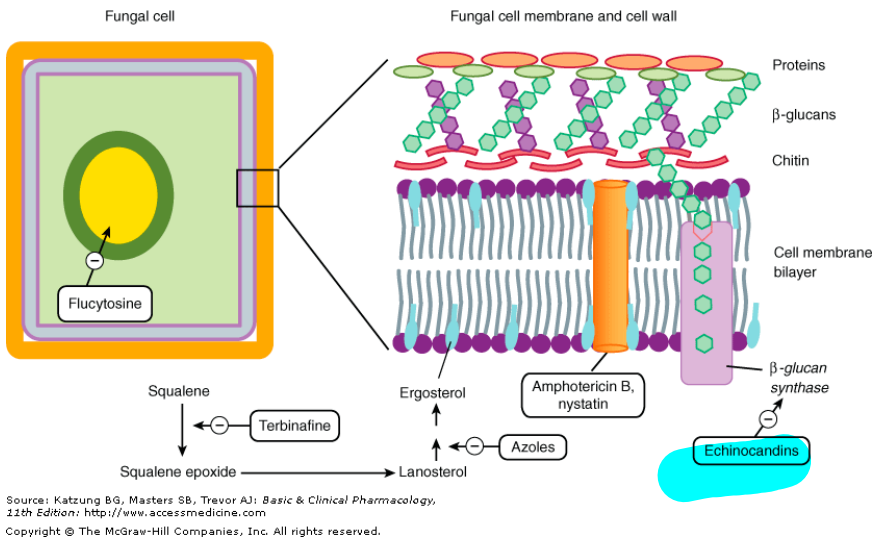
- **Adverse Effects:** بشكل عام بعمل ال azole
- Adverse effects of the azoles include vomiting, diarrhea, rash, and sometimes hepatotoxicity, especially in patients with preexisting liver dysfunction.
- **Ketoconazole** is a notorious inhibitor of hepatic cytochrome P450 isozymes and may increase the 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 systemic antifungal اخر

- 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.

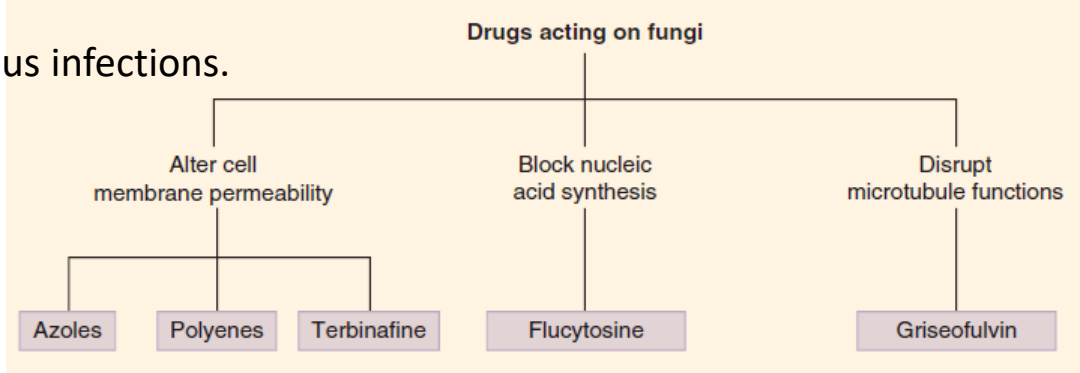
ال b- glucan هو جزء من cell wall ال

systemic drug for هيك خلصنا ال systemic infection.



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



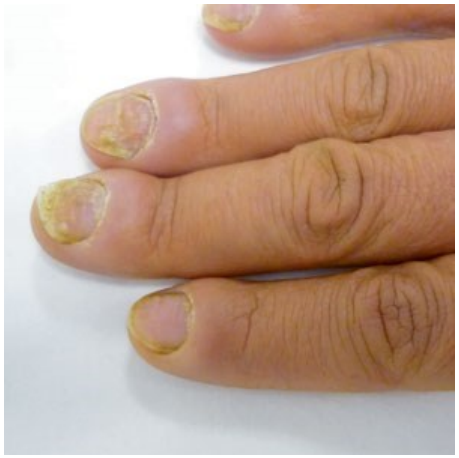
Griseofulvin

بنعطا oral والامتصاص تاعه بزيد مع ال fatty food🍗ال
mechanism تاعته مش مش مفهومة لسا،بس هو بعملي
deposited لل keratin الموجود بالجلد وبحميلي ال newly
formed من الجلد من ال infections

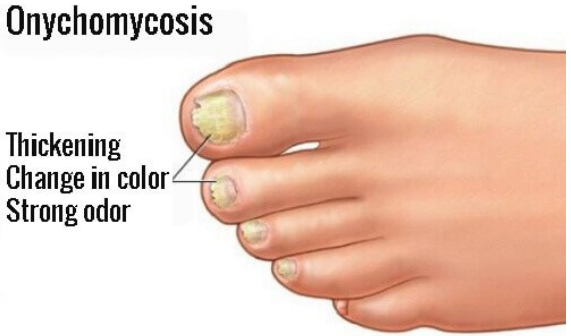
- Griseofulvin is only use is in the systemic treatment of dermatophytosis.
- It is administered in a microcrystalline form at a dosage of 1 g/d. Absorption is improved when it is given with fatty foods.
- Griseofulvin's mechanism of action at the cellular level is unclear, but it is deposited in newly 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

ال azole كان باخر step هون
من الاول تقريبا



- 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.



مافي interaction بيناتهم

Antifungal Drugs

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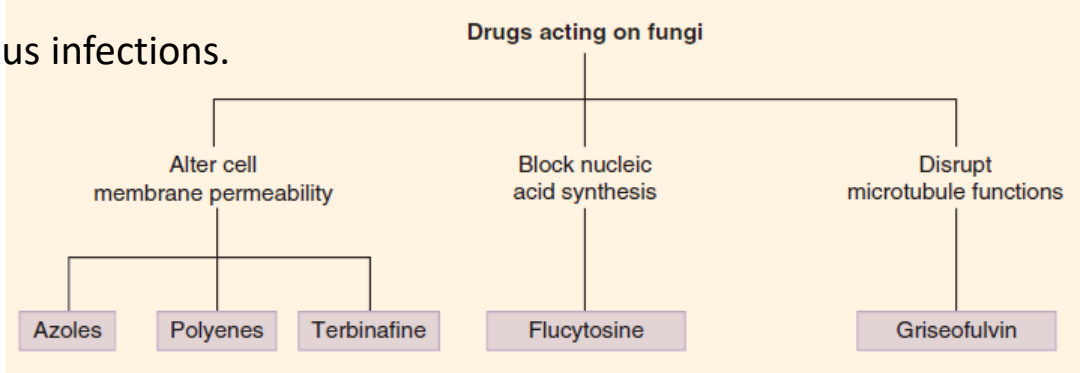
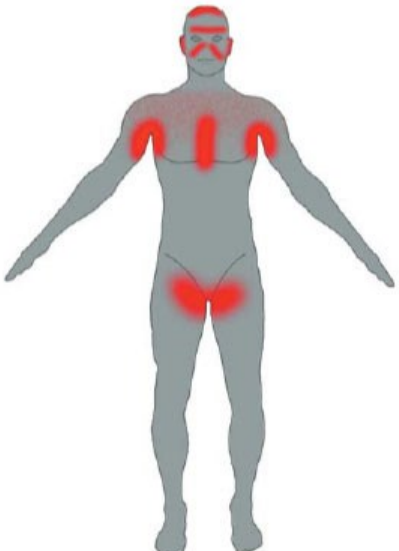
  - ✓ Oral systemic drugs for mucocutaneous infections
    - ✓ Griseofulvin
    - ✓ Terbenafine
  - ✓ Topical drugs for mucocutaneous infections.
    - ✓ Nystatin
    - ✓ Topical azoles
    - ✓ Terbinafine



Nystatin

ال mechanism تاعته شبيهة بال amphotericin b, الدواء
كثير toxic اذا انعطى parenteral عشان هيك بنعطيه
topical ، حتى الجلد او ال mucous membrane او GIT ما
بمتص بشكل كبير عشان هيك هو less toxic topical
حتى عشكل oral صار الاستخدام limited عشان طعمه السيء

- **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.



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. ctrepsis ال فكرة زي احسن بطعم oral عملوه clotrimazole ال
- 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.

dermatophyte= tinea infection ال

وهيك بنكون خلصنا بحمد الله شابتر ال antifungal

ادعولنا وادعوا لاهلنا في فلسطين💙🌸

The End