Antifungal drugs

dispensed more than antiprotozoal (especially the topical ones)

Pharmacology 3
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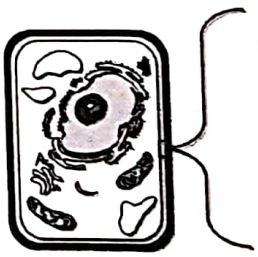
Fungi—Basic Concepts

- Fungi are eukaryotic like their human hosts.
- Have ergosterol in their membrane which fungal cells contain in place of cholesterol in human cell membranes
- Have cell wall, which human cells lack



Fungal cell

Cell membrane and cell wall

rather than Cholestrol

Fungal Infections

mycotic infection

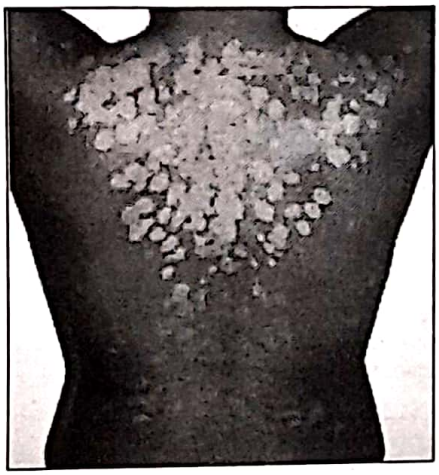
Mycoses :Infectious diseases caused by fungi , they are often chronic in nature.

- superficial(common):Candidiasis(thrush), dermatophytosis, onychomycosis.
- Subcutaneous Mycoses: Sporotrichosis
- Systemic(deep) fungal infections(serious): aspergillosis

Clinical Classification of Mycoses

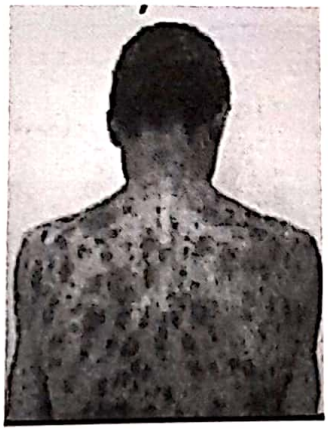
Classification	Site Infected	Example
Superficial	Outermost skin and hair	Malasseziasis (tinea versicolor)
Cutaneous	Deep epidermis and nails	Dermatophytosis
Subcutaneous	Dermis and subcutaneous tissue	Sporotrichosis
Systemic	Disease of more than one internal organ	
Opportunistic		Candidiasis
		Cryptococcosis
		Aspergillosis
Nonopportunistic		Mucormycosis
		Histoplasmosis
		Blastomycosis
		Coccidioidomycosis

Fungal Infections



Tinea Versicolor

Sporotrichosis



Histoplasmosis

مع وجود اختلاف مع الانسان مع هيك

Fungal infections treatment are more difficult than bacterial infections treatment , why ?????

1-Fungi has a cell wall which is quit rigid → chitin + cell membrane contain ergosterol → barrier of treatment

ergosterol targeted by anti fungal drugs.

scull + زي الأظافر

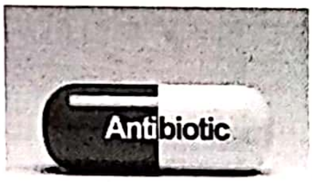
2-Fungal infections occur in poorly vascularized tissues or avascular structures such as superficial layer of the skin , hair, nails. هدول مكان render وصول الدوا للـ areas لو انفصل بعض system

3- Fungi are slow growing(cant target cell division)

صعب لأنه لازم يكونو بيتكاثرو بسرعة

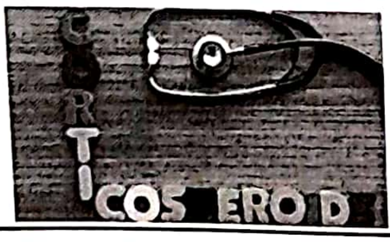
4- they are oportionistic infections (انتهازيين)

مين بنشوف الـ fungal infection أكثر شي ؟؟



① immuno-compremized including: cancer, diabetes, AIDs, نقل أعضاء دالي بياخذو cortecosteroid

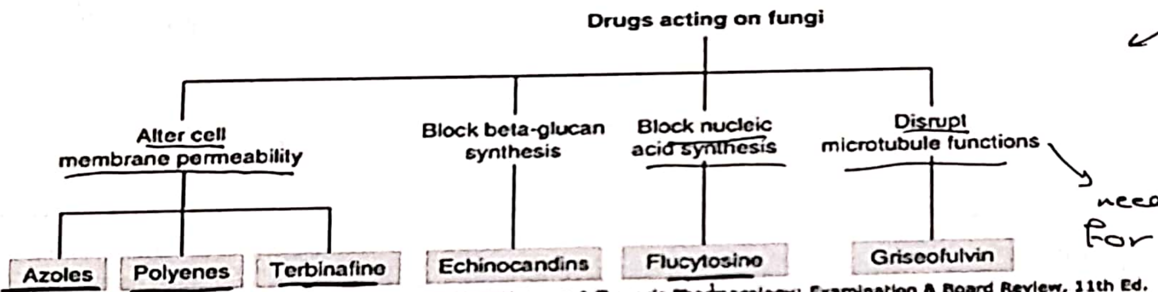
oral candiasis بطلعلهم ← inhald corticosteroid الي بيستخدمو *



* لأنه الـ corticosteroid بيعمل suprision للـ immune system وهاد بساعد حصول fungi infection

Antifungal drugs.

depending in their structur + their site of action → classified as



Source: A.J. Trevor, B.G. Katzung, M. Kruidering-Hall: Katzung & Trevor's Pharmacology: Examination & Board Review, 11th Ed.

needed for division

inhibit certain enzymes

وهاد بعمل تأثير على ال thiamidine (nuclic acid bases)

Antifungal drugs.

depending on their rout of adminstration

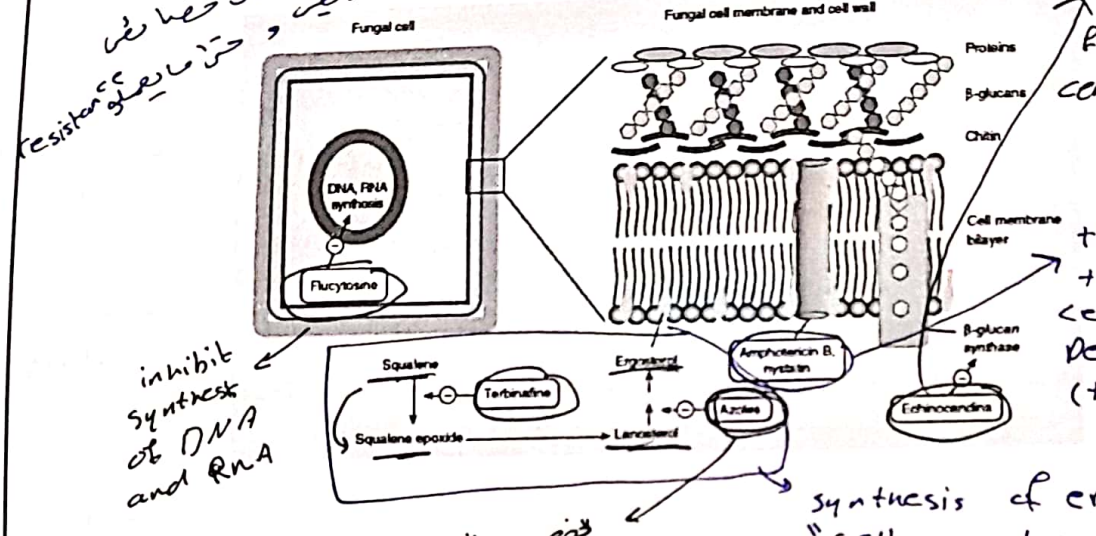
- Systemic antifungal drugs for systemic infections:
- **Amphotericin B.**
- **Flucytocine**
- **echinocandins**
- **Azoles**(triazoles).

local / supeficial

Oral systemic antifungal drugs for cutaneous infections: **Terbinafine, Griseofulvin.**

- Topical antifungal therapy: for topical use only (لأنه بسبب ما نعطيهاش orally ... systemic toxicity)
- ❖ **Nystatin.**
- ❖ **topical azoles(imidazoles):** أشهرهم **Clotrimazole, Miconazole. Ketoconazole.**
- ❖ **topical allylamines:Terbinafine.**

Targets of antifungal drugs.



inhibit synthesis of DNA and RNA

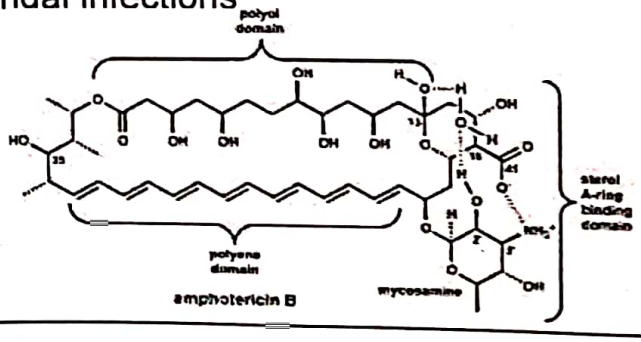
these agent they impair cell membran permeability (they cause pors)

synthesis of ergosterol "cell membran"

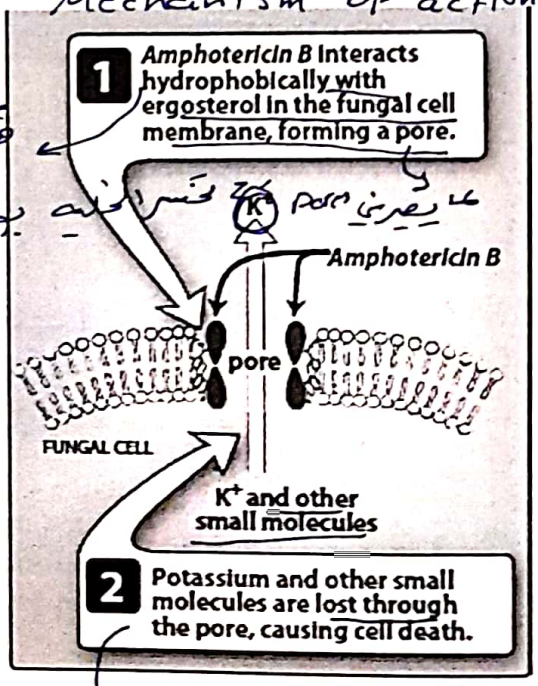
Drugs for Subcutaneous and Systemic Mycotic Infections

➢Amphotericin B:

- A naturally occurring polyene antifungal produced by *Streptomyces nodosus*
- Target: ergosterol (cell membrane)
- Fungicidal
- Treating progressive and potentially life-threatening fungal infections



Mechanism of action:



water insoluble

54

Amphotericin B

- Poorly absorbed from GIT. Orally only for GI fungal infections(FI).

so giving parentrally

لكن نعطي oral ليشتغل locally على ال GIT

زي neomycin نعطيه orally ليشتغل locally

- 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.

because of risk of dose related adverse reaction

scaling up للدوز لكن عادة بعلو شوي شوي برفعوها

- Highly ptn. Bound, poor penetration to body fluids and tissues.
- Slow elimination in urine and bile→long t1/2 (2ws).

Protein

* ليتأكدوا انه ما في عند المريض hyper-sensitivity وبراقبوه اذا في

بس 1 mg ← بعطوه IV

هو highly protein bound دخل بال plasma فترة طويلة كثير وال long half life و poor tissue distribution

وهاد خليه فاتنقى تتخلص منه بال dialysis في حالة over dose ويرضه ما فيش antidote

الحل هون symptomatic control + اعطي fluids

Amphotericin B

- Given parentrally:
- IV infusion- systemic FI: against *Candida albicans* and *Cryptococcus neoformans*; the organisms causing endemic mycoses, including *Histoplasma capsulatum*, *Blastomyces dermatitidis*,

اله أكثر من target يعني

- IT – fungal meningitis.

intra the cally

ما بعطيه IV للmeningitis poorly distributed لانه

- Intra articular – fungal joint infections.

بالمفاصل

- Eye drops – fungal corneal ulcer.

topical

- Irrigation of bladder – fungal cystitis.

* most of patient bothering (بتضايقو)

thrombo flabitis بتعمل infusion في مكان ال ← amphotracin B من ال
"Painful"

و بعمل generalized hypotension بسبب افراز ال histamine

Adverse effects

slow infusion لهيك بنعطي

- **Infusion related(immediate reactions):**
  shake and bake syndrome

* إذا المريض عنده renal problems فا dose ال must be adjusted أو يتغير أصلاً

fever, chills, muscle spasm , shock-like fall in BP. hypotension

- ✓ Slow infusion, start with small dose(a test dose of 1 mg IV)
- ✓ Premedication with: antihistamine, antipyretics. + corticosteroid

بنعطي fluid قبل وبعد amphotracin B لحماية الكلى

- *Dose-related*(Cumulative Toxicity): nephrotoxicity, anemia *due to reduced erythropoietin production by damaged renal tubular cells.*

- a bolus infusion of normal saline before and after amphotericin (dextrose)

arrhythmia لتحصل cardio vascular ← toxicity ال بيزيد ← hypokalemia وكمان بيعمل +

digoxin حضو مع

- **Neurotoxicity: Intrathecal** administration of amphotericin B may cause seizures.

→ affect kidney function

→ cause damage of renal tubules

fluid + electrolytes و secretion

they will alter erythropoietin release

- Three lipid formulations of amphotericin B :amphotericin B colloidal dispersion, amphotericin B lipid complex, and liposomal amphotericin B. Liposome → lipid bilayer
- They have been developed in an attempt to reduce the toxicity profile of this drug and to increase efficacy

by → solubility in lipid + وهاد بزيد lipid soluble الخلط ب

مع العلم أعلبهم نفس ال efficacy

- Prior to reconstitution Amphotericin B Intravenous should be stored in the refrigerator, protected against exposure to light. The reconstituted solution may be stored in the dark, at room temperature for 24 hours, or at refrigerator temperatures for 1 week with minimal loss of potency and clarity. → change

بالثلاجة وصار عليه تغير بالشكل لازم ينكب drug stability color بال

- Any unused material should then be discarded. Solutions prepared for intravenous infusion should be used promptly after preparation and should be protected from light during administration ليحميه foil بنلف ب

➢ Echinocandins → the

- Echinocandins are the newest class of antifungal agents to be developed.
- Caspofungin, micafungin are the only licensed agents in this category of antifungals. → they affect β-glucan that is needed for the synthesis of cell wall
- Caspofungin is used for **disseminated** and **mucocutaneous Candida infections** in patients who fail to respond to amphotericin B.

اذا كان ال topical infection صعب ومنتشر وما استجاب لل amphotracin بستخدم caspofungin + اذا كان عندي

- they are well tolerated. Infusion-related effects of **caspofungin** include headache, GI distress, fever, rash, and flushing (histamine release). Less common than amphotericin

contraindicated renal impairment مثلاً amphotracin

- Combined use of echinocandins with cyclosporine may elevate liver transaminases. → immune suppresent

(synergistic effect) فلوسيتوسين دخول

➢ Flucytosine (5-FC)

nucleic acids bases شبيه → antimetabolite يتحول

amphotracin → يعمل pores to increase the uptake of flucytosine

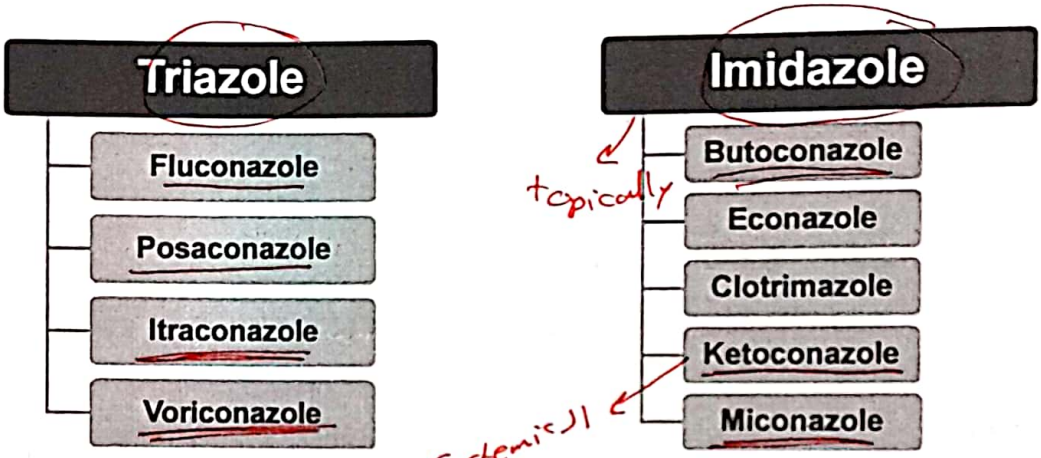
- Synthetic pyrimidine is often used with amphotericin B for the treatment of systemic mycoses and meningitis caused by Cryptococcus neoformans and Candida albicans.
- Orally, distributed to most body tissues (including the CNS) → amphotracin B (IV)
- Eliminated intact in the urine (dose reduced in renal impairment)
- When given with amphotericin B or triazoles (resistance decreased & synergistic antifungal effects).
- Narrow spectrum (clinical use limited to combination with amphotericin B or a triazole)
- Toxicity: reversible bone marrow depression, alopecia & liver dysfunction (prolonged high levels).

يؤثر بالـ DNA حق الـ anticancer زي ADR الـ

حصوصي إذا المريض بستخدم ادوية ثانية بتعمل فشل

dose adjustment لازم

Azole Antifungals



The azoles used for systemic mycoses include **ketoconazole, fluconazole, itraconazole, voriconazole,** and **posaconazole.**

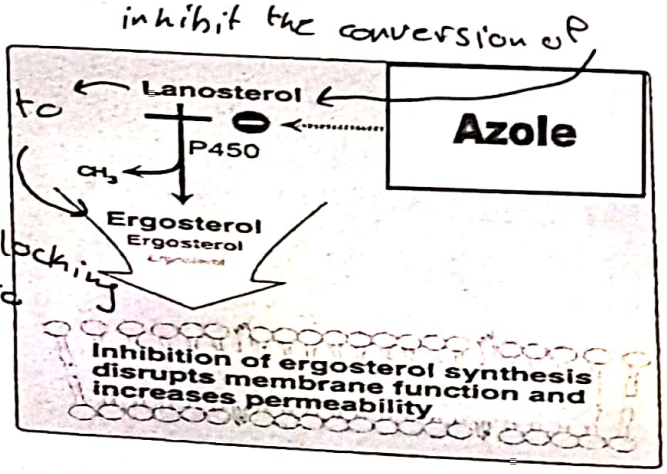
•**Miconazole**, and **clotrimazole** are used only in topical therapy.

Mechanism of action of azoles

Target: inhibit ergosterol synthesis.

They inhibit "Cytochrome P450" which is responsible for demethylation of lanosterol to form ergosterol and then the membrane permeability will increase.

Azoles are predominantly fungistatic



Characteristics of Azoles

they differ in their water solubility ← + their absorption in the CSF ; serum conc. + route of elimination (renal, hepatic or both)

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, but with the exception of **fluconazole**, drug levels achieved in the CNS are very low. صيلا الفوحيه الى تركيزها ب CSF اعلى بنا
- Liver metabolism is responsible for the elimination of azole antifungals except **fluconazole** (which is eliminated by the kidneys, largely in unchanged form).

Pharmacologic properties of systemic azole drugs. الـ $t_{1/2}$ و باقي رقام من للجدول

	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	>0.21	6	Hepatic	Oral, IV
Posaconazole	Low	High	—	25	Hepatic	Oral, IV
Isavuconazole	High	High	—	130	Hepatic	Oral, IV

عميزة الـ fluconazol و انه يمكن يستخدم بالباقي يستخدم

Fluconazol اكو على cryptococcal لعلاج meningitis

renal dysfunction حالة الـ

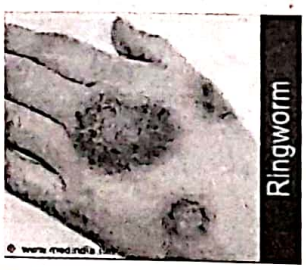
Clinical uses

- **Ketoconazole**— used orally + topically
- It has a narrow antifungal spectrum and causes more adverse effects than other azoles, ketoconazole is now rarely used for systemic mycoses.

drug-drug interaction + endocrain system adverse reaction

dermatophytes + ليهيك يستخدم لهاد

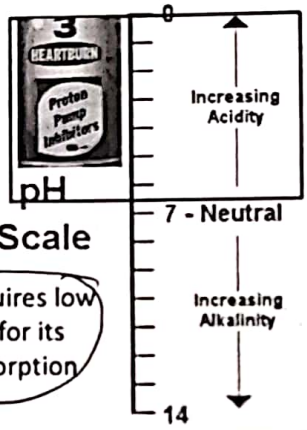
However, ketoconazole continues to be used for chronic mucocutaneous candidiasis and is also effective against dermatophytes It is also used topically in the treatment of **seborrheic dermatitis** and **dandruff**



Ketoconazole

~~available~~

available as cream + shampo



requires low PH for its absorption

systemic ketoconazole has fallen out of clinical use, why??
inhibits mammalian cytochrome P450.
Anti-androgenic effect
Fatal hepatotoxicity(rare)

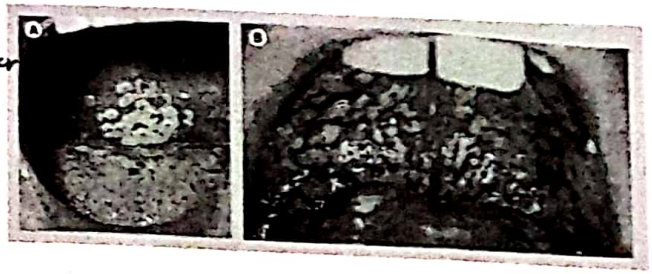
Clinical uses

cancer patient + AIDs + immunocompromized

- **Fluconazole**— (renally eliminated, has good CNS penetration)

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 for treatment and secondary prophylaxis against cryptococcal meningitis and is an alternative drug of choice (with amphotericin B) in treatment of active disease due to *Cryptococcus neoformans.*

fungal infection type



Fluconazole

Its oral bioavailability is high , it has a high degree of water solubility and good cerebrospinal fluid penetration. It is available in **oral and intravenous formulations.**

unlike the other medications it dosen't need low pH for its absorption

Because of fewer hepatic enzyme interactions and better gastrointestinal tolerance, fluconazole has the widest therapeutic index of the azoles, permitting more aggressive dosing in a variety of fungal infections.

وبالتالي ممكن نعطيها بجرعات عالية

→ unlike ketoconazol it dosen't need hepatic metabolism

therpy → ما في hepatic enzym interaction

↳ ما بيعمل inhibition أو induction للأدوية التانية

Azoles are considered teratogenic, and they should be avoided in pregnancy unless the potential benefit outweighs the risk to the fetus.

يعني حسب نسبة الفائدة للضرر

هل لازم أعالج الأم لأنه الوضع خطير وأضحي بالأضرار عالجنين ولا ؟

Scanned with CamScanner

- **Itraconazole** fluconazole مع similarity عنده
- has a broad antifungal spectrum compared to *fluconazole*. *Itraconazole* is the drug of choice for the treatment of blastomycosis, sporotrichosis.
- In esophageal candidiasis, the drug is active against some strains resistant to fluconazole. Itraconazole is also used extensively in the treatment of dermatophytoses, especially onychomycosis. infection of nails + hair skin
- is available in oral and intravenous formulations.
- The drug distributes well in most tissues, including bone and adipose tissues.
- Has a negative inotropic effect and should be avoided in patients with evidence of ventricular dysfunction, such as heart failure.

يعني في حالة الـ resistance لـ fluconazole بنستخدم كبديل

cardiac contractility يعني بقلل الـ → وممكن عنده مشكلة مع heart failure

يعني عكس عمل antagonist

positive inotropic عمل digoxin ← the effect of digoxin

voriconazole

- It is a drug of choice for treatment of invasive aspergillosis.
- It is an alternative drug in candidemia with activity against some fluconazole-resistant organisms.
- In AIDS patients has been used in the treatment of candidial esophagitis and stomatitis.
- Voriconazole causes immediate but transient visual disturbances including blurring of vision of unknown cause

Adverse Effects of systemic azoles

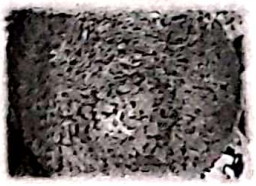
- include vomiting, diarrhea, rash, and sometimes hepatotoxicity, especially in patients with preexisting liver dysfunction.
- **Ketoconazole** is a notorious inhibitor of hepatic cytochrome P450 isozymesand may increase the plasma levels of many other drugs, including cyclosporine, oral hypoglycemics, phenytoin, and warfarin.
- 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.

Cutaneous mycotic infections (dermatomycoses)

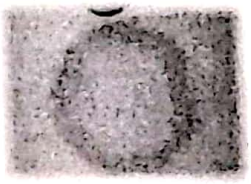
✓ Mold-like fungi that cause most cutaneous infections are called **dermatophytes or tinea.**

Tinea infections

Tinea pedis (infection of the feet)



Tinea capitis (scalp)



Tinea corporis (body)

Tinea unguium (nails)

Common dermatomycoses, such as tinea infections that appear as rings or round red patches with clear centers, are often referred to as ringworm.

Systemic drugs for mucocutaneous fungal infections

+ terpinafin

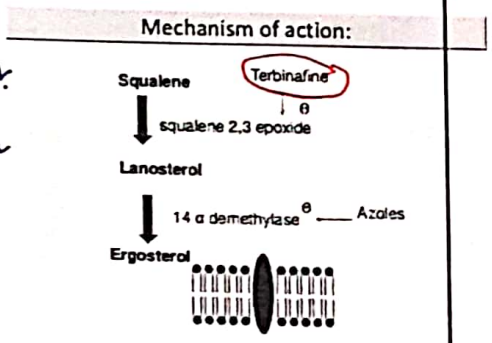
- **Griseofulvin** is not active topically and is fungistatic. بنعتا systemically
  Oral absorption depends on the drug physical state (ultra-micro-size formulations have finer particles, more effectively absorbed, aided by high-fat foods).
  fat food ultra micro Formulation يعني بتحسن الـ abs.

  Indicated for dermatophytoses of the skin and hair, but has been largely replaced by terbinafine and the azoles. requires a long duration of treatment (for example, 6 to 12 months for onychomycosis). Duration of therapy is dependent on the rate of replacement of health skin and nails.
  لازم المريض يعرف انه الـ improvement بده وقت من 6 - 12 شهر لعلاج الـ onychomycosis

- **Griseofulvin decreases the bioavailability of warfarin, resulting in decreased anticoagulant effect.**
  لأنه الـ d-d interaction

Terbinafine

- **MOA:** inhibit epoxidation of squalene accumulation is toxic to fungi.
  يعني هو بمنع تكون الـ ergosterol + تجمع الـ squalene اللي هو toxic لحالو
- **Clinical application:** subcutaneous fungal infection
  بعد ما يستخدم الدوا بتجمع وبين خلايا الـ keratin
  بالـ hair
  بالأظافر
- 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.



- Terbinafine is fungicidal and is available in both oral and topical forms.
  حتى لو أخذته oral بستخدم كريم

- Like griseofulvin, terbinafine accumulates in keratin, but it is much more effective than griseofulvin in onychomycosis

TOPICAL ANTIFUNGAL THERAPY

1. **Nystatin:**
2. **Topical azoles(imidazole) : clotrimazole, Miconazole, Ketoconazole.**

3. **Topical allylamines:Terbinafine.**

DOC

oncomycosis ← علاج

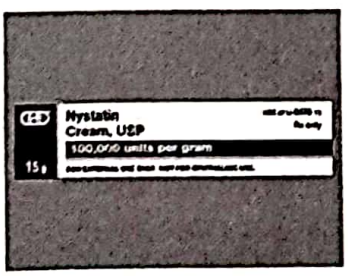
Nystatin

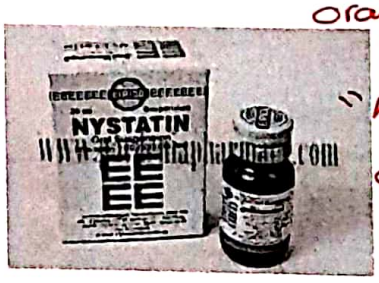
موجو بالكريمات ← orally +

الـ oral اسمه

- for the treatment of cutaneous and oral Candida infections.
- is negligibly absorbed from the gastrointestinal tract, and it is not used parenterally due to systemic toxicity.
- It is administered as an oral agent ("swish and swallow"or "swish and spit") for the treatment of oropharyngeal candidiasis (thrush), intravaginally for vulvovaginal candidiasis, or topically for cutaneous candidiasis.

بمتصض منه و بطلعه أو بجلعه





orally يأخذ
قليل جدًا
"negligibally"
absorbed

مقارنة بين miconazol nystatin

BOTH: Too toxic for systemic use. → must not taken parenterally

BOTH: Used only topically or locally (incomplete absorption orally) .

pessiers

- vaginally candidiasis: supp
- cutaneous candidiasis: cream

Nystatin

Oral gel has vile taste...

لا يستخدم كثيرا عند الأطفال

Orally: buccal and intestinal infection.

swish and spit

Miconazole

Taste is very well... DOC in children. → يؤخذ oral gel

oral u thrush

swish & spit ، swish & swallow ماعنده

poorly absorbed بس gel حتى لو بلع منه المريض عادي لأنه