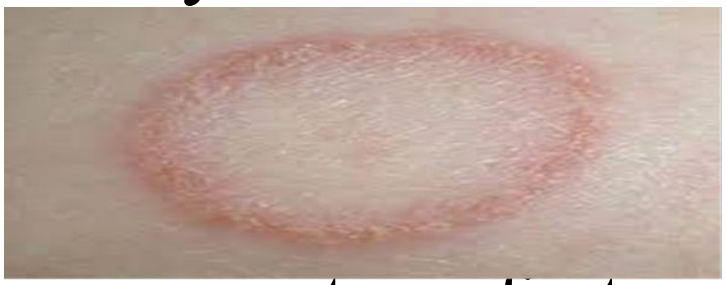
Antifungal Drugs

د.اسماء الثويني

Asist.Prof.M.B.ch.B/M.S.C./Ph.D.in Pharmacology and Therapeutics

Infectious diseases caused by fungi are called **mycoses**, and they are often chronic in .nature

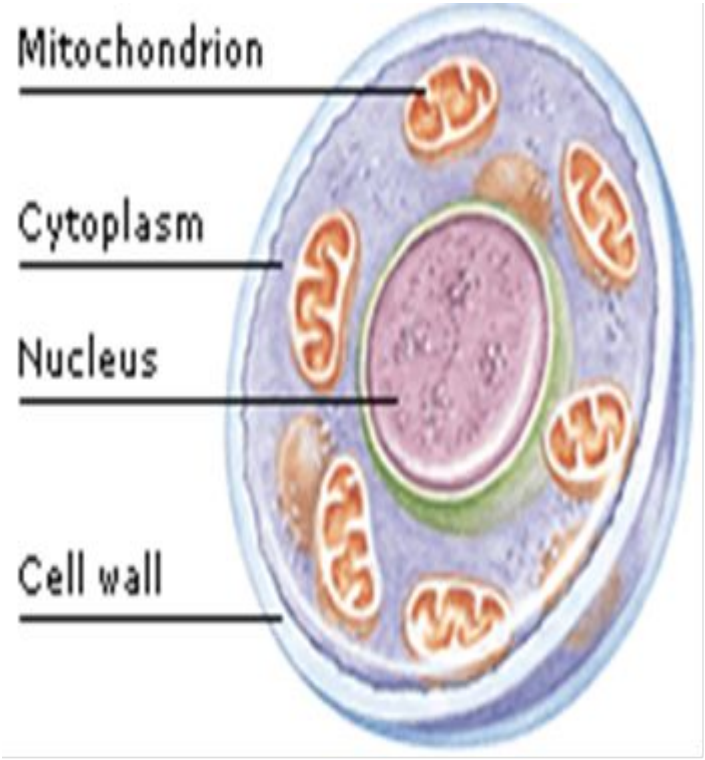


Many common mycotic infections are superficial and only involve the skin **(cutaneous mycoses),** but fungi may also penetrate the skin, causing **subcutaneous** .infections

The fungal infections that are most difficult to treat are **the systemic mycoses**, which are .often life-threatening

.

- Fungi have a rigid cell walls composed of ergosterol , so, they resist antibiotics.

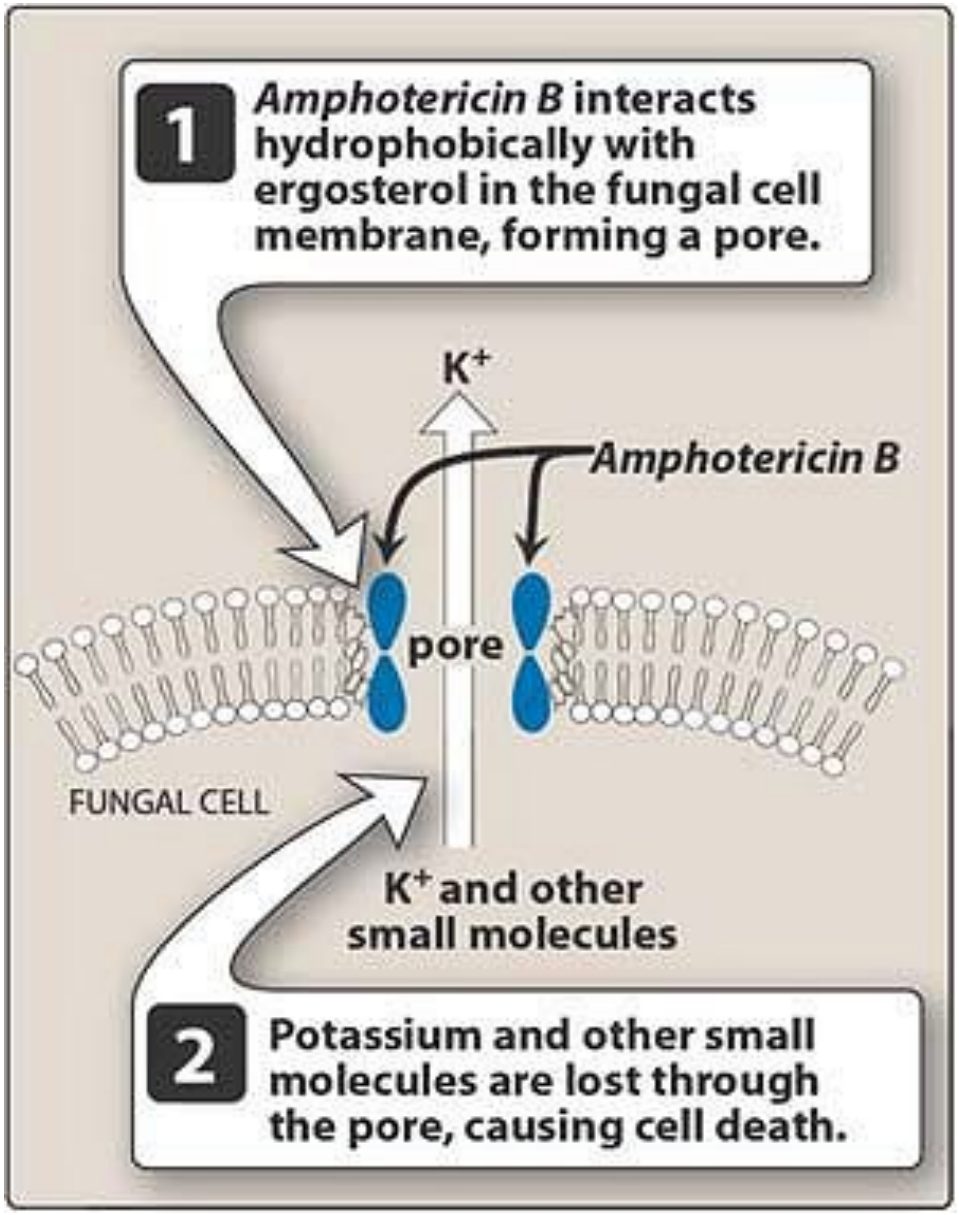


Fungal infections are generally resistant to antibiotics used in the treatment of bacterial infections, and conversely, bacteria are .resistant to the antifungal agents

Drugs for Subcutaneous and Systemic :Mycotic Infections

- ***Amphotericin B:***

Amphotericin B is the drug of choice for the treatment of life threatening systemic .mycosis


1
Amphotericin B interacts hydrophobically with ergosterol in the fungal cell membrane, forming a pore.
K^+
Amphotericin B
pore
FUNGAL CELL
K^+ and other small molecules
2
Potassium and other small molecules are lost through the pore, causing cell death.

:Antifungal spectrum

:Indications

Candida albicans, Histoplasma, Cryptococcus neoformans, Coccidia, aspergillus, and .Blastomyces dermatitidis

Pharmacokinetics

.is administered by slow, intravenous infusion

.amphotericin B cross the placenta

:Adverse effects

.has a low therapeutic index

fever and chills:these occure more commonly -1
1-3hrs after I.V. infusion, but they usually subside
.with repeated administration of the drug

Renal impairment:Nephrotoxicity may be -2
potentiated by sodium depletion; thus, a bolus
infusion of normal saline infusion before and after
amphotericin B may reduce the incidence of
.drug-induced nephrotoxicity

Azotemia (elevated blood urea) is exacerbated by other nephrotoxic drugs, such as aminoglycosides .and cyclosporine

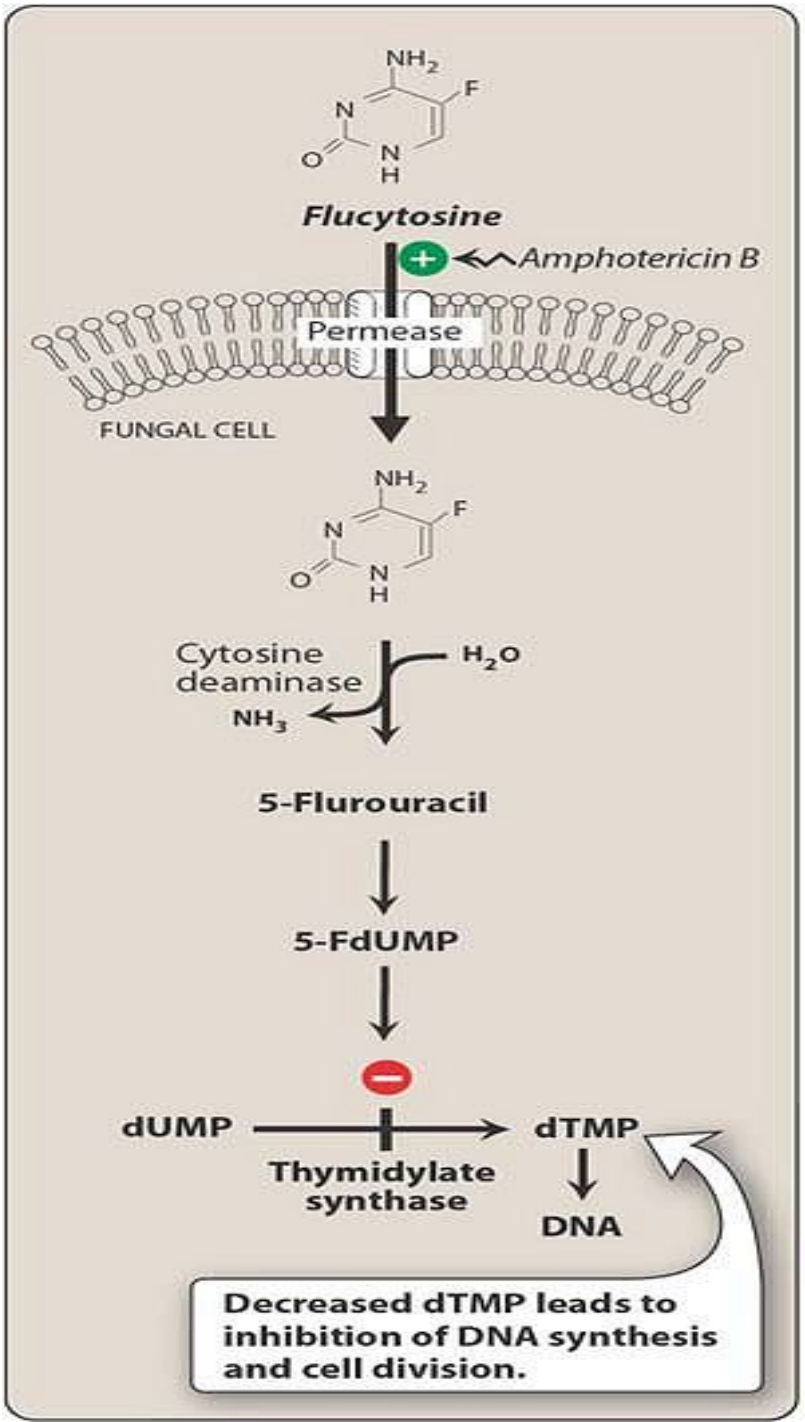
.hypotension -3

anemia -4

.thrombophlebitis -5

:B. Flucytosine

is a synthetic antimetabolite that is often used in combination with amphotericin B for the treatment of **systemic mycoses** and for meningitis caused by .Cryptococcus neoformans and Candida albicans


NH2
F
N
O
N
H
Flucytosine
Amphotericin B
Permease
FUNGAL CELL
NH2
F
N
O
N
H
Cytosine deaminase
H2O
NH3
5-Flurouracil
5-FdUMP
dUMP
dTMP
Thymidylate synthase
DNA
Decreased dTMP leads to inhibition of DNA synthesis and cell division.

:Pharmacokinetics

FC is well absorbed by the oral route. It-5 distributes throughout the body water and .penetrates well into the CSF

Excretion of the drug and its metabolites is by glomerular filtration, and the dose must be adjusted in patients with compromised renal .function

:Adverse effects

reversible neutropenia , thrombo-cytopenia, .and dose-related bone marrow depression

Reversible hepatic dysfunction with elevation of serum transaminases and alkaline .phosphatase may occur

Gastrointestinal disturbances, such as nausea, ,vomiting, and diarrhea, are common

..and severe enterocolitis may occur

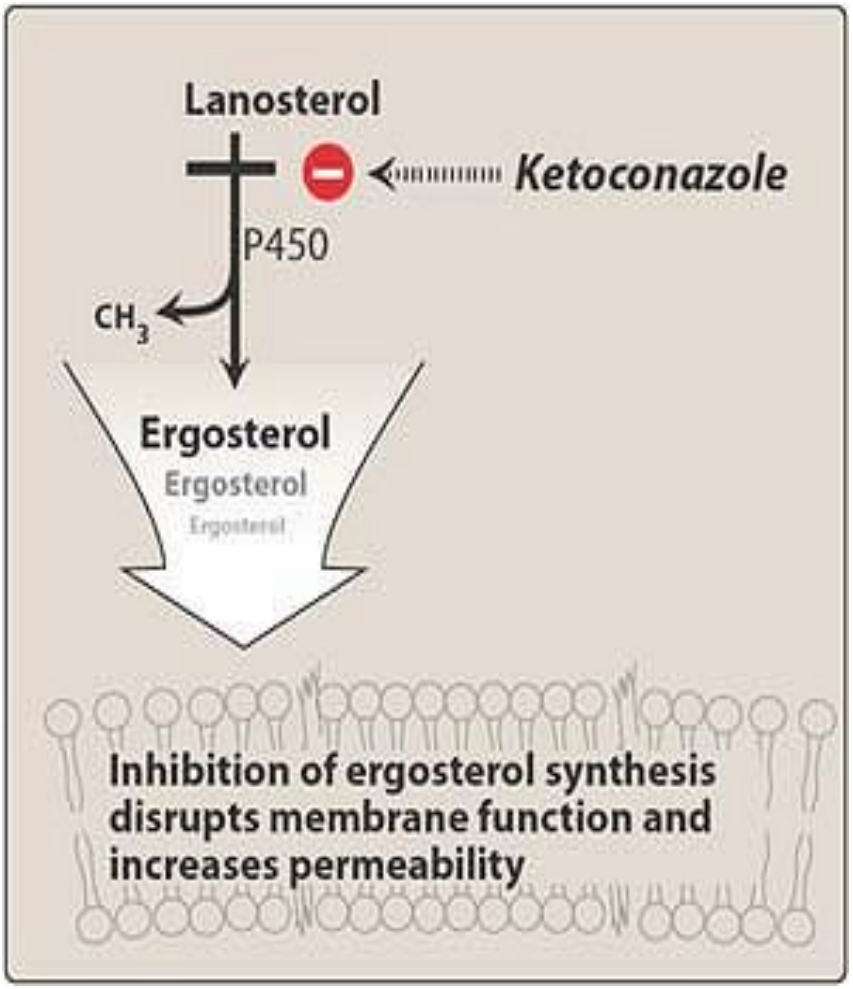
C. Ketoconazole (azoles)

1. Imidazole group: **ketoconazole,** Miconazole, Clotrimazole **and Econazole.** (MECK) (given topical in pregnancy)
2. Triazole group : Fluconazole, Itraconazole and Voriconazole.
3. Thiazoles group: Abafungin

.Azoles are predominantly fungistatic

Antifungal spectrum: Ketoconazole is active against many fungi, including Histoplasma, Blastomyces, .Candida, but not aspergillus species

:Mechanism of action



pharmacokinetics: Ketoconazole is .administered oraly

It requires gastric acid for absorbtion and is .absorbed through the gastric mucosa

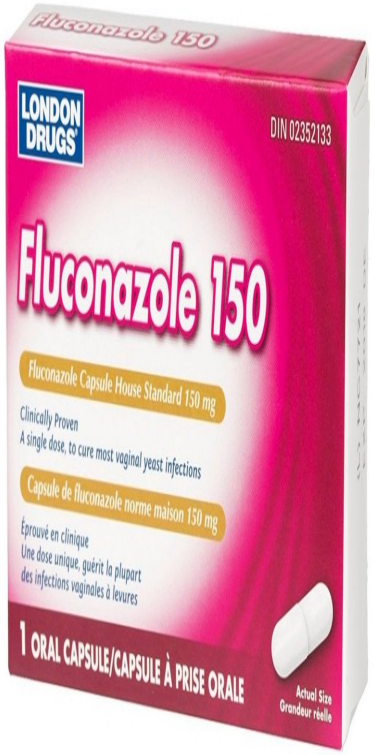
Drugs that raise gastric pH, such as antacids, or that interfere with gastric acid secretion, such as histamine receptor blockers and .proton-pump inhibitors, impair absorption

Administering acidifying agents, such as cola drinks, before taking the drug can improve .absorption in patients with achlorhydria

- ***Adverse effects:***
- 1-Gastrointestinal distress.
- 2-Endocrine effects: These result from the blocking of androgen and adrenal steroid synthesis by ketoconazole causing gynecomastia, decreased libido, impotence, and menstrual irregularities.
- 3- Hepatic dysfunction:

- ***Drug interactions:***
- 1-inhibiting cytochrome P-450, ketoconazole can potentiate the toxicities of cyclosporine, phenytoin, terfenadine and astemizole.
- 2- Rifampin, an inducer of the cytochrome P-450 system, can shorten the duration of ketoconazole and the other azoles.

D. Fluconazole



is clinically important because of its lack of endocrine side effects and ketoconazole its .excellent penetrability into the CSF

is the drug of choice for Cryptococcus neof for candidemia. Fluconazole is effective against all .forms of mucocutaneous candidiasis

Fluconazole is administered orally or intravenously. Its absorption is excellent and, unlike that of .ketoconazole dependent on gastric acidity

Nausea, vomiting, and rashes are a problem. Hepatitis is rare. Fluconazole is teratogenic, as are .other azoles, and should not be used in pregnancy

:E. Itraconazole

is an azole antifungal agent with a broad antifungal spectrum. Like fluconazole, it lacks the endocrinologic side effects of ketoconazole. Its mechanism of action is the same as that of the other azoles. Unlike ketoconazole, it is effective in acquired immunodeficiency syndrome associated histoplasmosis. Itraconazole is well-absorbed . orally

Adverse effects

include nausea and vomiting, rash (especially in immunocompromised patients), hypokalemia, hypertension, edema and .headache

should be avoided in pregnancy. Itraconazole

F. Voriconazole

has the advantage of being a broad-spectrum antifungal agent. It is available for intravenous .administration and also for oral administration

is approved for the treatment of invasive aspergillosis and seems to have replaced amphotericin B as the treatment of choice for this .indication

.Side effects are similar to those of the other azoles

- ***Abafungin:***
- It has similar activity to the previous agent used as topical cream with antibiotic activity against gram-positive bacteria.

- ***Echinocandins***

- They are the newest class of antifungal agent active against both candida and aspergillus include ***Caspofungin***, ***micafungin***, *and* ***anidulafungin*** available only in intravenous forms, and the metabolites are excreted by the kidneys and gastrointestinal tract.
- They act by inhibiting the synthesis of fungal cell wall.
- Minor gastrointestinal side effects and flushing and elevated liver enzymes reported infrequently .

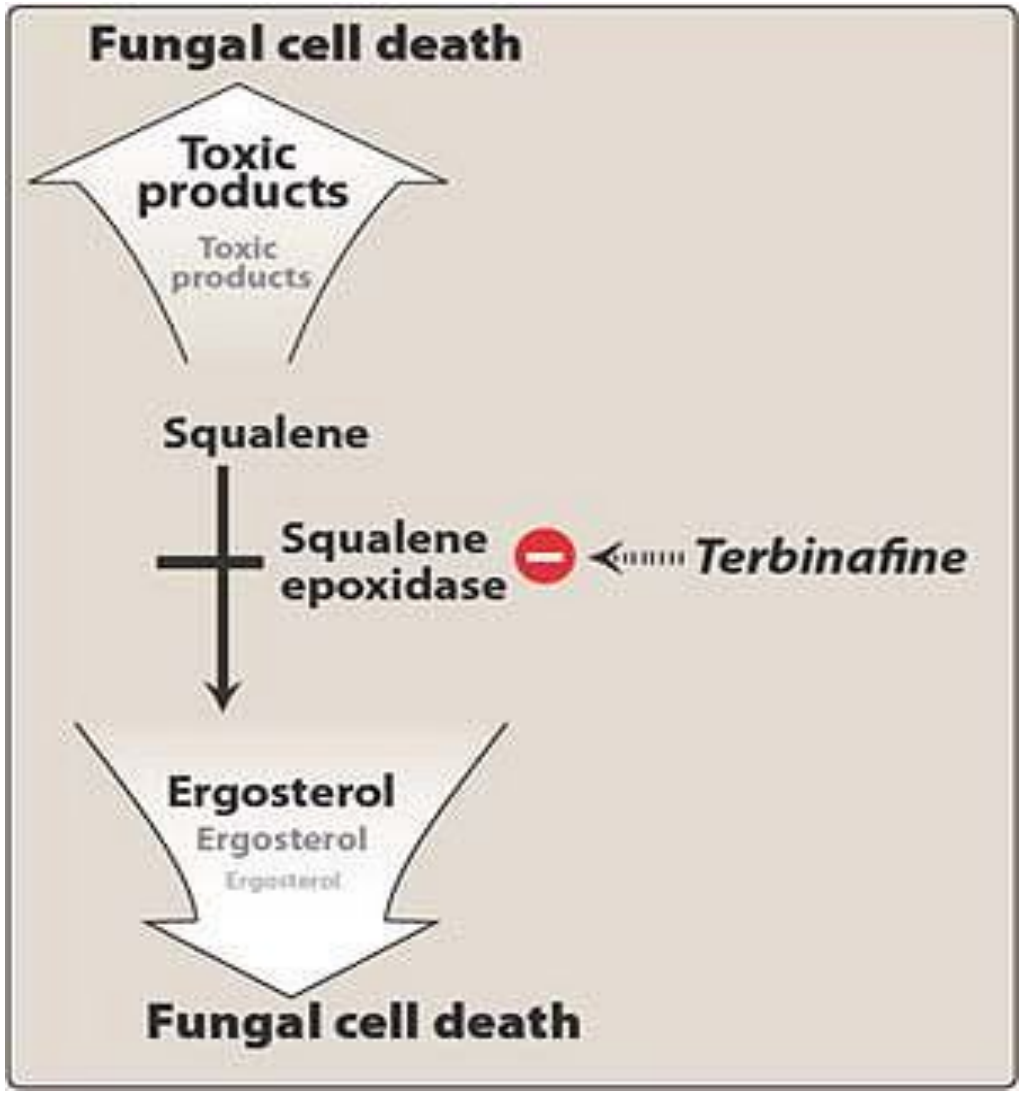
Drugs for Cutaneous Mycotic Infections

Fungi that cause superficial skin infections are called dermatophytes. Common .dermatomycoses, such as tinea infections

:A. Terbinafine

is the drug of choice for treating dermatophytoses and, especially, .onychomycoses (fungal infections of nails)

:Mechanism of action



:Antifungal spectrum

The drug is primarily fungicidal. Antifungal activity .is limited to dermatophytes and Candida albicans

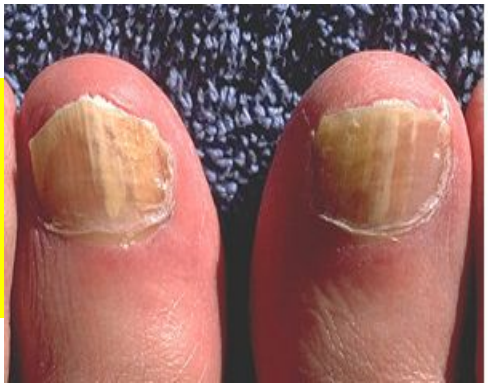
.Terbinafine is orally active

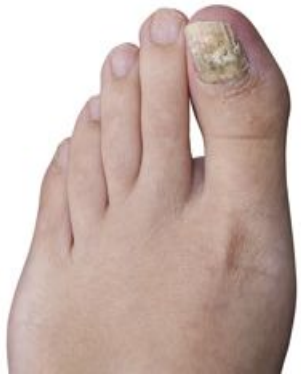
Terbinafine accumulates in breast milk and, .therefore, should not be given to nursing mothers

:Adverse effects

The most common adverse effects due to terbinafine are gastrointestinal disturbances (diarrhea, dyspepsia, and nausea), headache, and rash. Taste .and visual disturbances and hepatotoxicity

B. Griseofulvin





has been largely replaced by terbinafine for the treatment of dermatophytic infections of .the nails

.It is only fungistatic

Griseofulvin induces hepatic cytochrome P450 activity . It also increases the rate of metabolism of a number of drugs, including .anticoagulants

C. Nystatin

its structure, chemistry, mechanism of action, and resistance resemble those of .amphotericin B

Its use is restricted to topical treatment of Candida infections because of its systemic toxicity. It is administered as an oral agent .for the treatment of oral candidiasis

clotrimazole Miconazole butoconazole terconazole

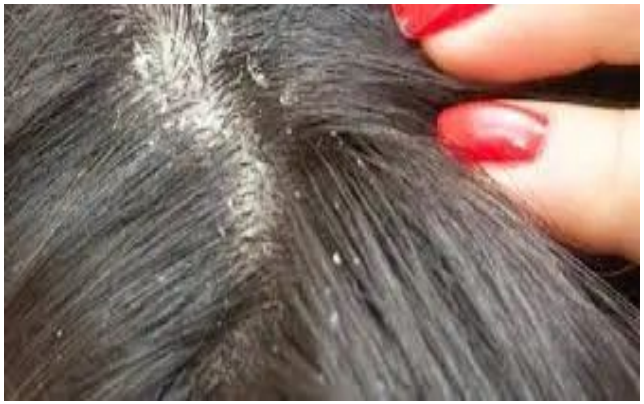
.are topically active drugs

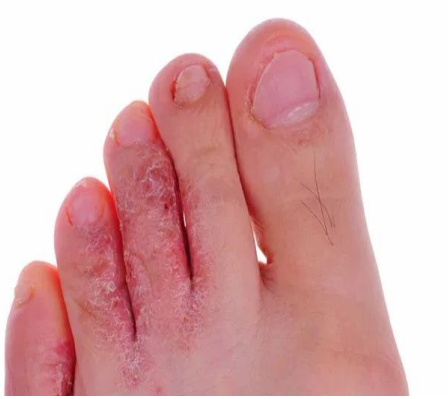
Their mechanism of action and antifungal spectrum .are the same as those of ketoconazole

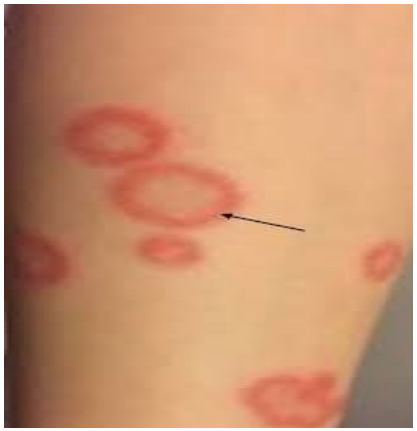
Topical use is associated with contact dermatitis, .vulvar irritation, and edema

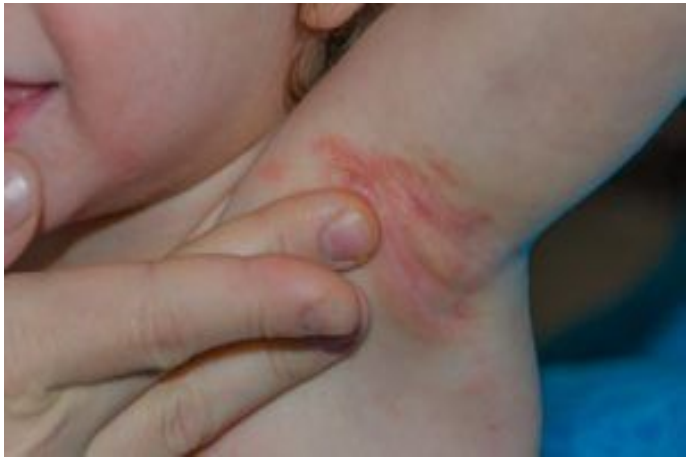
Miconazole is a potent inhibitor of warfarin metabolism and has produced bleeding in .warfarin-treated pateint

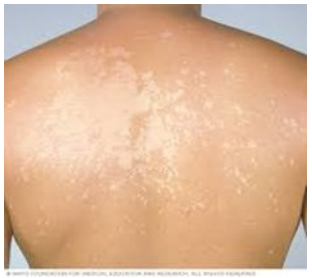
- ***Ciclopirox***
- It inhibits the transport of essential elements in the fungal cell, disrupting the synthesis of DNA, RNA, and proteins.
- Ciclopirox is active against Trichophyton, Candida Epidermophyton,Microsporum, and Malassezia.
- Ciclopirox 1% shampoo is used for treatment of seborrheic dermatitis, tinea pedis, tinea corporis, tinea cruris, cutaneous candidiasis, and tinea versicolor











thank you!