ANTI FUNGAL DRUGS

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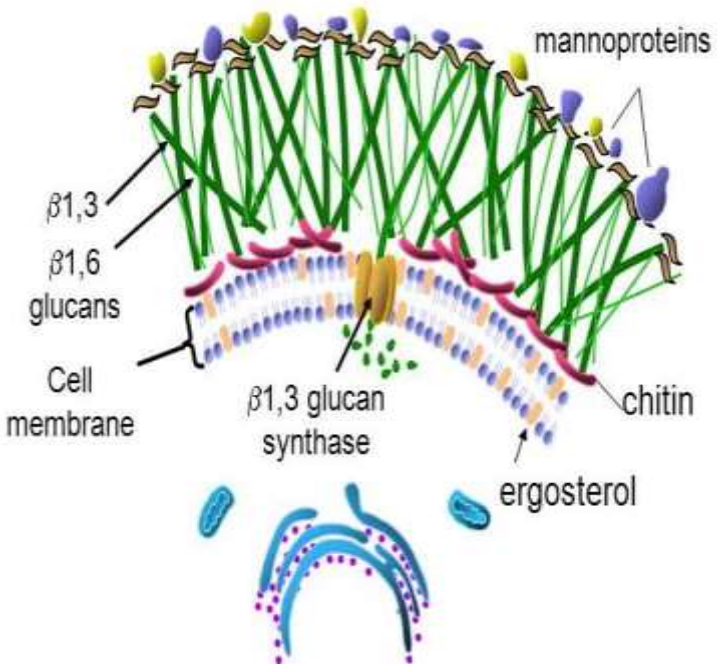
Overview

- Mycoses (mycotic infections) are often chronic.
- Can be cutaneous, subcutaneous or systemic.
- Relevant structural characteristics of fungi:

A. Eukaryotic
B. Rigid cell walls
C. Cell membrane contains ergosterol not cholesterol



CLASSIFICATION OF ANTIFUNGAL DRUGS

Drugs for systemic fungal infections

Polyene antibiotics

-Amphotericin B

Pyrimidine antimetabolites

-Flucytosine

Antifungal azoles

-Ketoconazole

-Fluconazole

-Itraconazole

Echinocandins

Caspofungin

Drugs for superficial fungal infections

Systemic drugs

-Griseofulvin

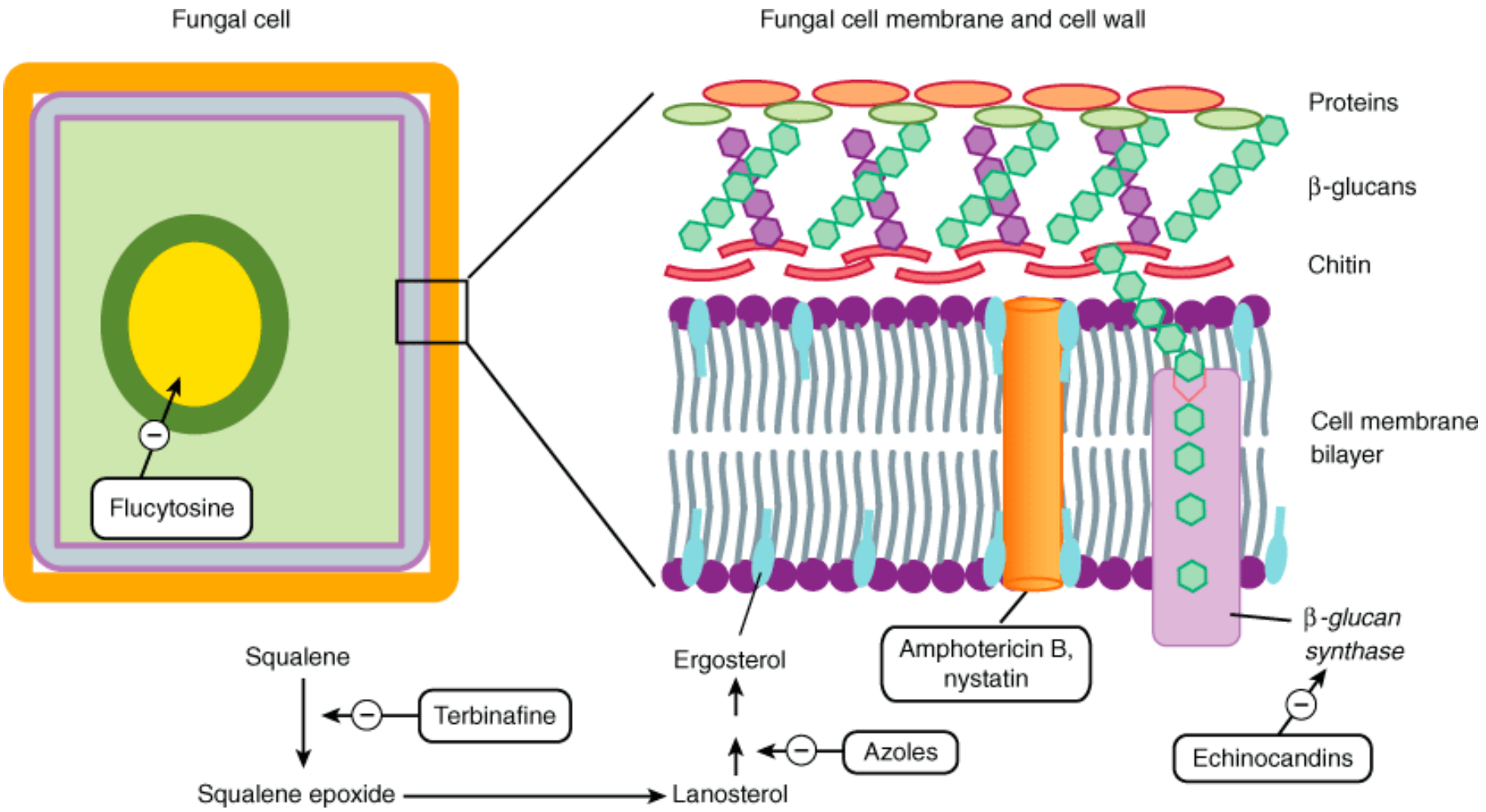
Topical drugs

-Nystatin

-Terbenafine

-Azoles (**miconazole**, econazole, clotrimazole, etc.)

Targets of antifungal drugs



PHARMACOLOGY OF AMPHOTERICIN B

Chemistry

-**Amphotericin B** is a polyene antibiotic (polyene: containing many double bonds)

Mechanism of action

-Binding to ergosterol present in the membranes of fungal cells

↓

Formation of "pores" in the membrane

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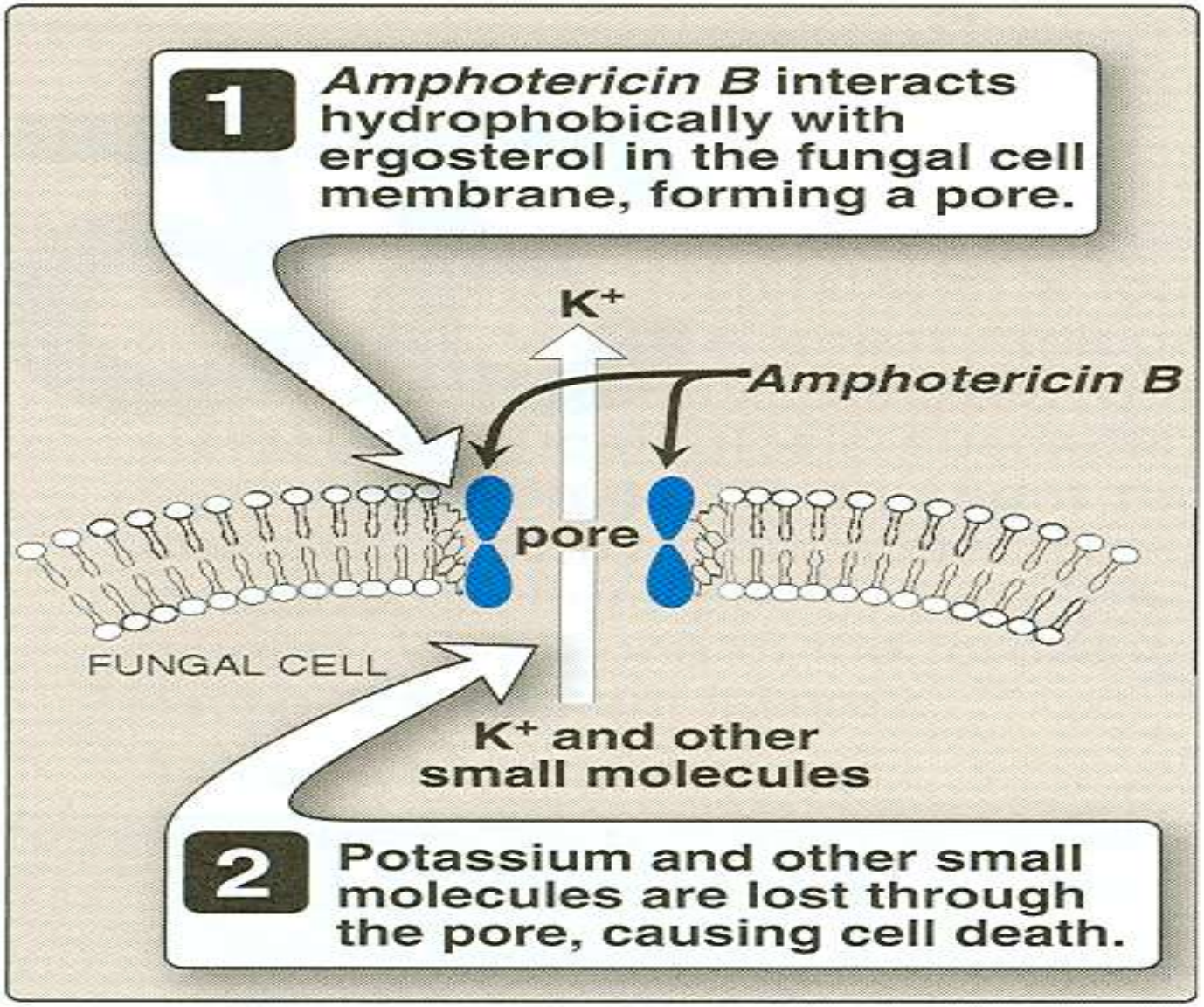
Leaking of small molecules (mainly K+) from the cells

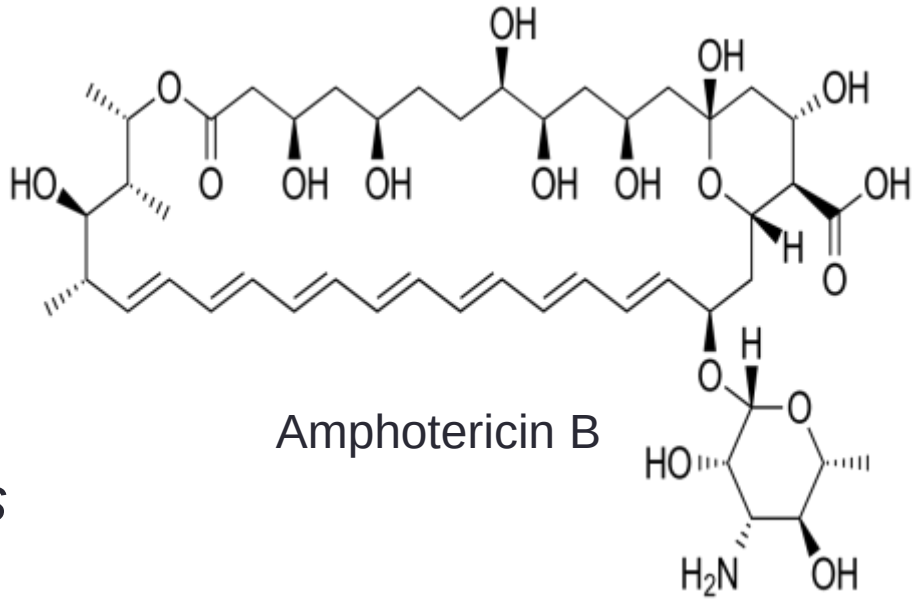
-The ultimate effect may be ***fungicidal*** or ***fungistatic*** depending on the organism and on drug concentration.


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.

Amphotericin B

Antifungal spectrum

- Fungicidal/fungistatic
- Effective against a wide range:
- *Candida albicans*
- *Histoplasma capsulatum*
- *Cryptococcus neoformans*
- *Coccidioides immitis*
- *Blastomyces dermatitidis*
- *Aspergillus*

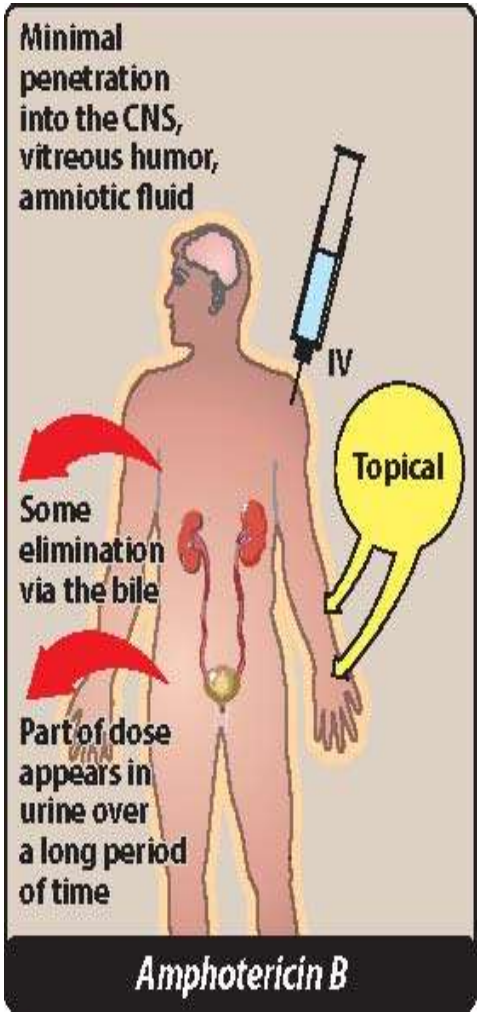


Amphotericin B

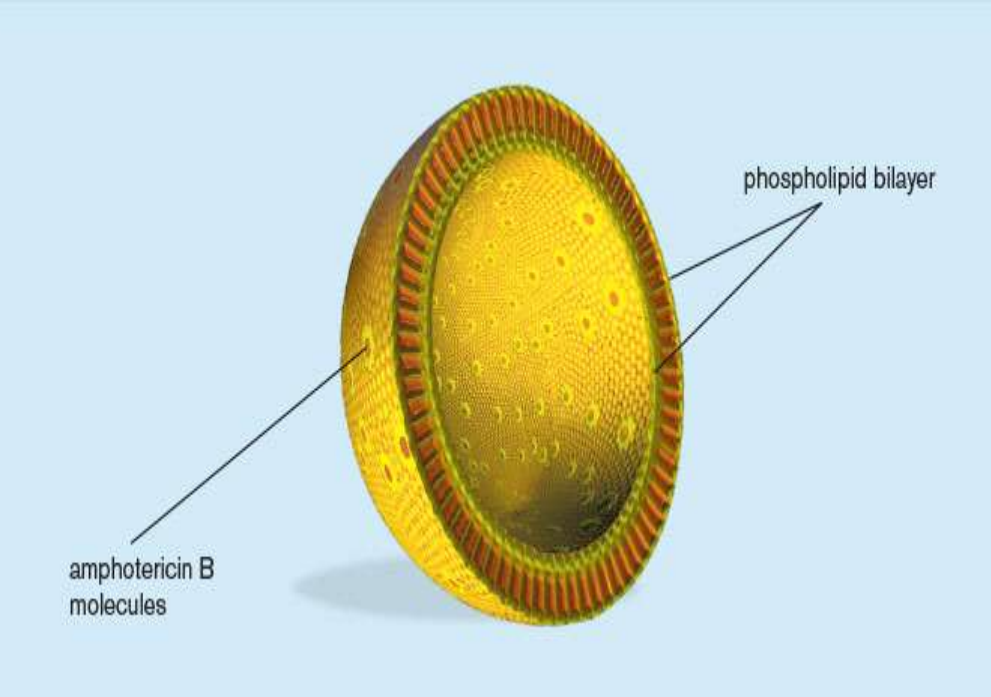
Amphotericin B

Pharmacokinetics

- Slow IV infusion
- Provided in liposomal preparations due to low water solubility (not cheap)
- Extensively protein-bound
- Well distributed but little into CSF
- Low levels of drug/metabolites are excreted in urine



Amphotericin Liposome



Adverse effects

(the therapeutic index of the drug is very narrow)

-Headache, arthralgias, nausea and vomiting fever and chills, hyperpnea, shock-like fall in blood pressure (they may appear during IV infusion and may be reduced by concomitant administration of antipyretics or meperidine)

-Malaise, weight loss

-Nephrotoxicity

-Normocytic anemia, likely due to decreased production of erythropoietin (frequent).

-Thrombophlebitis.

-Delirium, seizures (after intrathecal injection).

Therapeutic uses

Amphotericin is the drug of choice for:

-Disseminated histoplasmosis

-Disseminated and meningeal cryptococcosis

-Invasive aspergillosis

-Deep candidiasis

-Mucormycosis

Amphotericin is an alternative drug for:

-Blastomycosis

-Extracutaneous sporotrichosis

[Amphotericin is preferred when these mycoses are rapidly progressive, occur in immunocompromised host or involve the CNS]

Antimetabolite Antifungals

PHARMACOLOGY OF FLUCYTOSINE

Chemistry

-Flucytosine is a fluorinated pyrimidine

Mechanism of action

-The drug is accumulated in fungal cells by the action of a ***membrane permease*** and is converted by a ***cytosine deaminase*** to 5-fluorouracil

5-fluorouracil is metabolized to 5-fluorouridylic acid

which can be

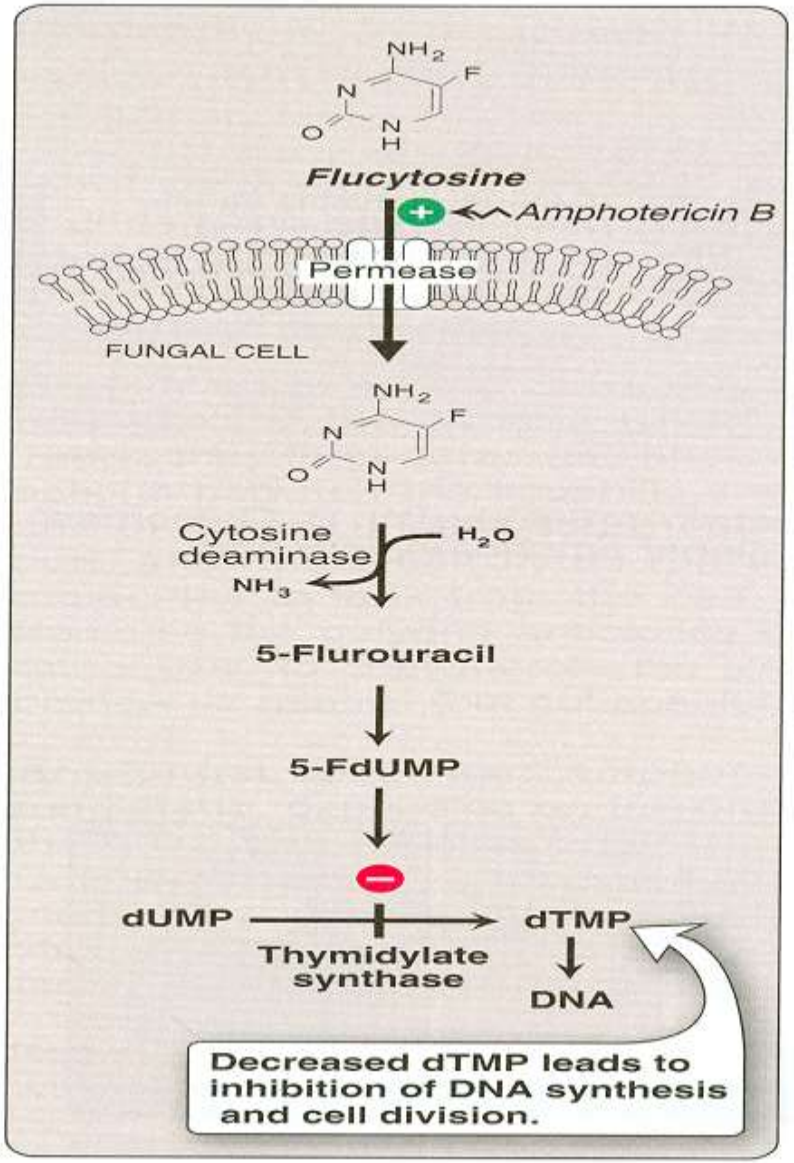
a) incorporated into the RNA (this leads to a ***misreading of the fungal genetic code***)

b) further metabolized to 5-deoxyfluorouridylic acid, a potent inhibitor of thymidylate synthase (this leads to a ***blockade of fungal DNA synthesis***)

- ***fungicidal*** or ***fungistatic*** depending on the organism and on drug concentration.
- Best if always used in combination

Action of flucytosine in fungi.

5-Flucytosine is transported into the fungal cell, where it is deaminated to 5-fluorouracil (5-FU). The 5-FU is then converted to 5-fluorouracil-ribose monophosphate (5-FUMP) and then is either converted to 5-FUTP and incorporated into RNA or converted by ribonucleotide reductase to 5-FdUMP, which is a potent inhibitor of thymidylate synthase.



Antifungal spectrum and resistance

-Antifungal spectrum includes

Cryptococcus neoformans,

Candida albicans,

-Resistance may arise rapidly during therapy.

Pharmacokinetics and administration

Administered orally

Excreted renally

Adverse effects

-Anorexia, nausea and vomiting, diarrhea
-Severe ulcerative enterocolitis (rare)
-Skin rashes
-Headache, dizziness, confusion
-Reversible bone marrow depression (leukopenia, thrombocytopenia)
-Liver dysfunction (5-10%)
-Alopecia, peripheral neuritis (rare)
[toxicity may be due to the conversion of flucytosine to 5-fluorouracil by the intestinal flora of the host]

Therapeutic uses

-Deep candida infections, cryptococcal meningitidis (always in combination with amphotericin B)

Contraindications

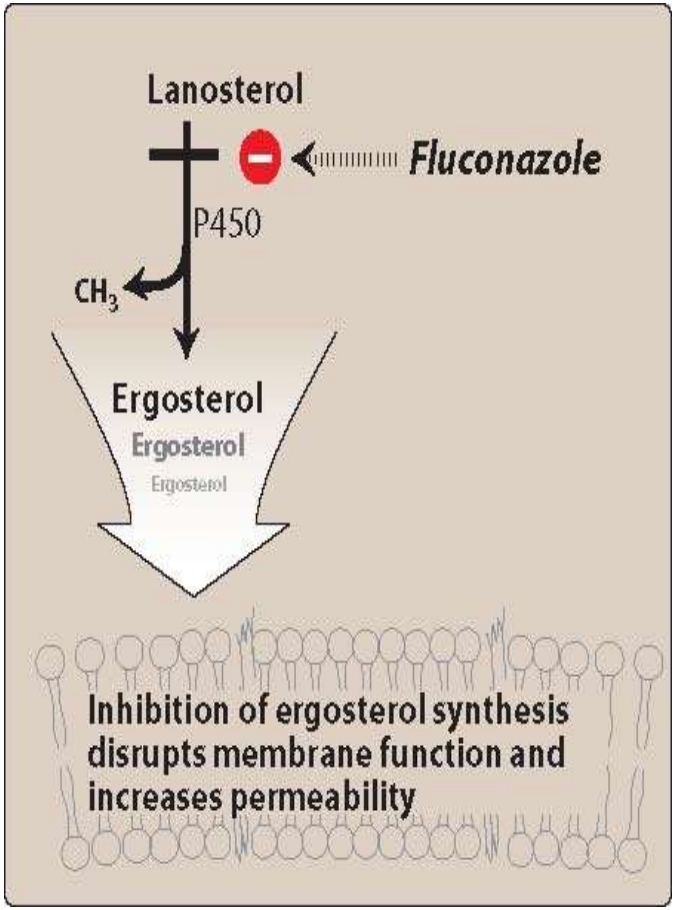
-Pregnancy (5-fluorouracil is teratogenic)

Triazole Antifungals

Drugs: fluconazole, itraconazole, posaconazole, voriconazole, isavuconazole

Mechanism of action

- Inhibit *14 α-demethylase* (a cytochrome P450 [CYP450] enzyme)
- Block the demethylation of lanosterol to ergosterol
- Disrupt cell membrane structure/function
- Disrupt fungal growth



Antifungal spectrum
Broad spectrum
Other effects
-Azoles may inhibit certain mammalian cytochrome P450 isozymes and therefore they may 1) inhibit the synthesis of androgens and of corticosteroids 2) potentiate the effects of several drugs including cyclosporine, phenytoin, terfenadine, astemizole, tolbutamide and warfarin.

Pharmacokinetics and administration

-F(oral): itraconazole » 55%, fluconazole >90%.
(acidity favors oral absorption of ketoconazole)
-Distribution in all body tissues. Penetration into CNS is generally negligible, ***but good for fluconazole***.
-Renal excretion: fluconazole » 75%, others < 1%
-Administration: oral, IV, topical

Adverse effects

-Anorexia, nausea and vomiting (may require antiemetics)
-Gynecomastia, decreased libido, impotence, menstrual irregularities (with ketoconazole, due to blockade of adrenal steroid synthesis)
-Hepatitis (is rare, but can be fatal)
-Hypokalemia, hypertension (itraconazole)
-Azoles are potent teratogenic drugs in animals

Contraindications

Pregnancy

Fluconazole

- Wide tissue distribution, pass B.B.B.
- Less hepatotoxic.
- Less drug interaction.
- Less effect on sex hormones
- Broader spectrum.
- Least active amongst the group
- Used for the prophylaxis against invasive fungal infections in transplant patients
- Effective against most forms of mucocutaneous candidiasis
- Given as a single-dose oral treatment vulvovaginal candidiasis

PHARMACOLOGY OF GRISEOFULVIN

Chemistry

-Griseofulvin is a benzofuran derivative

-The drug is practically insoluble in water

Mechanism of action

-An active transport accumulates the drug in sensitive fungal cells where

↓

griseofulvin causes disruption of the mitotic spindle by interacting with polymerized mycrotubules(ppt in healthy keratin, prevent fungal invasion)needs 6 mo. TTT

-The ultimate effect is ***fungistatic***

Antifungal spectrum and resistance

-Antifungal spectrum includes only *Dermatophytes.*

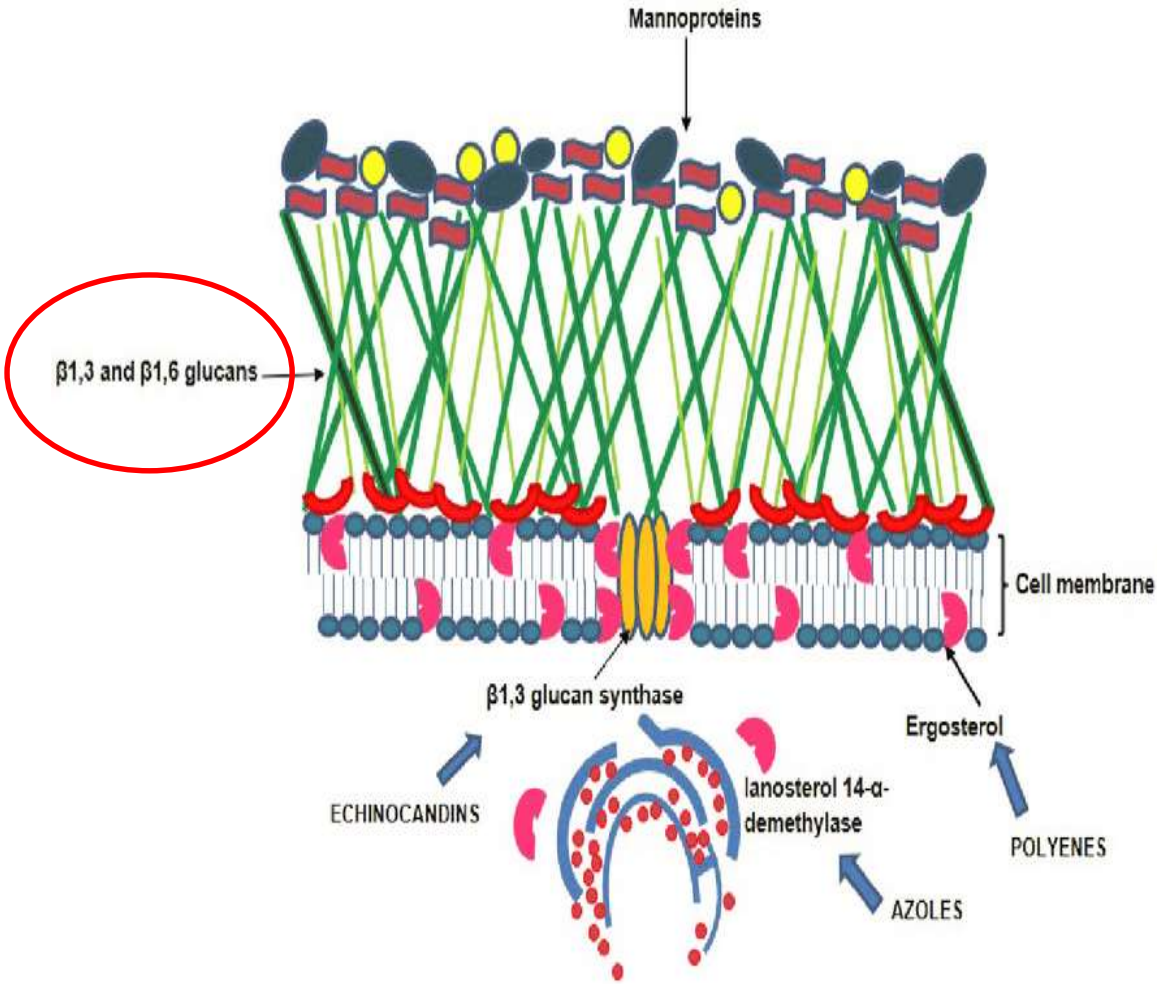
-The drug is ineffective against other fungi producing superficial lesions (like *Candida* and *Malassezia furfur*) and those producing deep mycoses.

-Resistance is uncommon.

Echinocandins

Mechanism of action

- Inhibit of *β(1,3)-D-glucan synthase* → inhibit β(1,3)-D-glucan synthesis → inhibit cell wall synthesis



Echinocandins

- Newest class of antifungal agents
- Intravenous
- inhibiting the synthesis of (1–3)-glucan
- Well tolerated
- **Caspofungin**

Caspofungin

- First-line for patients with invasive candidiasis e.g., candidemia
- Second-line for invasive aspergillosis

- Must be administered by slow IV infusion because it can cause histamine-like reaction

- MUST NOT be given with cyclosporine → hepatotoxicity

Pharmacokinetics and administration

-F(oral): » 50%
-Distribution is ***mainly in keratinized tissues where the drug is tightly bound*** and where it can be detected 4-8 hours after oral administration.
-Administration: oral

Adverse effects

-Xerostomia, nausea and vomiting, diarrhea
-Headache
-Hepatotoxicity (rare)
-Leukopenia, neutropenia
-Allergic reactions
-Teratogenic effects in several animal species

Therapeutic uses

-Mycotic disease of the skin, hair and nails (long treatments are needed)

Drugs For Cutaneous Mycotic Infections

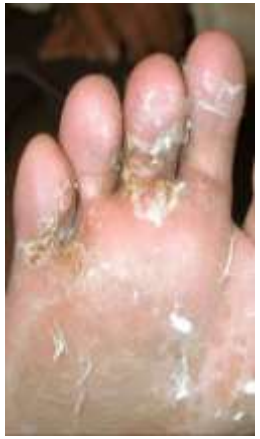
DRUGS FOR CUTANEOUS MYCOSES

Butenafine LOTRIMIN ULTRA
Butoconazole GYNAZOLE
Clotrimazole LOTRIMIN AF
Ciclopirox PENLAC
Econazole ECOZA
Griseofulvin GRIFULVIN V, GRIS-PEG
Miconazole FUNGOID, MICATIN, MONISTAT
Naftifine NAFTIN
Nystatin MYCOSTATIN
Oxiconazole OXISTAT
Sertaconazole ERTACZO
Sulconazole EXELDERM
Terbinafine LAMISIL
Terconazole TERAZOL
Tioconazole VAGISTAT-1
Tolnaftate TINACTIN

Drugs For Cutaneous Mycotic Infections

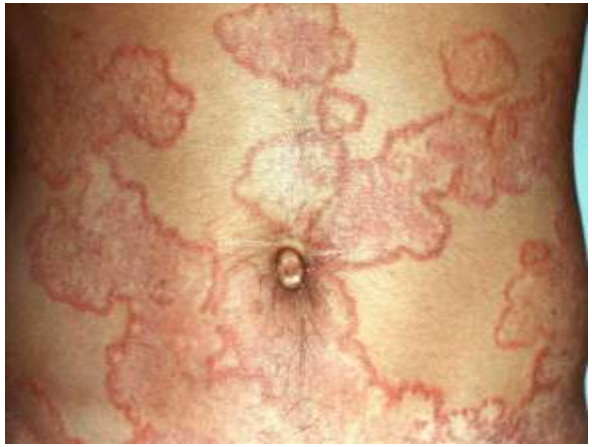
- Dermatophytes/tinea
- Classified according to affected site, e.g., tinea pedis
- Main fungal classes that cause cutaneous infections:

1. Trichophyton
2. Microsporum
3. Epidermophyton



tinea pedis

tinea capitis



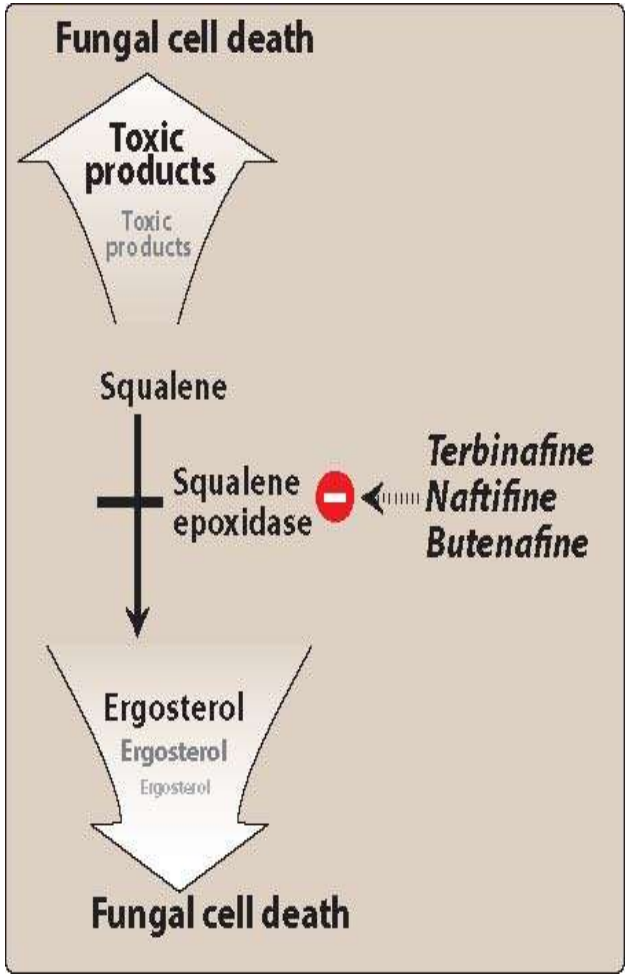
tinea corporis

Squalene Epoxidase Inhibitors

Squalene Epoxidase Inhibitors

Mechanism of action

- Inhibition of *squalene epoxidase*
- Blocking the biosynthesis of ergosterol
- Squalene accumulation affects membrane permeability

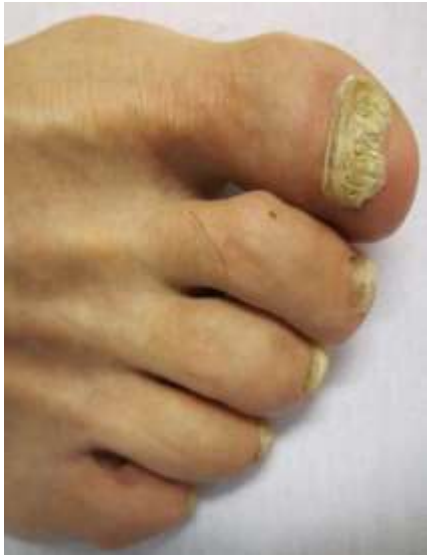


Terbinafine

- Drug of choice for treating dermatophyte onychomycoses
- More effective than itraconazole or griseofulvin for Trichophyton
- Useful in the treatment of tinea capitis

-oral terbinafine (topical ineffective)

-topical can be used with other types, e.g., pedis, corporis…



dermatophyte onychomycosis (fungal infection of the nail)

Terbinafine

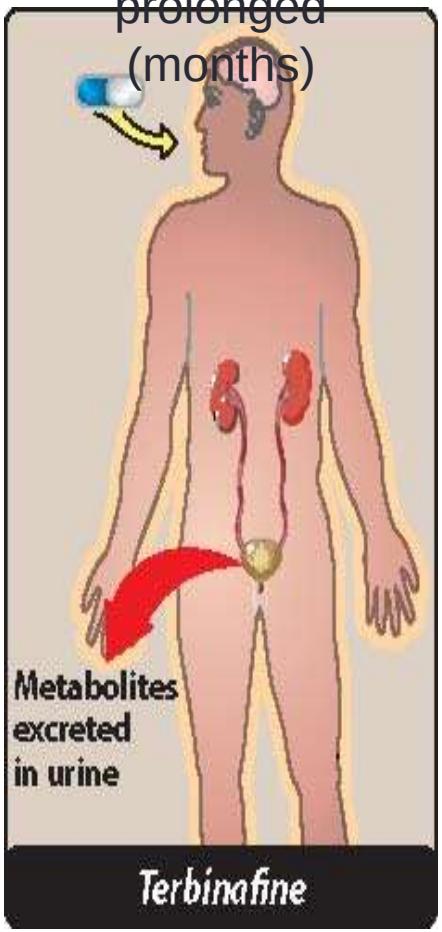
Antifungal spectrum

- Effective against: Trichophyton, Candida, Epidermophyton, Scopulariopsis

Pharmacokinetics

- Oral and topical
- Extensively metabolized by CYP450 and excreted renally
- Potent inhibitor of CYP2D6

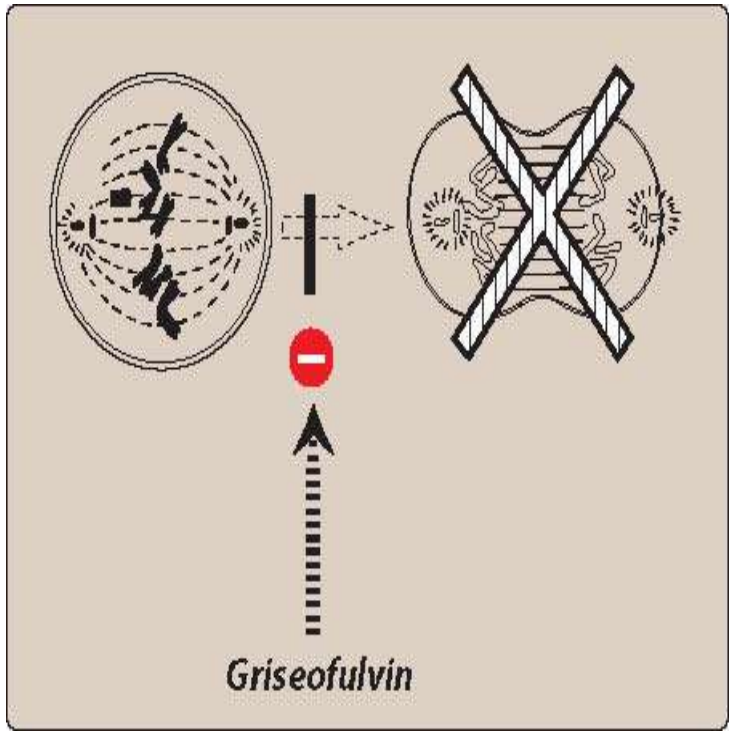
Oral treatment is ~~prolonged~~ (months)



Griseofulvin

Griseofulvin

- **MOA**: disruption of the mitotic spindle and inhibition of fungal mitosis
- Has been largely replaced by oral terbinafine for nail infection
- Still used to treat dermatophytosis of the scalp and hair
- Fungistatic
- Requires long duration of treatment.
- INDUCES hepatic CYP450 activity
- Contraindicated in pregnancy and porphyria patients



Nystatin

Nystatin

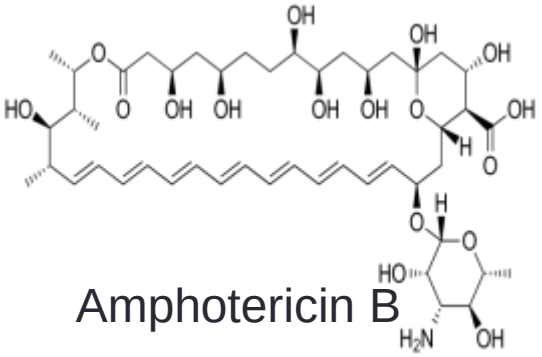
- Polyene
- Very similar to amphotericin B
- Used for the treatment of oral and cutaneous Candida
- **Routes:**

❑No parenteral use (toxic)

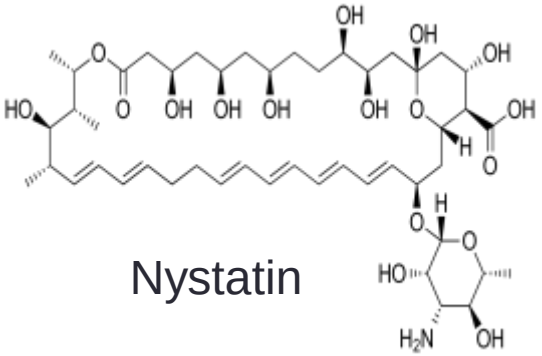
❑Orally (“swish and swallow” or “swish and spit”)

❑Intravaginally

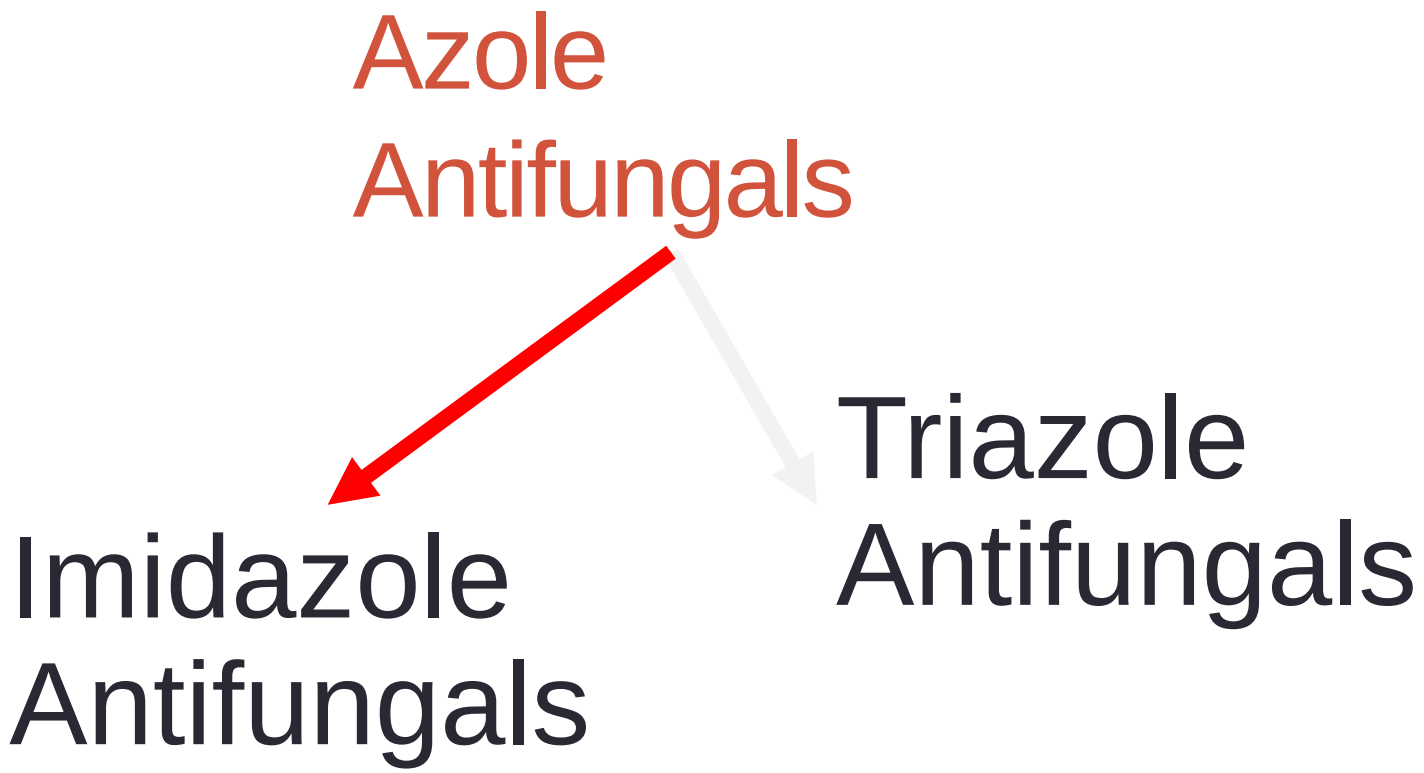
❑topically



Amphotericin B



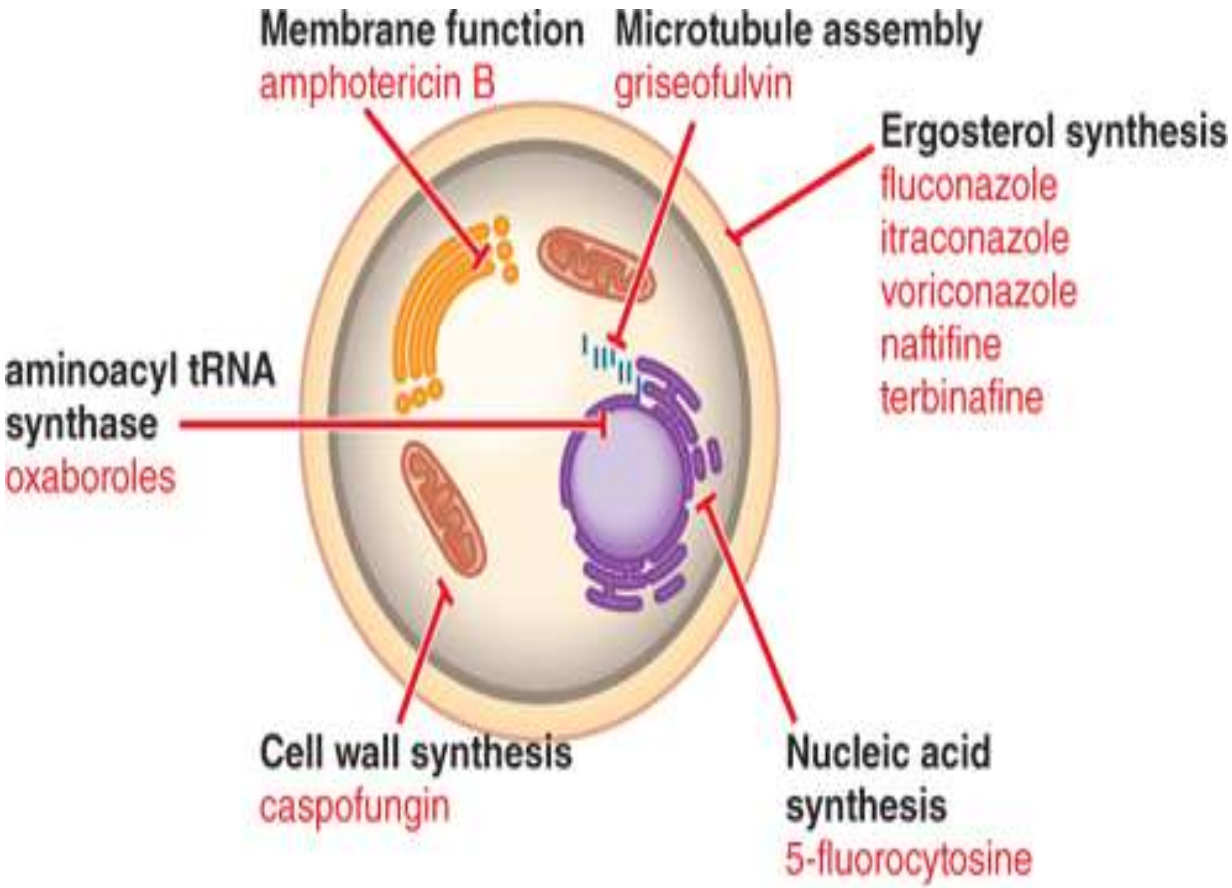
Nystatin


Azole
Antifungals
Imidazole
Antifungals
Triazole
Antifungals

Imidazoles

- Wide range of antifungal activity
- Still used topically for the treatment of tinea corporis, tinea cruris, tinea pedis, and oropharyngeal and vulvo-vaginal candidiasis
- Miconazole: available as a buccal tablet
- Clotrimazole: available as throat lozenge
- Ketoconazole: historically used for systemic mycoses (highly toxic – causes severe liver injury)

Summary



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