Antifungal drugs

* Infectious diseases caused by fungi called **Mycoses**

* Fungi, like mammalian cells but unlike bacteria, are eukaryotic and possess nuclei, mitochondria and cell membranes. However, their membranes contain distinctive sterols, **ergosterol and lanesterol**.

* Fungi are heterotrophic (not self-sustaining) organisms that live as saprobes or parasites.

* They are complex organisms in comparison to bacteria, they have rigid cell wall composed of **chitin (N –acetylglucosamine).**Thus antibacterial agents are not effective against fungi.

* Two types of mycotic infections:-

1. Superficial mycoses ….. Affect skin, mucous membrane

Ex: Dermatomycoses: affect skin, hair, and nail.

Dermatophytes: affect keratin layer of skin, hair, and nail.

Candidiasis: affect skin and mucous membrane of mouth, GIT,

female genital tract.

2. Deep mycoses …… affect internal organ like lung , heart ,brain lead to pneumonia, endocarditis, meningitis respectively. Systemic infection caused by dimorphic fungi, yeasts.

Ex: *Cryptococcus. neoformans, Candida.spp., Aspergellosis*.

** Causes of fungal infections:-

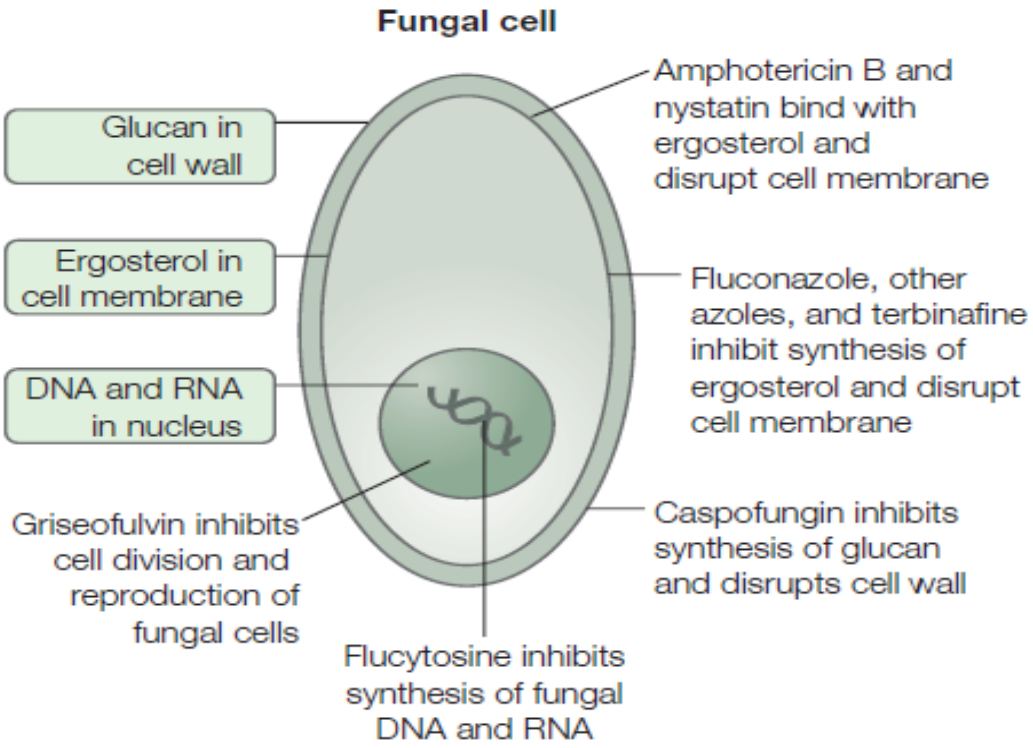
1. Abuse of broad spectrum antibiotics
2. Decrease in the patient immunity

Fungal infections are usually more difficult to treat than bacterial infections:-

1. Because fungal organisms grow slowly.
2. Because fungal infections often occur in tissues that are poorly penetrated by antimicrobial agents (e.g., avascular tissues).

3. Therapy of fungal infections usually requires prolonged treatment.

Classification of Antifungal Drugs:-



(Sites of action of antifungal drugs)

A) Drugs that disrupt cell membrane :

i) Polyenes antifungal :

1. Amphotericin B :-

- Amphotericin B is a naturally occurring polyene antifungal produced by ***Streptomyces nodosus.***

- used I.V for systemic infection because Poor gastro-intestinal absorption

- Although it is toxic potential, amphotericin B remains the drug of choice for the treatment of several life-threatening mycoses.

Mechanism of action:

1. Amphotericin B binds to ergosterol in the plasma membranes of sensitive fungal cells.

2. There, it forms pores (channels), The pores disrupt membrane function, allowing electrolytes (particularly potassium) and small molecules to leak from the cell, resulting in cell death.

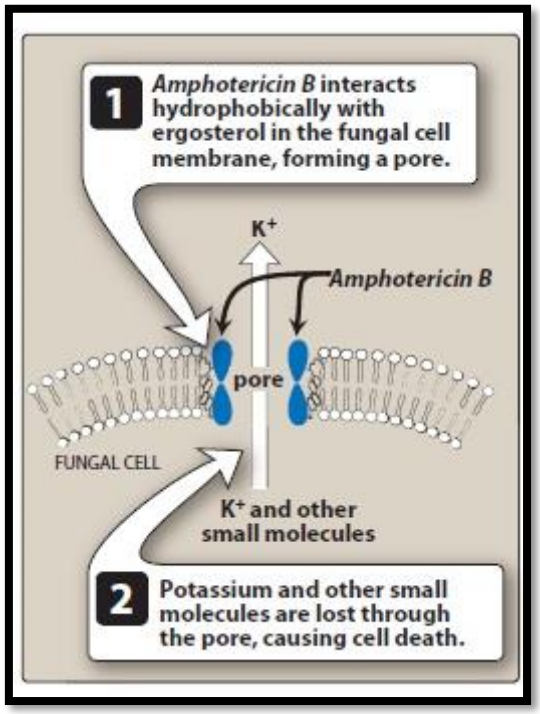


Fig (1): show the mechanism of action of Amphotericin B.

Antifungal spectrum:

fungicidal or fungistatic, depending on the organism and the concentration of the drug.

It is effective against a wide range of fungi, including **Candida.albicans, Histoplasma.capsulatum, Cryptococcus.neoformans, Coccidioides. immitis, Blastomyces.dermatitidis**, and many strains of Aspergillus.

Adverse effects:

1. Fever, chills, headache, nausea, vomiting, and hypotension during intravenous infusion.
2. Reversible nephrotoxicity
3. Hypokalaemia and hypomagnesaemia;
4. Anaemia is common.

2. Nystatin:-

a. Nystatin works in the same way as amphotericin B, but its greater toxicity therefore avoid systemic use.

b. Its indications are limited to cutaneous/mucocutaneous and intestinal infections, especially those caused by *Candida* species.

c. Preparations include tablets, pastilles, lozenges or suspension.

d. Cutaneous infections treated with ointment and suppositories treat vaginitis.

ii) Azoles antifungal drugs:

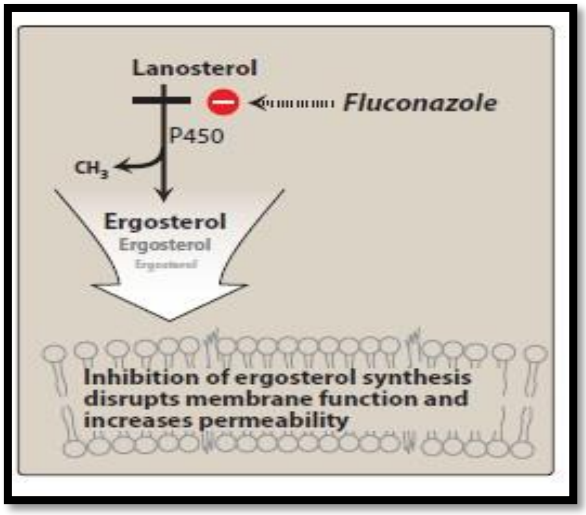
Azole antifungals made up of two different classes of drugs **Imidazoles** and **Triazoles**.

** imidazoles given topically for cutaneous infections.

** triazoles are given systemically for the treatment or prophylaxis of cutaneous and systemic fungal infections.

Mechanism of action:-

Azoles are fungistatic. They inhibit C-14 α-demethylase (a cytochrome P450 enzyme), thereby blocking the demethylation of lanosterol to ergosterol, the principal sterol of fungal membranes .The inhibition of ergosterol biosynthesis disrupts membrane structure and function, which in turn, inhibits fungal cell growth.



(Mode of action of Azole antifungals.)

1- Fluconazole:-

- **Fluconazole** is a potent and broad-spectrum antifungal agent. It is active against many *Candida* species, *Cryptococcus neoformans* and *Histoplasma.capsulatum*.
- **Fluconazole** used clinically to treat superficial *Candida* infections and oesophageal *Candida*.
- It also is the drug of choice for Cryptococcus neoformans after induction therapy with *amphotericin B* and *flucytosine* and used for the treatment of candidemia and coccidioidomycosis.

2- **Itraconazole AND Voriconazole (Triazoles)**

***Itraconazole** and **voriconazole** are available as oral and parenteral formulations.

* I.V use indicated for severe fungal infections.

* The antifungal spectrum of *Itraconazole* is the drug of choice for the treatment **of blastomycosis, sporotrichosis, paracoccidioidomycosis, and histoplasmosis.**

3-Imidazole:- (Ketoconazole, Clotrimazole, Miconazole, Oxiconazole)

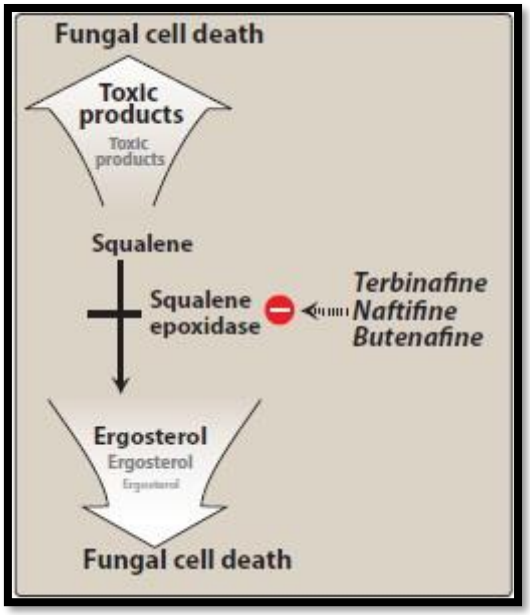
The topical imidazoles have a variety of uses, including tinea corporis, tinea cruris, tinea pedis, and oropharyngeal and vulvovaginal candidiasis.

iii) Allylamines (sequalene epoxidase inhibitors)

(Terbinafine, Naftifine)

Mechanism of action:-

These agents act by inhibiting **squalene epoxidase**, thereby blocking the biosynthesis of ergosterol, an essential component of the fungal cell membrane. Accumulation of toxic amounts of squalene results in increased membrane permeability and death of the fungal cell.



(Mode of action of allylamines)

**** Therapeutic uses:-**

1. Oral terbinafine FOR treatment of:
   a. **dermatophyte onychomycoses (fungal infections of nails)**
   b. **tinea capitis (infection of the scalp).**
2. Topical terbinafine (cream, gel or solution) used to treat tinea pedis, tinea corporis (ringworm), and tinea cruris (infection of the groin).
3. Naftifine is active against Trichophyton, Microsporum, and Epidermophyton. Naftifine for topical treatment of tinea corporis, tinea cruris, and tinea pedis.

B) Drugs that inhibits DNA synthesis:

**** Flucytosine:** often used in combination with amphotericin B.

**** Mechanism of action:-**

- Flucytosine enters the fungal cell via a cytosine specific permease, an enzyme not found in mammalian cells. Then subsequently converted to a series of compounds, including 5-fluorouracil, which disrupt nucleic acid and protein synthesis.

****Antifungal spectrum:**

- is used to treat systemic candidiasis and cryptococcosis.

** **Adverse effects:**
Flucytosine causes reversible neutropenia, thrombocytopenia, and dose-related bone marrow depression.

C) Drugs inhibit cell wall synthesis:-

**Echinocandins (Caspofungin and Micafungin)

Echinocandins are semisynthetic lipopeptides.

** Mechanism of action:

Echinocandins interfere with the synthesis of the fungal cell wall by inhibiting the synthesis of d-glucan, leading to lysis and cell death.

**** Antifungal spectrum:**
- The echinocandins have potent activity against Aspergillus and most Candida species, including those species resistant to azoles.

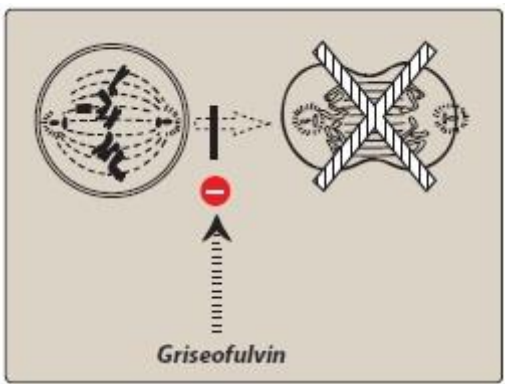
** **Adverse effects** being fever, rash, nausea, and phlebitis at the infusion site. They can also cause a histamine-like reaction (flushing) when infused too rapidly.

D) Drugs that inhibit fungal DNA and RNA:

**** Griseofulvin:**

- Griseofulvin is fungistatic and requires a long duration of treatment (for example, 6 to 12 months for onychomycosis)
- Griseofulvin is orally active, but its spectrum is limited to dermatophytes. It is concentrated in keratinized cells.

**** Mechanism of action:**
Griseofulvin causes disruption of the mitotic spindle and inhibition of fungal mitosis.



(Inhibition of mitosis by *griseofulvin*)