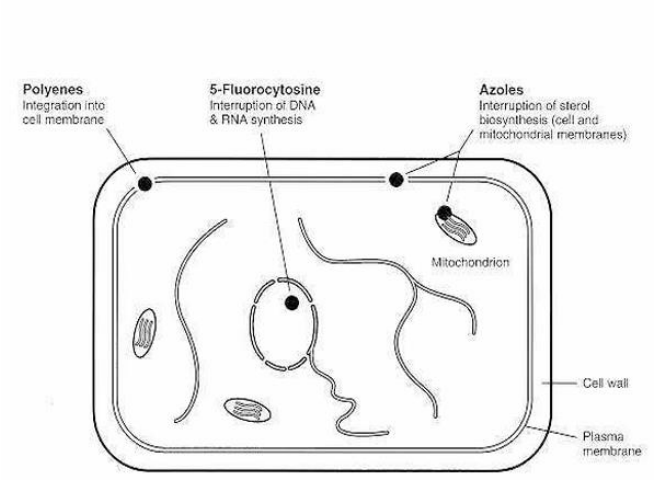
Antifungal agents (1)



- **Fungi consist of:**

1-Rigid cell wall composed of chitin (N acetylglucosamine) (bacterial cell wall is composed of peptidoglycan)

2-Plasma or cell membrane which contains ergosterol (human cell membrane is composed of cholesterol) (selectivity to some antifungal agents)

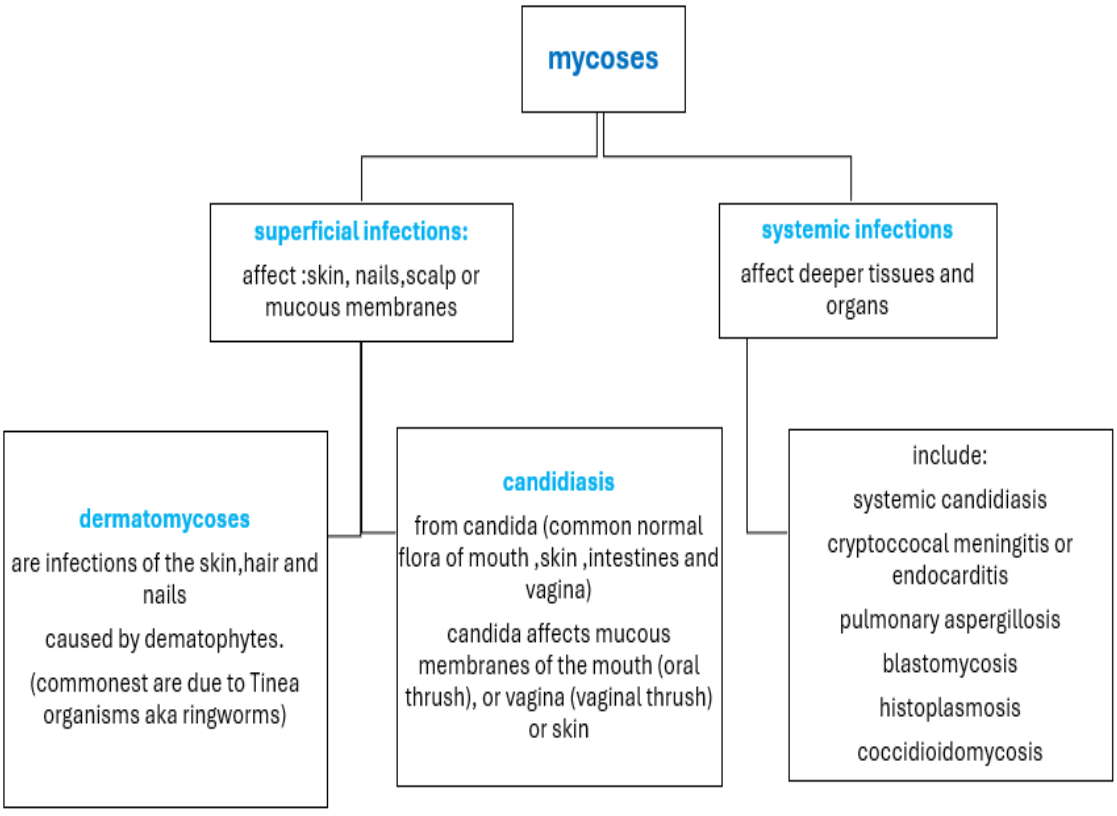
Notes:

1-Fungi have nucleus and well defined nuclear membrane, and chromosomes

2-Fungi are eukaryotic organisms that live as saprobes or parasites

3-They are complex organisms in comparison to bacteria (prokaryotic cells=have no nuclear membranes and no mitochondria), Therefore antibacterial agents are not effective in fungal infections and antifungal agents are ineffective in bacterial infections.

4-fungal infections are termed mycoses.



Fungal infections of all types are common in:

1Patients with AIDS

2-Debilitated patients

3-Patients underwent organ transplantation and on immunosuppressants

4-patients under anti-cancerous therapy

Antifungal drug classes

1-polyenes 2-azoles 3-allylamines 4-Echinocandins (people are always eager)

Polyenes (polyene macrolide antibiotics)

1-mechanism of action:

1-Bind to ergosterol in fungal plasma membrane leading to formation of pores and hence increased permeability of the membrane.

2- This allows leakage of intracellular ions and enzymes especially loss of intracellular k+ causing death to the fungus

Note: They bind selectively to ergosterol in fungus but not to cholesterol in mammalian plasma membranes

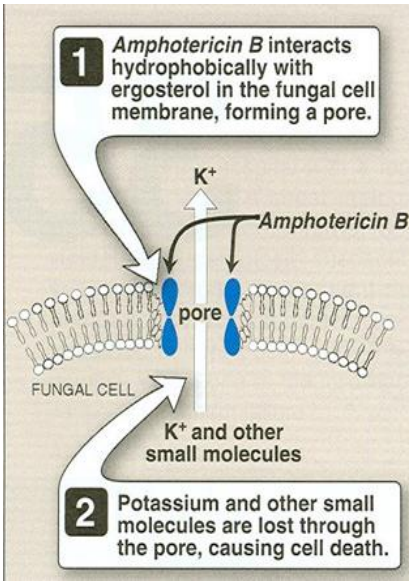
2- Mechanisms of resistance to polyenes:

1-Decreased ergosterol content of the fungal membrane 2- Impaired binding to ergosterol

3-types:

1-Amphotericin B

pho=photo



- It is a macrolide antibiotic, poorly absorbed orally, useful for fungal infection of gastrointestinal tract

- Drug of choice for most systemic infections, given as slow IV infusion

- Locally used in corneal ulcers (ophthalmic oint.), arthritis (intra-articular) and bladder irrigation Penetration through BBB is poor but increases in inflamed meninges

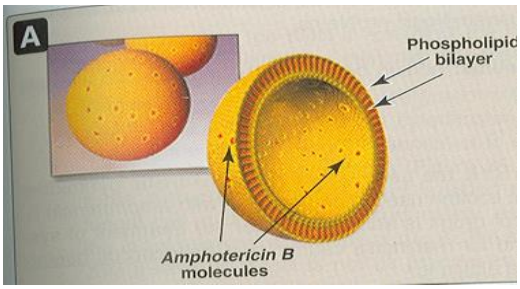
- Excreted slowly via kidneys, traces found in urine for months after cessation of drug (some elimination via bile is available)

- Half life :15 days

Side effects:

1-Most serious is renal toxicity, which occurs in 80% of patients	2-Hypokalemia in 25% of patients
3-Hypomagnesaemia	4-Anemia & thrombocytopenia
5-Impaired hepatic function	6-Anorexia, nausea, vomiting, abdominal, joint and muscle pain, loss of weight, and fever
7-Anaphylactic shock	

Note: To reduce the toxicity of Amphotericin B, several new formulations have been developed in which amphotericin B is packaged in a lipid-associated delivery system (Liposomal preparations).they have more efficacy, less nephrotoxicity but very expensive.



2-Nystatin

- It is a polyene macrolide, similar in structure to Amphotericin B and with same MOA

- Too toxic for systemic use

- Not absorbed from GIT, skin or vagina, therefore administered orally to prevent or treat superficial candidiasis of mouth, esophagus or intestinal tract

- Oral suspension of 100,000 U/ml 4 times a day and tablets 500,000 U of Nystatin are used to decrease GIT colonization with Candida

- For vaginal candidiasis in form of vaginal cream or pessaries used for 2 weeks

- In cutaneous infection available in cream, ointment or powder forms and applied 2-3 times a day

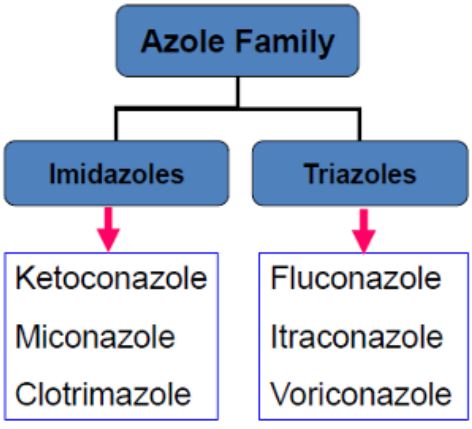
3-Natamycin

- It is a macrolide polyene antifungal used to treat fungal keratitis, an infection of the eye. It is especially effective against Aspergillus and Fusarium corneal infections

- Also effective in Candida, Cephalosporium and Penicillium

- Not absorbed when given orally- Available in cream and ophthalmic eye drops

Azoles



• Azole antifungal agents have added greatly to the therapeutic options for treatment of systemic fungal infections

• The azole antifungal agents in clinical use contain either two or three nitrogens in the azole ring and are thereby classified as imidazoles (e.g., ketoconazole; miconazole; clotrimazole) or triazoles (e.g., itraconazole; and fluconazole), respectively

• Azoles mechanism of action:

- Azoles are fungistatic ,They inhibit cytochrome P450 demethylase enzyme which is important for formation of ergosterol

- This inhibition disrupts membrane structure and function and, thereby, inhibits fungal growth

•Mechanism of resistance to Azoles:

Mutation in the gene encoding for demethylase

Allylamines

1-Types:1- Terbinafine 2-Naftifine 3- Butenafine (brain think now!)

2-mechanism of action:

Inhibit fungal squalene epoxidase, thereby decreasing the synthesis of ergosterol. This plus the accumulation of toxic amounts of squalene result in the death of the fungal cell

Significantly higher concentrations of Terbinafine are needed to inhibit human squalene epoxidase, an enzyme required for the cholesterol synthetic pathway (representing some selectivity to fungi)

Echinocandins

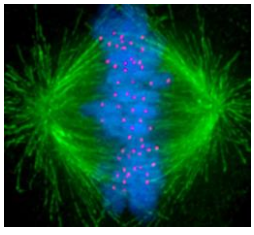
1-Types: 1-Caspofungin 2-Micafungin 3-Anidulafungin (cam)

2-mechanism of action:

Interfere with the synthesis of the fungal cell wall by inhibiting the synthesis of D-glucan, leading to lysis and fungal cell death

Other medications

1-Griseofulvin



An Antifungal that inhibit mitosis

Mechanism of action:

- inhibits fungal mitosis by inhibiting mitotic spindle formation

-The drug binds to tubulin, interfering with microtubule function, thus inhibiting mitosis

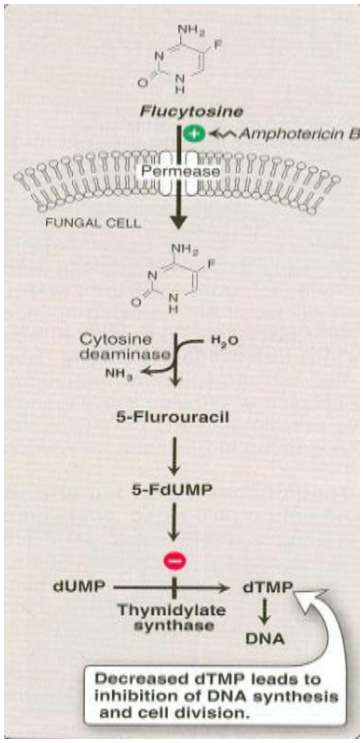
2-Flucytosine (5FC=5-fluorocytosine)

flu=flu

A synthetic pyrimidine antimetabolite that inhibits DNA synthesis

Mechanism of action:

-It enters fungal cells by permease (an enzyme not found in mammalian cells) and is then converted by a series of steps to 5-fluorodeoxyuridine 5'-monophosphate.



-This false nucleotide inhibits thymidylate synthase, thus depriving the fungus of thymidylic acid an essential DNA component

-The mononucleotide is further metabolized to a trinucleotide (5-fluorodeoxyuridine 5triphosphate) and is incorporated into fungal RNA, thus disrupting nucleic acid and protein synthesis.

Note: Amphotericin B increases cell permeability, allowing more Flucytosine to penetrate the cell. Thus,Flucytosine and Amphotericin B are synergistic

Features:

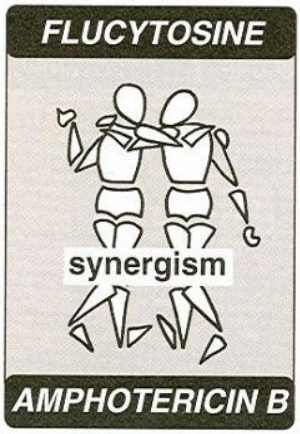
- Has useful activity against Candida and Cryptococcus

- It is fungistatic, effective in combination with Itraconazole for treating chromoblastomycosis and with Amphotericin B for treating cryptococosis

- Highly effective in cryptococcal meningitis in AIDS patients

- is absorbed rapidly and well from GIT

- Widely distributed in body and penetrates well into CSF



Side effects:

1-Reversible neutropenia, thrombocytopenia and occasional bone marrow depression

2- Nausea, vomiting, diarrhea, severe enterocolitis

3- Reversible hepatic enzyme elevation in 5% of patients