Antifungal Agents
Lecture 1

Antifungal Agents

- **Objectives:**

By the end of lectures all students should know:

Available antifungal drugs;

Their MOA;

Their Pharmacokinetic properties;

Their clinical uses

Their major side effects and drug interactions

- **Fungi consist of:**

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

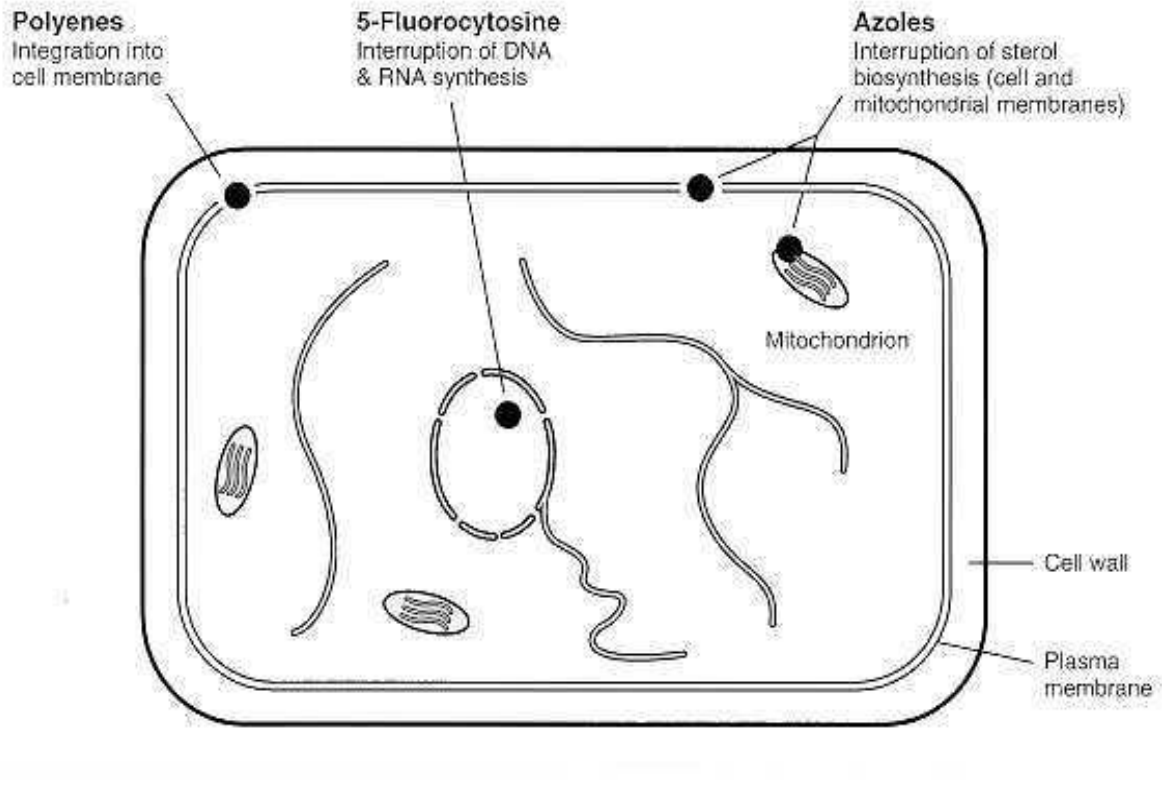
-Plasma or cell membrane which contains ergosterol (human cell mebmrane is composed of cholesterol) (selectivity to some antifungal agents)

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

Fungi are eukaryotic organisms that live as saprobes or parasites

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


Polyenes
Integration into cell membrane
5-Fluorocytosine
Interruption of DNA & RNA synthesis
Azoles
Interruption of sterol biosynthesis (cell and mitochondrial membranes)
Mitochondrion
Cell wall
Plasma membrane

- **Fungal infections are termed *mycoses* and can be divided into:**

  (1) Superficial infections: affecting skin, nails, scalp or mucous membranes

  (2) Systemic infections: affecting deeper tissues and organs

- **Superficial fungal infections can be classified into the dermatomycoses and candidiasis (Candida is a common normal flora of mouth, skin, intestines and vagina)**

- **Dermatomycoses are infections of the skin, hair and nails, caused by dermatophytes. The commonest are due to *Tinea* organisms which are also known as ringworms**
- **In superficial candidiasis, the fungus candida infects the mucous membranes of the mouth (oral thrush), or the vagina (vaginal thrush) or the skin**

- **Systemic fungal infections include:**

- Systemic candidiasis

- Cryptoccocal meningitis or endocarditis

- Pulmonary aspergillosis

- Blastomycosis

- Histoplasmosis

- Coccidioidomycosis

- Paracoccidioidomycosis…etc

- **Fungal infections whether, superficial or systemic, are common in patients with weak immune system e.g.:**

- Patients with AIDS

- Debilitated patients

- Patients underwent organ transplantation and on immunosuppressants

- Patients under anticancerous therapy

Antifungal Drugs Classes

1. Polyenes (polyene macrolide antibiotics)

Amphotericin B

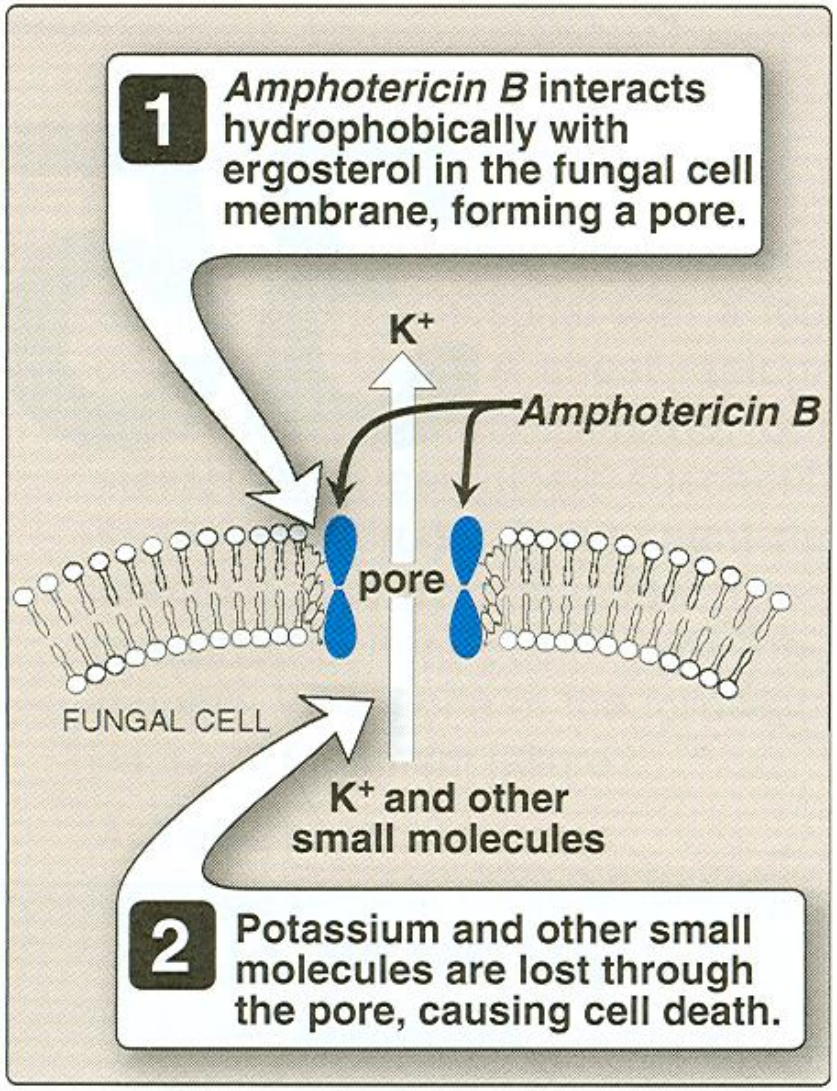
Nystatin

Natamycin

- **Polyenes mechanism of action:**

Bind to ergosterol in fungal plasma membrane leading to formation of pores and hence increased permeability of the membrane. This allows leakage of intracellular ions and enzymes especially loss of intracellular k^+ causing death to the fungus

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

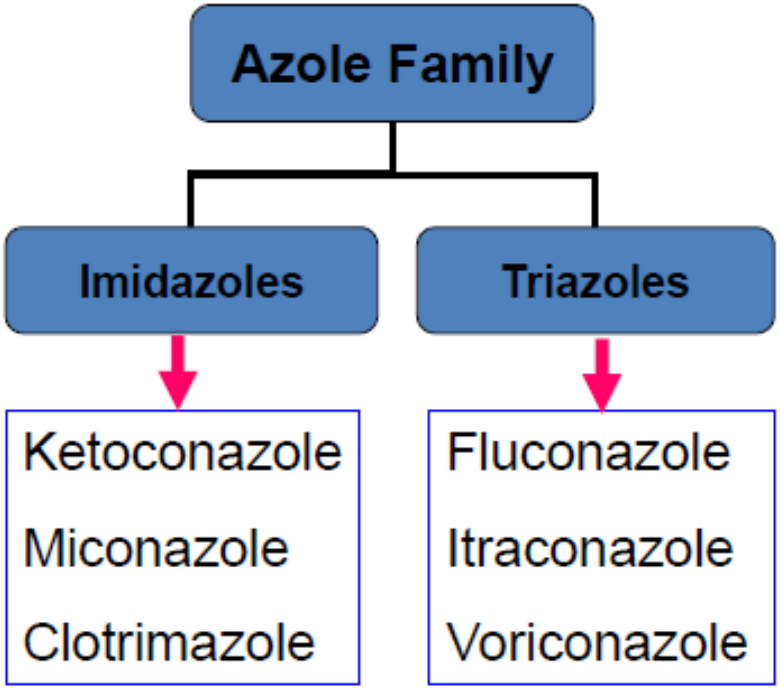

1
Amphotericin B interacts hydrophobically with ergosterol in the fungal cell membrane, forming a pore.
K^+
Amphotericin B
pore
FUNGAL CELL
K^+ and other small molecules
2
Potassium and other small molecules are lost through the pore, causing cell death.

- **Mechanisms of resistance to polyenes:**

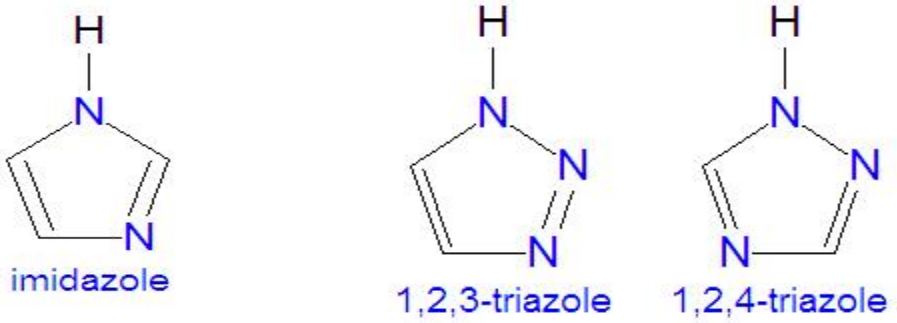
- Decreased ergosterol content of the fungal membrane

- Impaired binding to ergosterol

2. Azoles:


Azole Family
Imidazoles
Triazoles
Ketoconazole
Miconazole
Clotrimazole
Fluconazole
Itraconazole
Voriconazole

- **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

3. Allylamines:

Terbinafine

Naftifine

Butenafine

- **Mechanism of action Allylamines:**

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:**

  Caspofungin

  Micafungin

  Anidulafungin

- **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

- **Antifungals that inhibit mitosis:**

Griseofulvin

- **Mechanism of action:**

It inhibits fungal mitosis by inhibiting mitotic spindle formation

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

- **Drugs that inhibit DNA synthesis (antimetabolites):**

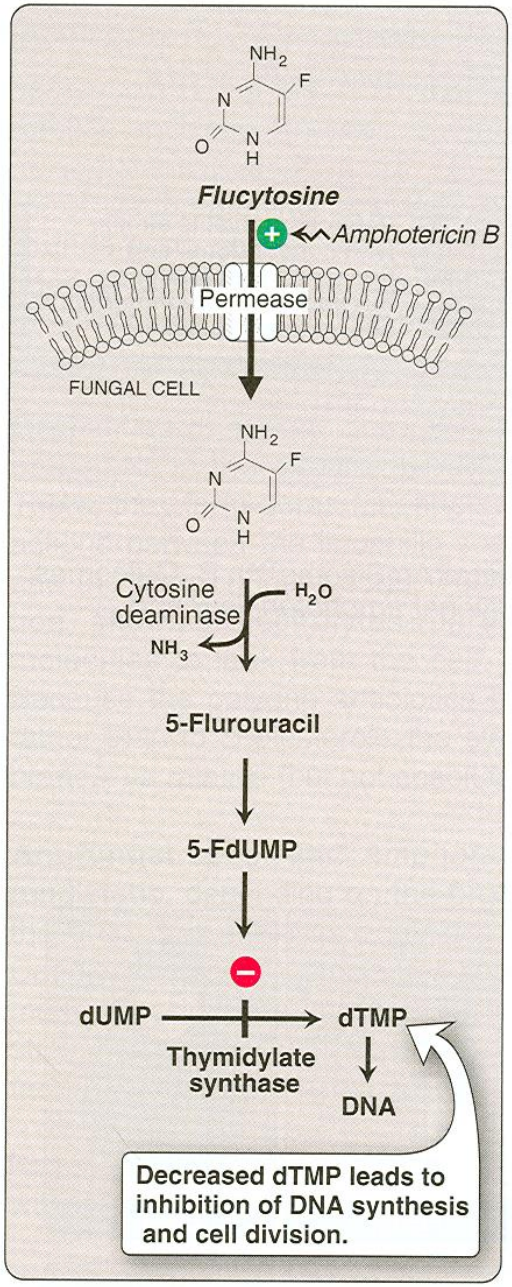
Flucytosine (5FC=5-fluorocytosine)

- **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 5'-triphosphate) and is incorporated into fungal RNA, thus disrupting nucleic acid and protein synthesis. Amphotericin B increases cell permeability, allowing more Flucytosine to penetrate the cell. Thus, Flucytosine and Amphotericin B are synergistic

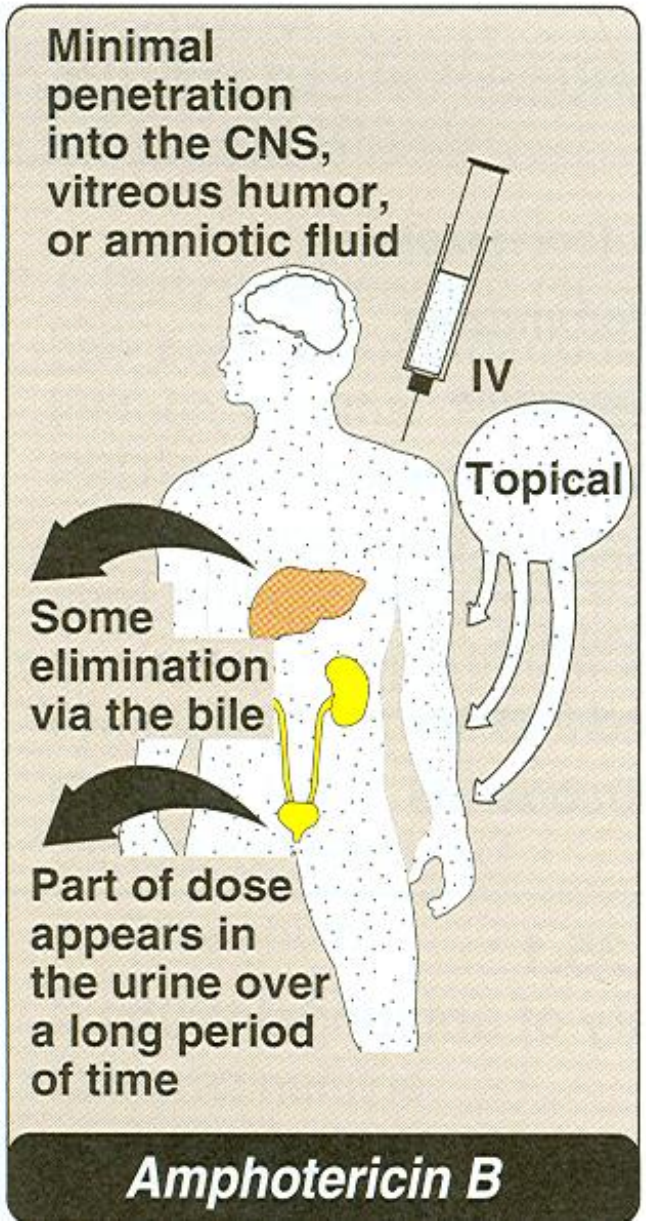

NH2
F
N
O
N
H
Flucytosine
Amphotericin B
Permease
FUNGAL CELL
NH2
F
N
O
N
H
Cytosine deaminase
H2O
NH3
5-Flurouracil
5-FdUMP
dUMP
dTMP
Thymidylate synthase
DNA
Decreased dTMP leads to inhibition of DNA synthesis and cell division.

Amphotericin B

- 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
- Half life 15 days


Minimal penetration into the CNS, vitreous humor, or amniotic fluid
IV
Topical
Some elimination via the bile
Part of dose appears in the urine over a long period of time
Amphotericin B

- **Side effects to Amphotericin:**

- Most serious is renal toxicity, which occurs in 80% of patients

- Hypokalaemia in 25% of patients

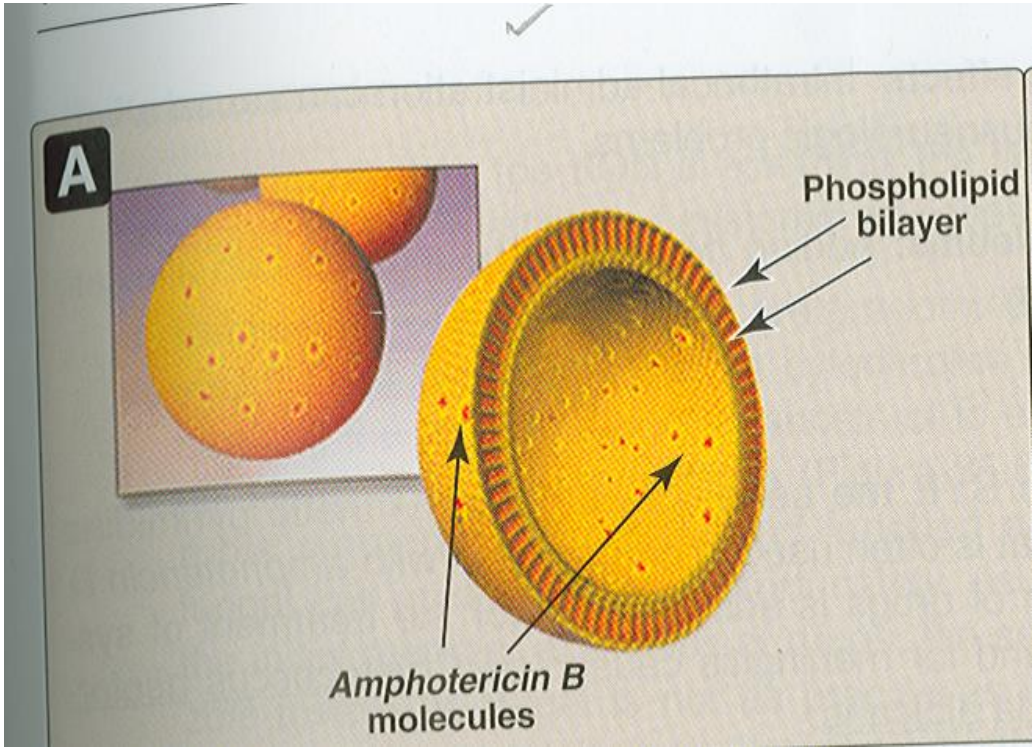
- Hypomagnesaemia

- Anemia & thrombocytopenia

- Impaired hepatic function

- Anorexia, nausea, vomiting, abdominal, joint and muscle pain, loss of weight, and fever
- Anaphylactic shock
- 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)

- **Such delivery systems have more efficacy , less nephrotoxicity but very expensive**



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**

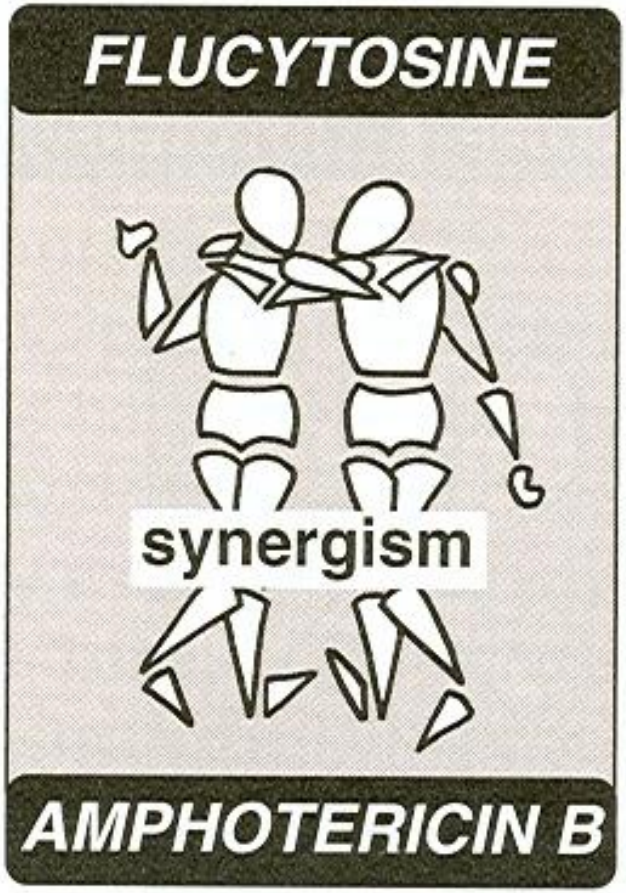
- Oral suspension of 100,000 U/ml 4 times a day and tablets 500,000 U of Nystatin are used to decrease GIT colonization with Candida
- For vaginal candidiasis in form of vaginal cream or pessaries used for 2 weeks
- In cutaneous infection available in cream, ointment or powder forms and applied 2-3 times a day

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**

Flucytosine

- **Has useful activity against Candida and Cryptococcus**
- **It is synthetic pyrimidine antimetabolite that is often used in combination with Amphotericin B**
- **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**


FLUCYTOSINE
synergism
AMPHOTERICIN B

- Flucytosine is absorbed rapidly and well from GIT
- Widely distributed in body and penetrates well into CSF

- **Side effects to Flucytosine:**

- Reversible neutropenia, thrombocytopenia and occasional bone marrow depression
- Nausea, vomiting, diarrhea, severe enterocolitis
- Reversible hepatic enzyme elevation in 5% of patients