Antifungal Agents

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Antifungal Agents

- **Objectives:**

By the end of lectures all students should know

- Available antifungal drugs;

their MOA;

their Pharmacokinetic properties;

their clinical uses and

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)

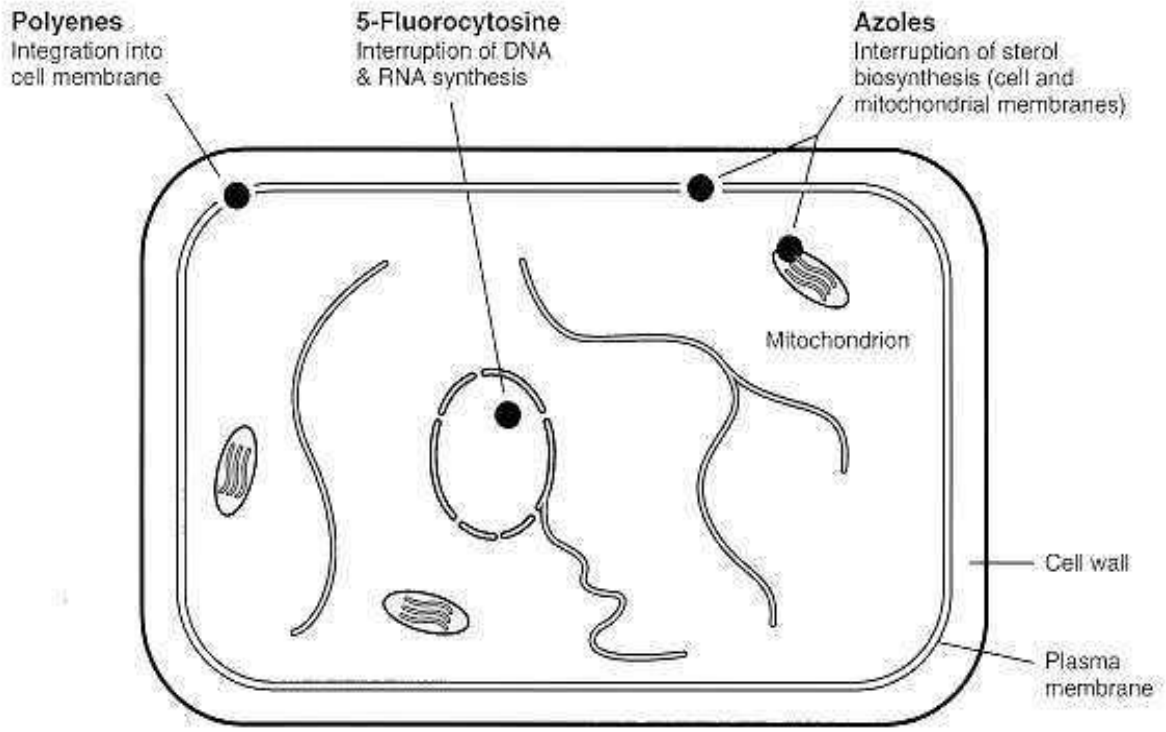
- Plasma or cell membrane which contains ergosterol (human cell mebmrane is composed of cholesterol) (selectivity to some antifungal agents)

- 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 commonly 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

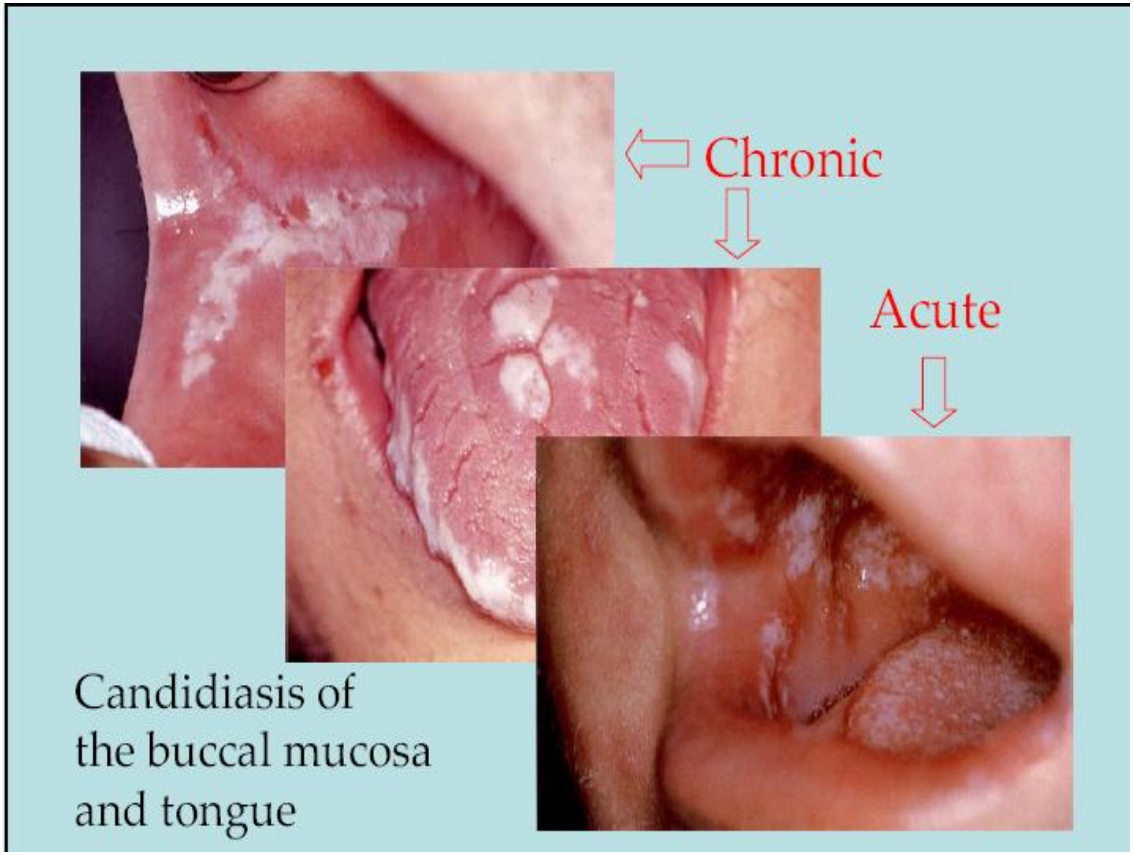
- Pulmonary aspergillosis

- Blastomycosis

- Histoplasmosis

- Coccidioidomycosis

- Paracoccidioidomycosis…etc



Candidiasis of
the buccal mucosa
and tongue

- **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

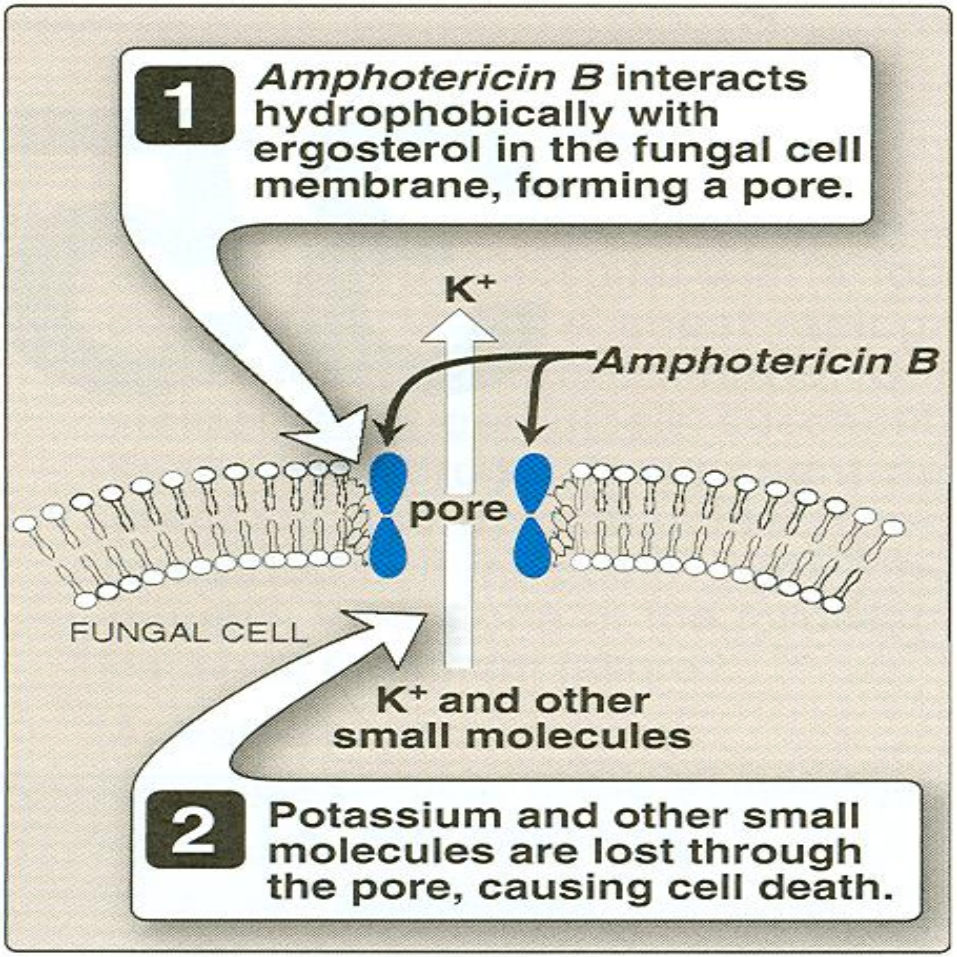
Nystatin

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 in mammalian plasma membranes

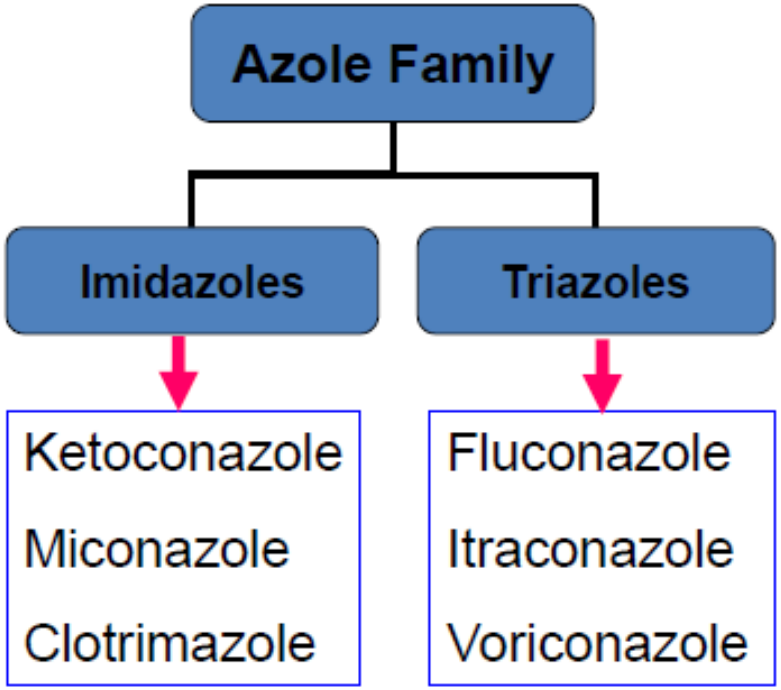

1
Amphotericin B interacts hydrophobically with ergosterol in the fungal cell membrane, forming a pore.
K+
Amphotericin B
pore
FUNGAL CELL
K+ and other small molecules
2
Potassium and other small molecules are lost through the pore, causing cell death.

- **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

- **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

- **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):**

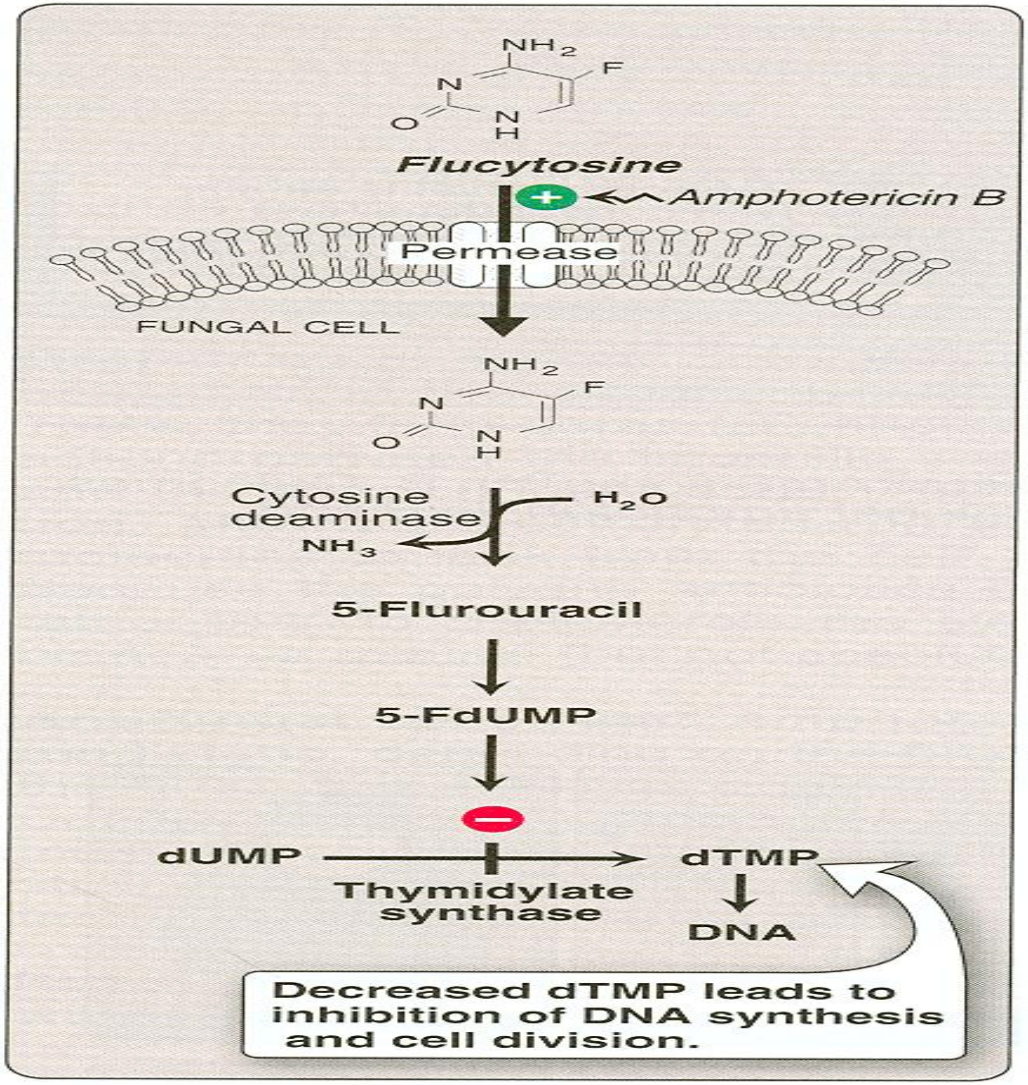
  Flucytosine (-5FC)

- **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 Flucytocine to penetrate the cell. Thus, Flucytosine and Amphotericin B are synergistic

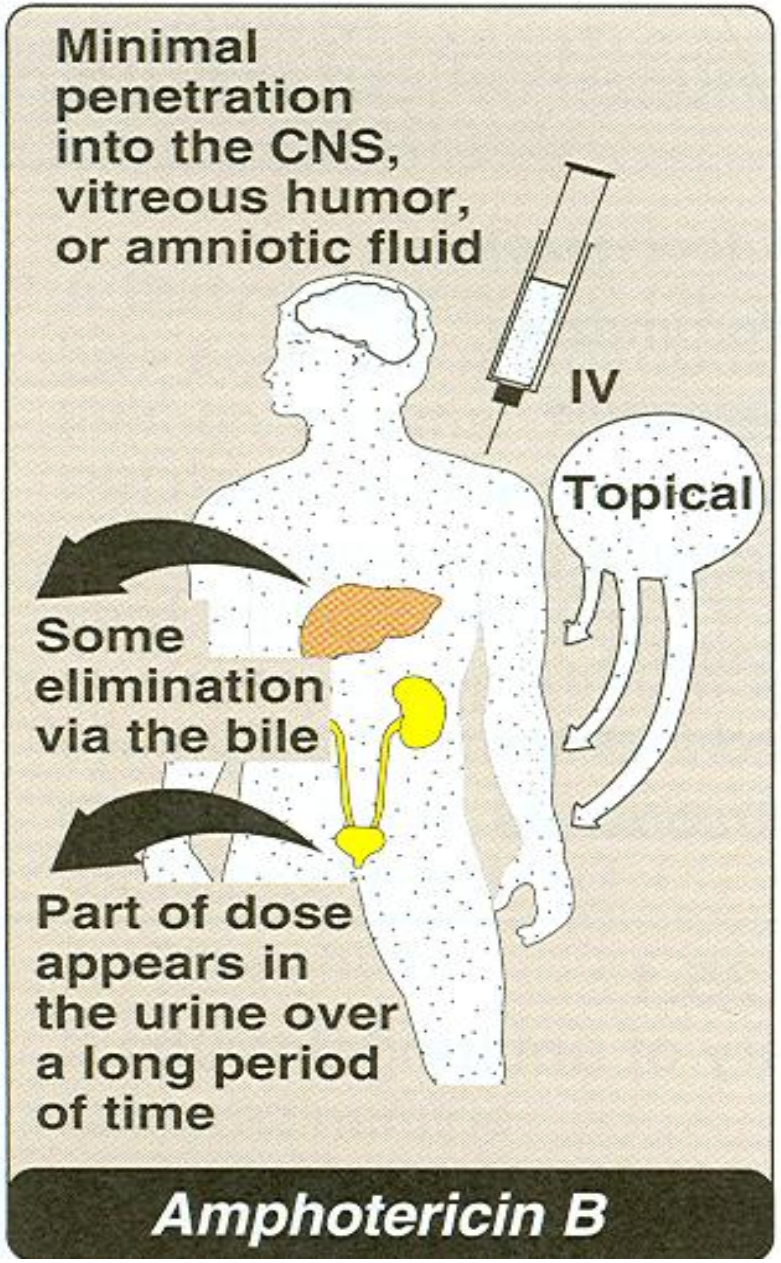

Flucytosine
Amphotericin B
Permease
FUNGAL CELL
Cytosine deaminase
H_2O
NH_3
5-Flurouracil
5-FdUMP
dUMP
Thymidylate synthase
dTMP
DNA
Decreased dTMP leads to inhibition of DNA synthesis and cell division.

Amphotericin B

- It is 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, arthritis 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

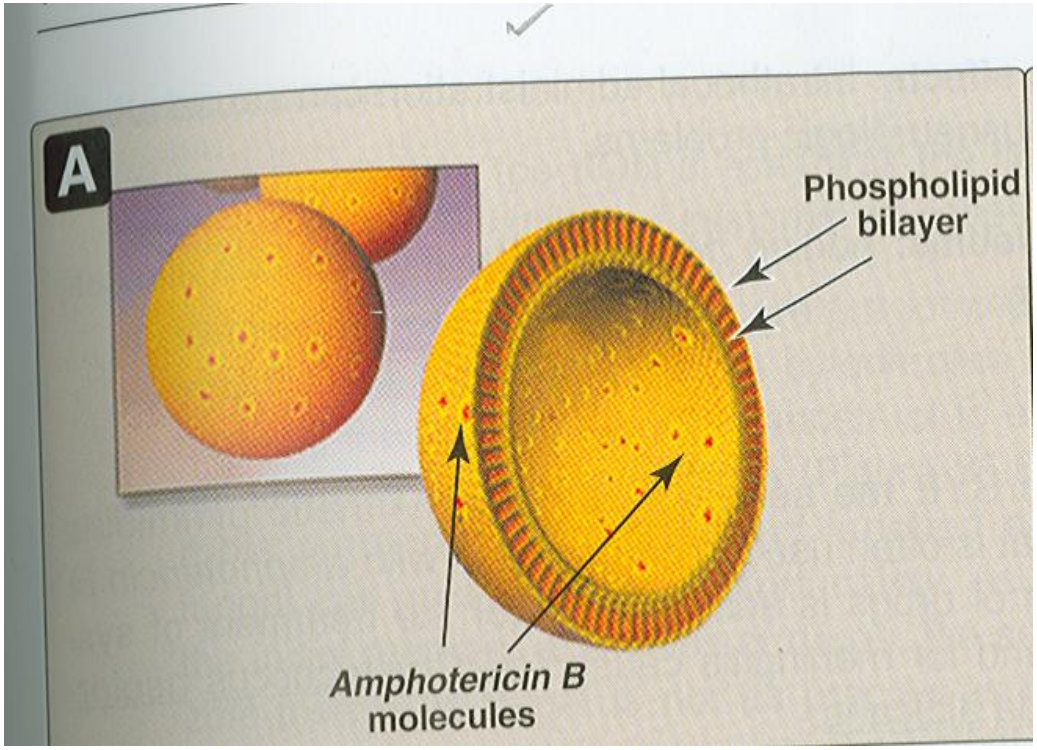
- Hypomagnesaemia

- 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 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**

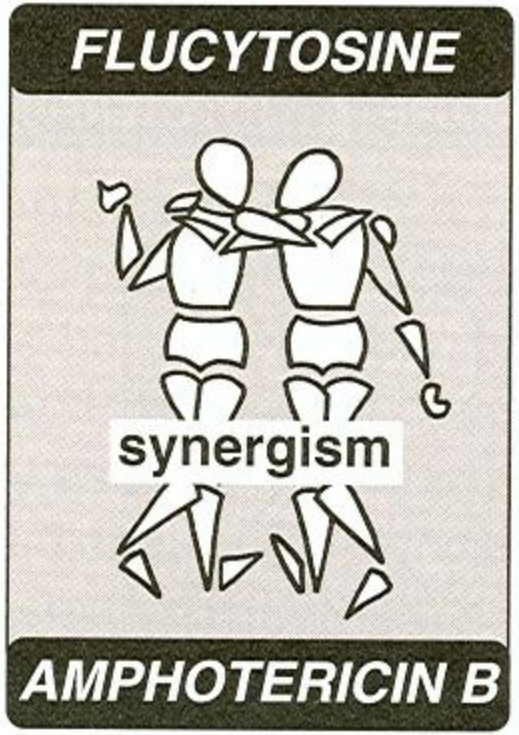
- Oral suspension of 100,000 U/ml 4 times a day and tablets 500,000 U of Nystatin are used to decrease GIT colonization with Candida
- For vaginal candidiasis in form of pessaries used for 2 weeks
- In cutaneous infection available in cream, ointment or powder forms and applied 2-3 times a day

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 flucytocin:**

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

Ketoconazole

- **The first orally active narrow spectrum azole available for the treatment of systemic mycoses**
- **Well absorbed orally as acidic environment favors its dissolution**
- **Only administered orally**
- **Bioavailability is decreased with H_2 receptor blocking drugs, proton pump inhibitors and antacids and is impaired with food**

- Ketokonazole is 84 % bound to plasma proteins
- It does not enter CSF
- Metabolized extensively in liver by cytochrome P450 (CYP3A4) and the inactive metabolites are excreted in bile
- Induction of microsomal enzymes by other drugs like rifampicin reduces its blood concentration

- Ketoconazole is active against many fungi, including Histoplasma, Blastomyces, Candida, and Coccidioides, but not aspergillus species
- Ketoconazole is available in oral tablet, aerosol , cream and shampoo dosage forms
- The shampoo and aerosols foams containing Ketoconazole are highly effective in treating seborrheic dermatitis

- Ketocoazole inhibits adrenal and gonadal steroidogenesis (cortisol, progesterone, estrogens, and testosterone). This leads to menstrual irregularities in females, loss of libido, impotency and gynaecomastia in males
- Ketoconazole could be used in the management of Cushing's syndrome and Ca of prostate

- **Ketoconazole side effects:**

- Dose dependant nausea, anorexia ,vomiting

- Liver toxicity (main toxicity) is rare but may prove fatal

- Hair loss

- As it inhibits steroid biosynthesis, several endocrinological abnormalities may be evident as menstrual abnormalities, gynecomastia, decreased libido and impotency

- Fluid retention and hypertension

- Ketokonazole is contraindicated in pregnancy

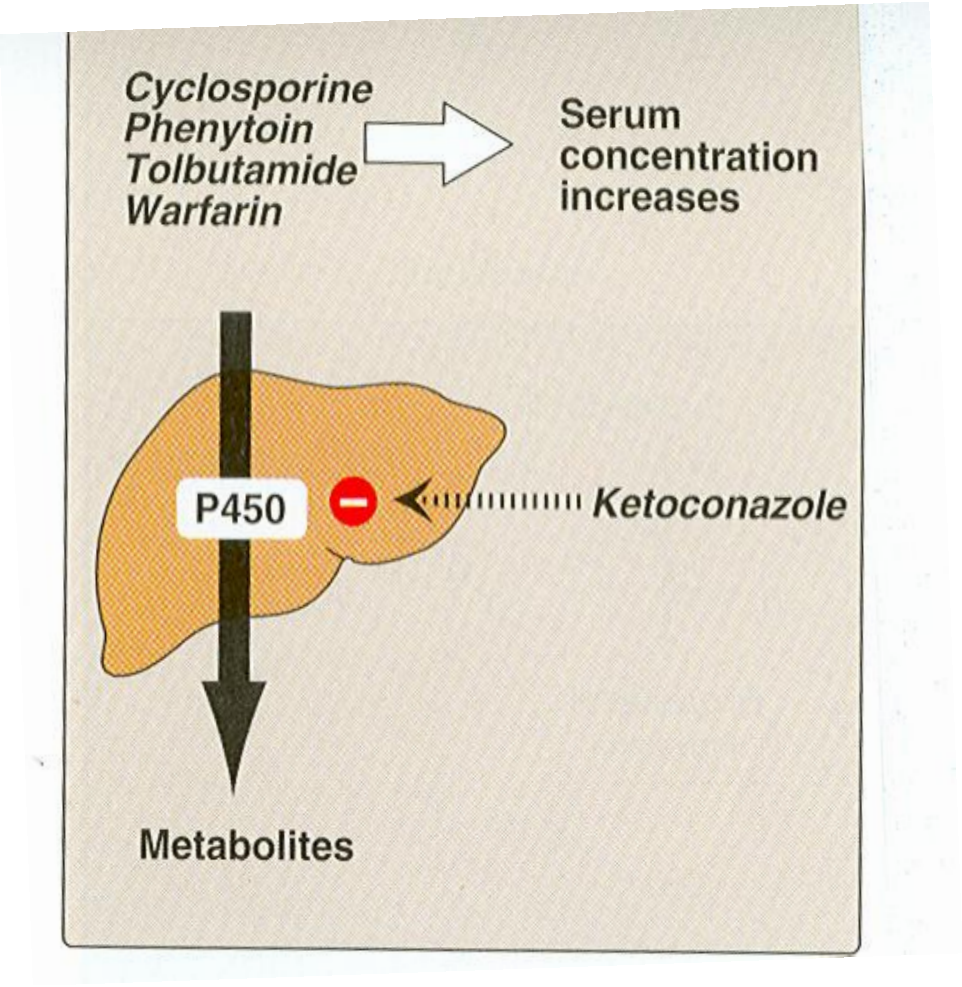
- **Ketoconazole drug-drug interactions:**

- Ketokonazole inhibit cytochrome P450 system, so it can potentiate the toxicities of drugs such as Cyclosporine, Phenytoin, Tolbutamide, and Warfarin, among others…

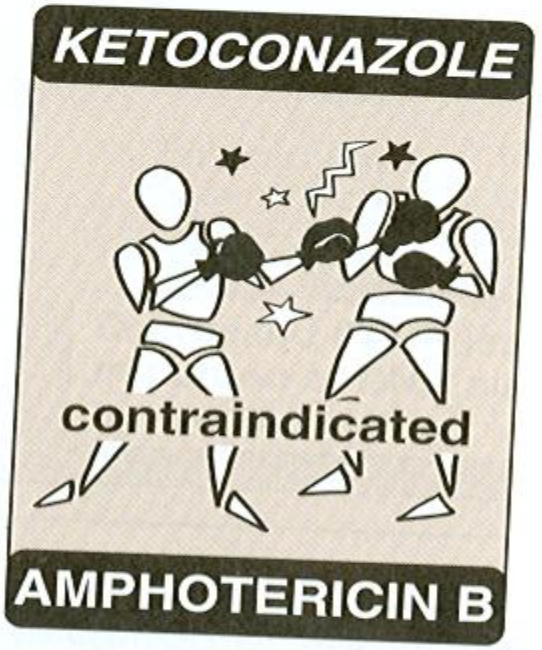
- Cyclosporin and phenytoin inhibit its metabolism and hence increase Ketokonazole toxicity

- Warfarin and Rifampin increase its metabolism and hence decrease concentration (shorten its DOA)

- H_2 blockers, Antacids, proton pump inhibitors and Sucralfate decrease its absorption


Cyclosporine
Phenytoin
Tolbutamide
Warfarin
Serum concentration increases
P450
Ketoconazole
Metabolites

- **Ketokonazole decreases ergosterol in the funagal membrane thus, it reduces the fungicidal action of Amphotericin B**



Triazoles

- **The triazoles (Fluconazole, Itraconazole, Voriconazole) are newer antifungal agents, and are less toxic and more effective**
- **They damage the fungal cell membrane by inhibiting enzyme demethylase**
- **They are selective**
- **Penetrate to CNS**
- **Resistant to degradation**
- **Cause less endocrine disturbances**

Fluconazole

- **Completely absorbed from GIT**
- **Excellent bioavailability by oral route including CSF**
- **Concentration in plasma is same by oral or IV route**
- **Bioavailability not altered by food or gastric acidity**
- **It has least effect on hepatic microsomal enzymes**
- **Drug interactions are less common**

- Fluconazole easily penetrates CSF and is a drug of choice in cryptococcal meningitis and coccido mycosis
- It can safely be administered prophylactically in patients receiving bone marrow transplants
- Resistance not a problem except in patients with HIV
- Renal excretion

- **Clinical uses to Fluconazole:**

- Candidiasis

- Cryptococcosis

- In AIDS

- Coccidial meningitis it is drug of choice

- It has also activity against histoplasmosis, blastomycosis, spirotrichosis and ring worm but Itraconazole is better in the same dose

- Not effective in aspergillosis

- **Side effects to Fluconazole:**

- Nausea, vomiting, headache, skin rash, abdominal pain, diarrhea, reversible alopecia

- No endocrine adverse effects

- Hepatic failure may lead to death

- It is highly teratogenic

Itraconazole

- **A new synthetic triazole**
- **It lacks endocrine side effects of ketoconazole**
- **It has broad spectrum activity**
- **Administered orally as well as IV**
- **Food increases its absorption**

- Itraconazole is extensively metabolized in liver by cytochrome P450 (CYP3A4)
- It is highly lipid soluble, it is well distributed to bone , sputum and adipose tissue
- Highly bound to plasma protein
- Does not penetrate CSF adequately , therefore its concentration is less to treat meningeal fungal infection

- Itraconazole steady state reaches in 4 days, so loading doses are recommended in deep mycosis
- Intravenously reserved only in serious infections

- **Side effects to Itraconazole:**

  Nausea, vomiting, hypertriglyceridemia, hypokalaemia, increased aminotransferase, hepatotoxicty and rash (leads to drug discontinuation)

Voriconazole

- A new drug available in oral and IV dosage forms
- It is similar to Itraconazole but more potent
- High biological availability when given orally
- Hepatic metabolism predominant
- Inhibition of P450 less
- Reversible visual disturbances

Posaconazole

- **Is a new oral, broad-spectrum antifungal agent similar to Itraconazole**
- **It was approved to prevent Candida and Aspergillus infections in severely immunocompromised patients and for the treatment of oropharyngeal candidiasis**
- **Due to its spectrum of activity, Posaconazole could possibly be used in the treatment of fungal infections caused by Mucor species and other zygomycetes**
- **Given orally and well tolerated**

- Like Ketokonazole, Posaconazole can cause an elevation of liver function tests and it inhibits cytochrome P450 system

- **Side effects to Posaconazole:**

The most common side effects observed were gastrointestinal symptoms (nausea, vomiting, diarrhea, and abdominal pain) and headaches

Caspofungin

- **It is Echinocandin class of antifungal drugs that interfere with the synthesis of fungal cell wall by inhibiting synthesis of D-glycan (by inhibiting D-glycan synthase)**
- **Especially useful for aspergillus and candida**
- **not active orally given IV**
- **Highly bound to serum proteins**

- Slowly metabolized by hydrolysis and N-acetylation
- Eliminated equally by urinary and fecal route
- Adverse effects include nausea , vomiting, flushing and liver dysfunction
- Very expensive

Antifugal Drugs for Cutaneous Mycotic Infections

- **Topical antifungal preparations**

- Topical Azole derivatives

- Nystatin and Amphotericin B

- Tolnaftate

- Terbinafine…etc

- **Oral anti fungal agents used for topical infections**

- Oral Azoles

- Griseofulvin

- Terbinafine

Topical Azoles

- **Miconazole, Clotrimazole, Butoconazole and Terconazole are topically active drugs that are only rarely administered parenterally because of their severe toxicity**
- **Their mechanism of action and antifungal spectrum are the same as those of Ketoconazole**

- Topical use of azoles is associated with contact dermatitis, vulvar irritation, and edema. Miconazole is a potent inhibitor of Warfarin metabolism and has produced bleeding in Warfarin-treated patients even when it is applied topically. No significant difference in clinical outcomes is associated with any azole or Nystatin in the treatment of vulvar candidiasis

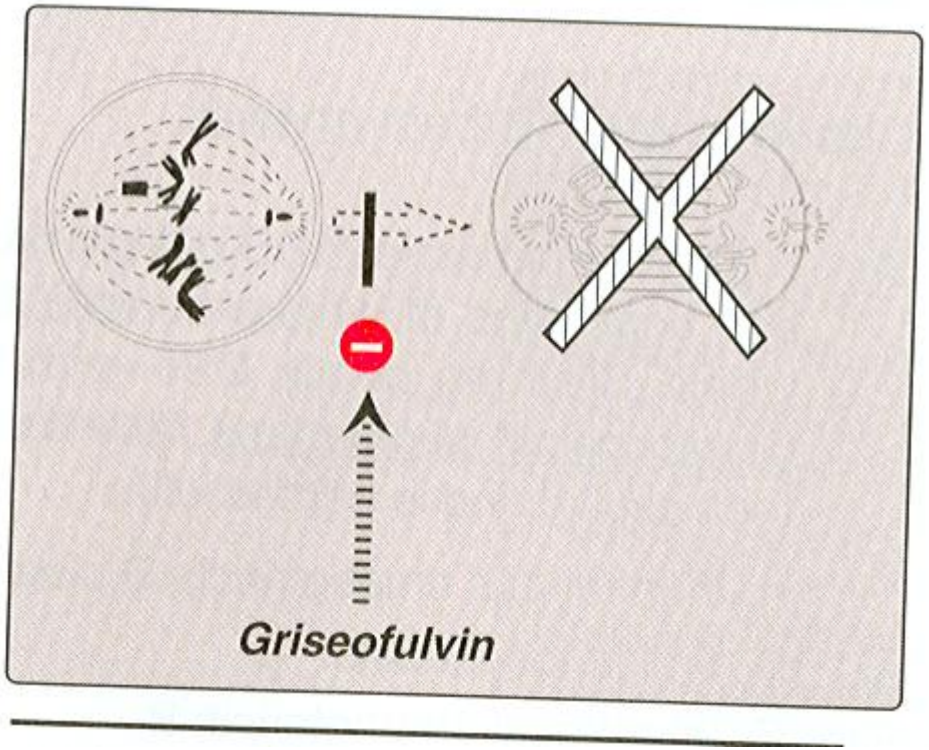
Tolnaftate

- **Effective in most cutaneous mycosis**
- **It is ineffective against Candida**
- **In tinea pedis cure rate is around 80%**
- **Exact mechanism of action is not entirely known, it is believed to inhibit the squalene epoxidase, an important enzyme in the biosynthetic pathway of ergosterol**
- **Available in as cream, gel, powder and topical solution**

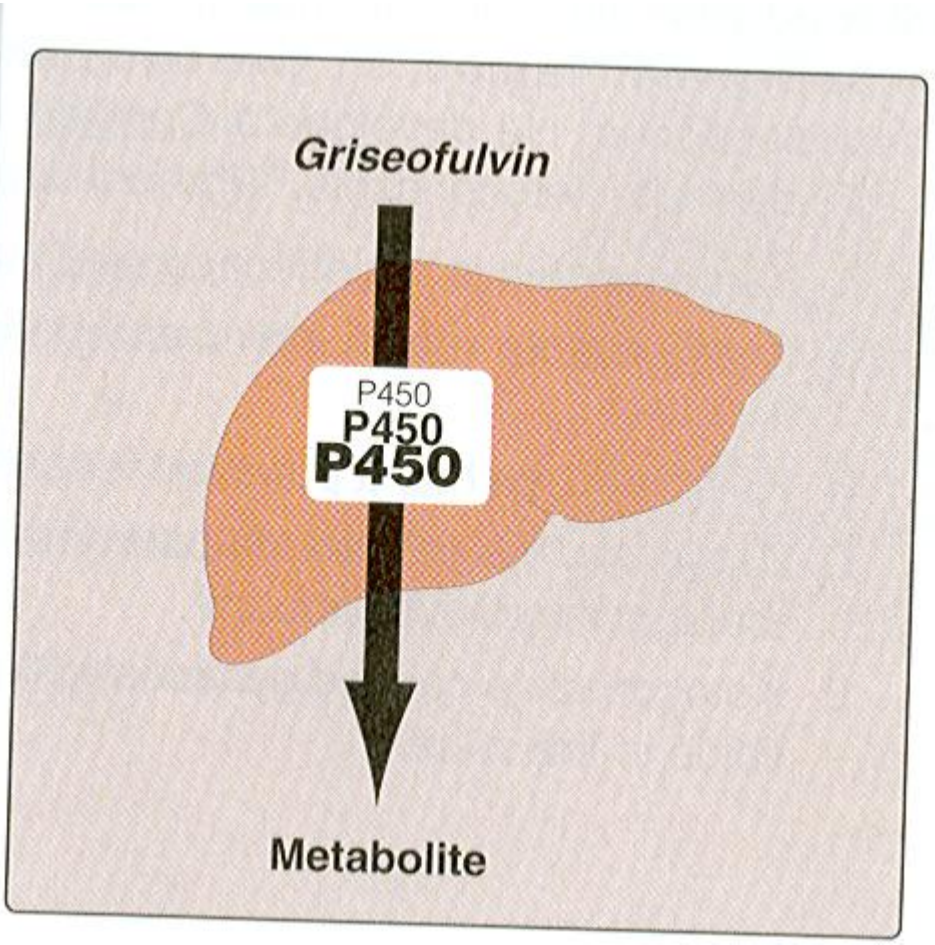
Griseofulvin

- **It has largely been replaced by terbinafine for treatment of dermatophytic infections of the nails because of toxicity**
- **Very insoluble in water**
- **It is useful for dermatophytes**
- **It is fungistatic for species of dermatophytes, it has narrow spectrum.**

It interacts with microtubules and interferes with mitosis


Griseofulvin

- Griseofulvin absorption increases with fatty meal
- Barbiturates decrease the absorption from GIT
- It is ineffective topically it has to be given orally for Rx of hair and nail dermatophyte infections
- The drug has to deposit first in keratin of growing skin, nail and hair to get rid of disease
- Extensively metabolized in liver and induces CYP450


Griseofulvin
P450
P450
P450
Metabolite

- **Clinical uses of Griseofulvin:**

- Mycotic diseases of skin, hair (particularly for scalp) and nail

- It is also highly effective in athlete's foot

- Treatment required is 1 month for scalp and hair ringworm, 6-9 months for finger nails, and at least 1 year for toe nails.

- Not effective in subcutaneous or deep mycoses.

- **Griseofulvin side effects:**

- Headache

- Peripheral neuritis , lethargy , mental confusion, impairment in performance of routine task

- Fatigue, vertigo ,syncope, blurred vision

Terbinafine

- **It is synthetic allylamine**
- **It is a drug of choice for treating dermatophytes**
- **As compared to Griseofulvin it is better tolerated and requires shorter duration of therapy**
- **It inhibits fungal sequalene epoxidase decreasing synthesis of ergosterol**
- **It is fungicidal but activity is limited to Candida albicans and dermatophytes**

- Effective for the treatment of onychomycosis (fungal infections of nails). 250 mg daily for 6weeks for finger nail infection and for 12 weeks in toe nail infection
- Well absorbed orally, bioavailability decreases due to first pass metabolism in liver
- Protein binding more than 99% in plasma
- The drug accumulates in skin, nails and fat
- Severely hepatotoxic (liver failure may lead to death)

- Initial half life of Terbinafine is 12 hrs but terminal half life extends to 200-400 hrs which reflects its slow release from the tissues
- Can be found in plasma for 4-8 weeks after prolong therapy
- Terbinafine accumulates in breast milk and, therefore, should not be given to nursing mothers
- Metabolites excreted in urine and its clearance is reduced in moderate and hepatic impairment
- Not recommended in azotemia or hepatic failure

- **Side effects to Terbinafine:**

- GIT disturbance

- Taste and visual disturbance

- Transient rise in serum liver enzymes

**** Rifampicin decreases and Cimetidine increases its blood concentrations**