ANTI-FUNGAL AGENTS

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AMPHOTERICIN B

Chemistry:

- Amphotericin B is one of a family of some 200 polyene macrolide antibiotics.
- Those studied to date share the characteristics of four to seven conjugated double bonds, an internal cyclic ester, poor aqueous solubility, substantial toxicity on parenteral administration, and a common mechanism of antifungal action.
- Amphotericin B is a heptaene macrolide containing seven conjugated double bonds in the trans position and 3-amino-3,6-dideoxymannose (mycosamine) connected to the main ring by a glycosidic bond.

Mechanism of Action:

- The antifungal activity of amphotericin B depends principally on its binding to a sterol moiety, primarily ergosterol that is present in the membrane of sensitive fungi.
- By virtue of their interaction with these sterols, polyenes appear to form pores or channels that increase the permeability of the membrane, allowing leakage of a variety of small molecules.

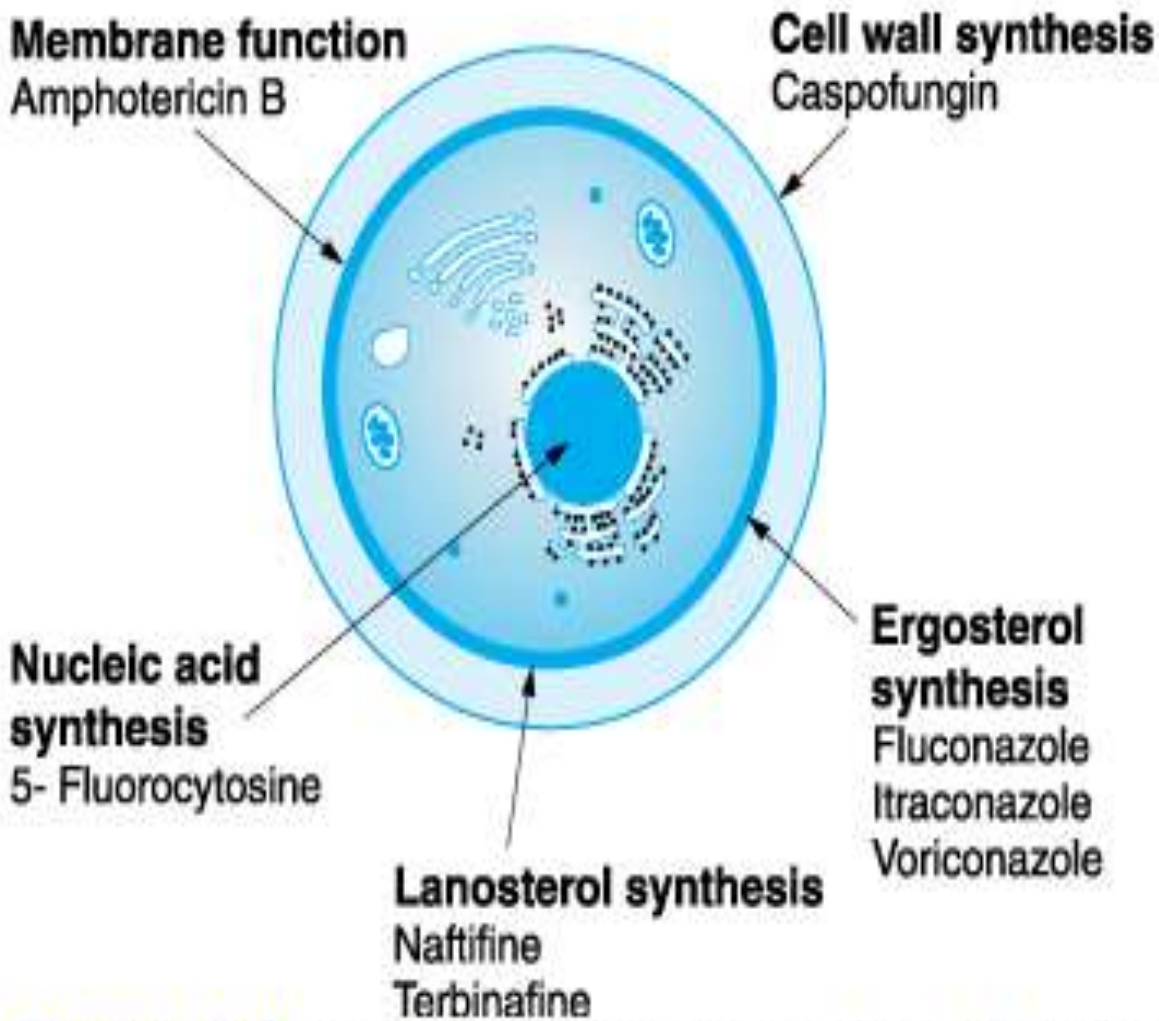


Figure 48-1. *Mechanism of action of amphotericin, imidazoles, triazoles, and allylamines in fungi.*

ANTIFUNGAL ACTIVITY:

- Amphotericin B has useful clinical activity against:
- *Candida* spp.,
- *Cryptococcus neoformans,*
- *Blastomyces dermatitidis*,
- *Histoplasma capsulatum,*
- *Sporothrix schenckii*,
- *Coccidioides immitis*,
- *Paracoccidioides braziliensis,*
- *Aspergillus* spp.,
- *Penicillium marneffei,*
- The agents of mucormycosis.
- Amphotericin B has limited activity against the protozoa Leishmania braziliensis and Naegleria fowleri. The drug has no antibacterial activity.

FUNGAL RESISTANCE:

- Some isolates of *Candida lusitaniae* have appeared to be relatively resistant to amphotericin B.
- *Aspergillus terreus* may be more resistant to amphotericin B than other *Aspergillus* species, although the host's immune response is the most significant factor in determining outcome in invasive aspergillosis.
- Mutants selected *in vitro* for nystatin or amphotericin B resistance replace ergosterol with certain precursor sterols.
- The rarity of significant amphotericin B resistance arising during therapy has left it unclear whether ergosterol-deficient mutants retain sufficient pathogenicity to survive in deep tissue.

PHARMACOKINETICS:

- Not absorbed orally
- Widely distributed in the body
- Terminal elimination half-life is 15 days
- About 60% AMB metabolized in liver
- Excretion occurs slowly both urine as well as bile

ADVERSE EFFECTS:

- Renal Toxicity
- Hypokalemia
- Anaemia
- Impaired hepatic function
- Thrombocytopenia
- Anaphylactic reaction
- Inj. Administration frequency in chilis, fever, tinnitus & headach and about Vomit in one in five patient.
- Local thrombophlebitis after i.v. inj.
- Neurotoxicity
- Skin rashes

USES:

- Candidiasis
- Otomycosis
- Mycoses
- Leishmaniasis

Drug Interaction:

- Flucytosine + AMB = Supraadditive action (incase of fungi sensitivity)

  =Increase the penetration of 5-FC into fungus
- Rifampicin + Minocycline + AMB = Potentiate action of AMB
- Aminoglycoside + Vancomycin + Cyclosporin + other nephrotoxic drugs = Enhance the renal impairment caused by AMB.

GRISEOFULVIN

- It was one of the early antibiotics extracted from *penicillium griseofulvum.*

Mechanism of Action:

- A prominent morphological manifestation of the action of griseofulvin is the production of multinucleate cells as the drug inhibits fungal mitosis.
- In mammalian cells treated with high concentrations, griseofulvin causes disruption of the mitotic spindle by interacting with polymerized microtubules.
- Although the effects of the drug are thus similar to those of colchicine and the vinca alkaloids, its binding sites on the microtubular protein are distinct.
- In addition to its binding to tubulin, griseofulvin also may bind to a microtubule-associated protein.

Antifungal Activity:

- Griseofulvin is fungistatic *in vitro* for various species of the dermatophytes *Microsporum*, *Epidermophyton*, and *Trichophyton*. The drug has no effect on bacteria or on other fungi.

Resistance:

- Although failure of ringworm lesions to improve is not rare, isolates from these patients usually are still susceptible to griseofulvin *in vitro*.

PHARMACOKINETICS:

- Absoption of griseofulvin from G.I.T is somewhat irregular because of its very low water solubility (given orally).
- Plasma concentration are reached in about 5 hrs.
- It is taken up selectively by newly formed skin & concentration in the keratin.
- The plasma half-life is 24 hrs. but it retained in the skin for much longer time.

ADVERSE EFFECTS:

- G.I. Upset
- Headache
- Photosensitivity
- Allergic reaction
- Peripheral neuritis
- Leukopenia
- Albuminuria

USES:

- Dermatophytosis
- It should be reserved for cases with nails, hair or large body surface involvement.
- It is effective in athletes foot but not in pityriasis versicolor.

INTERACTION:

- Griseofulvin + Warfarin = Increase warfarin metabolism
- Griseofulvin + oral contraceptives = Reduce efficacy of oral contraceptives
- Phenobarbitone + Griseofulvin = Induce metabolism (sometimes therapy failure)
- Griseofulvin + Alcohols = cause intolerance

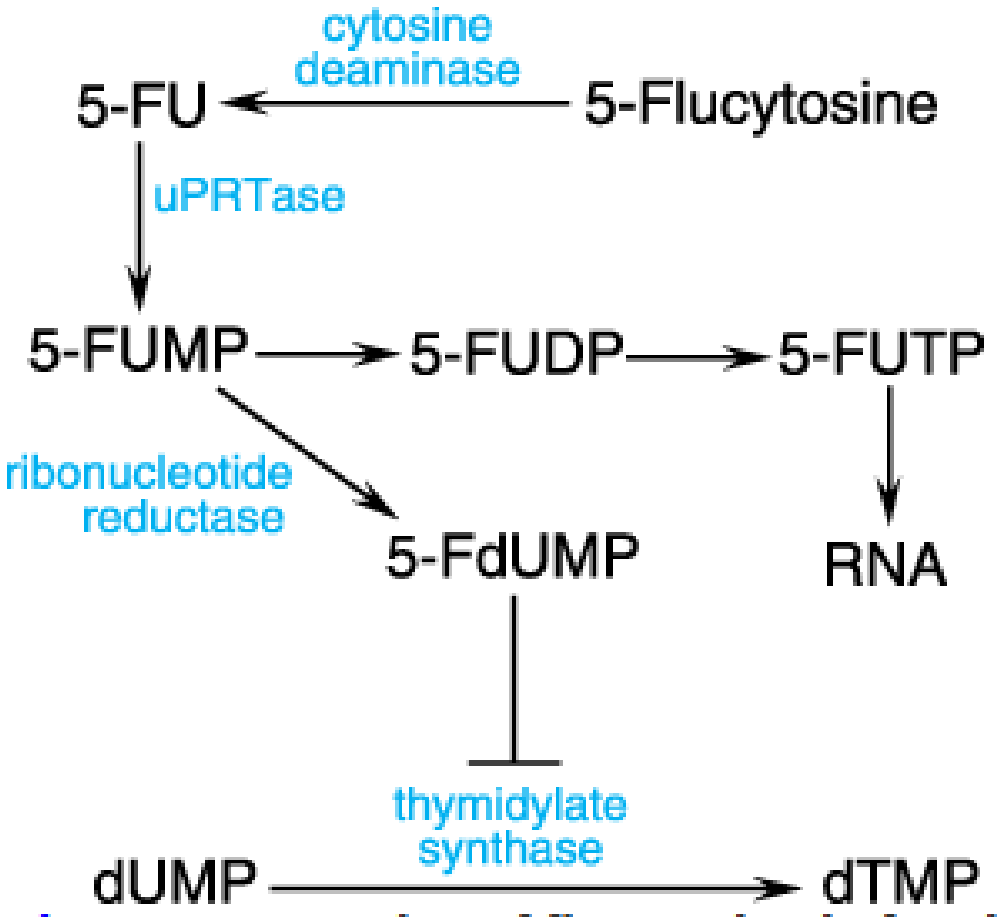
FLUCYTOSINE

Chemistry:

- *Flucytosine* is a fluorinated pyrimidine related to *fluorouracil* and *floxuridine*. It is 5-fluorocytosine.

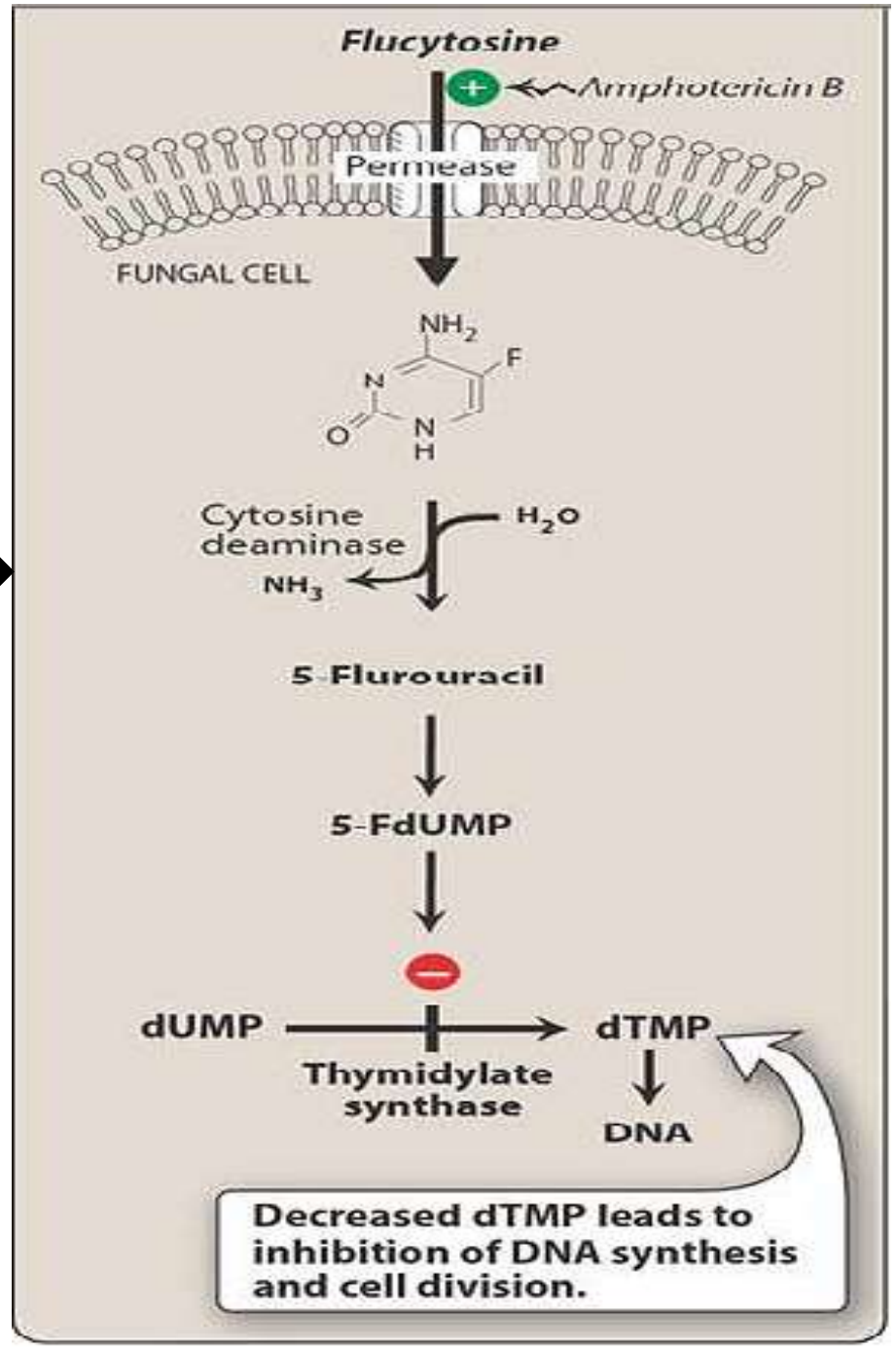
Mechanism of Action:

- All susceptible fungi are capable of deaminating flucytosine to 5-fluorouracil, a potent antimetabolite that is used in cancer chemotherapy.
- Fluorouracil is metabolized first to 5-fluorouracil-ribose monophosphate (5-FUMP) by the enzyme uracil phosphoribosyl transferase (UPRTase, also called uridine monophosphate pyrophosphorylase).
- As in mammalian cells, 5-FUMP then is either incorporated into RNA (*via* synthesis of 5-fluorouridine triphosphate) or metabolized to 5-fluoro-2'-deoxyuridine-5'-monophosphate (5-FdUMP), a potent inhibitor of thymidylate synthetase.
- DNA synthesis is impaired as the ultimate result of this latter reaction. The selective action of flucytosine is due to the lack or low levels of cytosine deaminase in mammalian cells, which prevents metabolism to fluorouracil.



- 5-Flucytosine is transported by cytosine permease 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-fluorouridine triphosphate (5-FUTP) and incorporated into RNA or converted by ribonucleotide reductase to 5-fluoro-2'-deoxyuridine-5'-monophosphate (5-FdUMP), which is a potent inhibitor of thymidylate synthase.
- 5-FUDP, 5-fluorouridine-5'-diphosphate;
- dUMP, deoxyuridine-5'-monophosphate;
- dTMP, deoxyuridine-5'-monophosphate.

MECHANISM OF ACTION



ANTIFUNGAL ACTIVITY:

- Flucytosine has clinically useful activity against *Cryptococcus neoformans*, *Candida* spp., and the agents of chromoblastomycosis.
- Within these species, determination of susceptibility *in vitro* has been extremely dependent on the method employed, and susceptibility testing performed on isolates obtained prior to treatment has not correlated with clinical outcome.

FUNGAL RESISTANCE:

- Drug resistance arising during therapy (secondary resistance) is an important cause of therapeutic failure when flucytosine is used alone for cryptococcosis and candidiasis.
- In chromoblastomycosis, resurgence of lesions after an initial response has led to the presumption of secondary drug resistance.
- In isolates of *Cryptococcus* and *Candida* species, secondary drug resistance has been accompanied by a change in the minimal inhibitory concentration from less than 2.5 mg/ml to more than 360 mg/ml.
- The mechanism for this resistance can be loss of the permease necessary for cytosine transport or decreased activity of either UPRTase or cytosine deaminase.

- In *Candida albicans*, substitution of thymine for cytosine at nucleotide 301 in the gene encoding UPRTase (*FUR1*) causes a cysteine to become an arginine, modestly increasing flucytosine resistance.
- Flucytosine resistance is further increased if both *FUR1* alleles in the diploid fungus are mutated.
- This specific mutation has been found only in a group of genetically related isolates called "Clade 1," and its clinical significance is unknown.

PHARMACOKINETICS:

- It usually given by i.v. but also be given orally
- Widely distributed through body fluids including CSF
- 90% drug excreated unchanged via kidney
- Plasma half-life is 3-5 hrs.
- The dosage should be lessen in case of renal impaired

ADVERSE EFFECTS	THERAPEUTIC USES
G.I. Disturbances	Chromoblastomycosis
Anaemia	Cryptococcosis with AMB
Neutropenia	
Thrombocytopenia	
Alopcia	
Hepatitis	

IMIDAZOLES AND TRIAZOLES

- The azole antifungals include two broad classes, imidazoles and triazoles, which share the same antifungal spectrum and mechanism of action.
- The systemic triazoles are metabolized more slowly and have less effect on human sterol synthesis than do the imidazoles.
- Because of these advantages, new congeners under development are mostly triazoles. Of the drugs now on the market in the United States, *clotrimazole*, *miconazole*, *ketoconazole*, *econazole*, *butoconazole*, *oxiconazole*, *sertaconazole*, and *sulconazole* are imidazoles; *terconazole*, *itraconazole*, fluconazole , *voriconazole*, and *posaconazole* (an experimental drug) are triazoles.
- The topical use of azole antifungals is described in the second section of this chapter. The structure of a triazole is as follows:

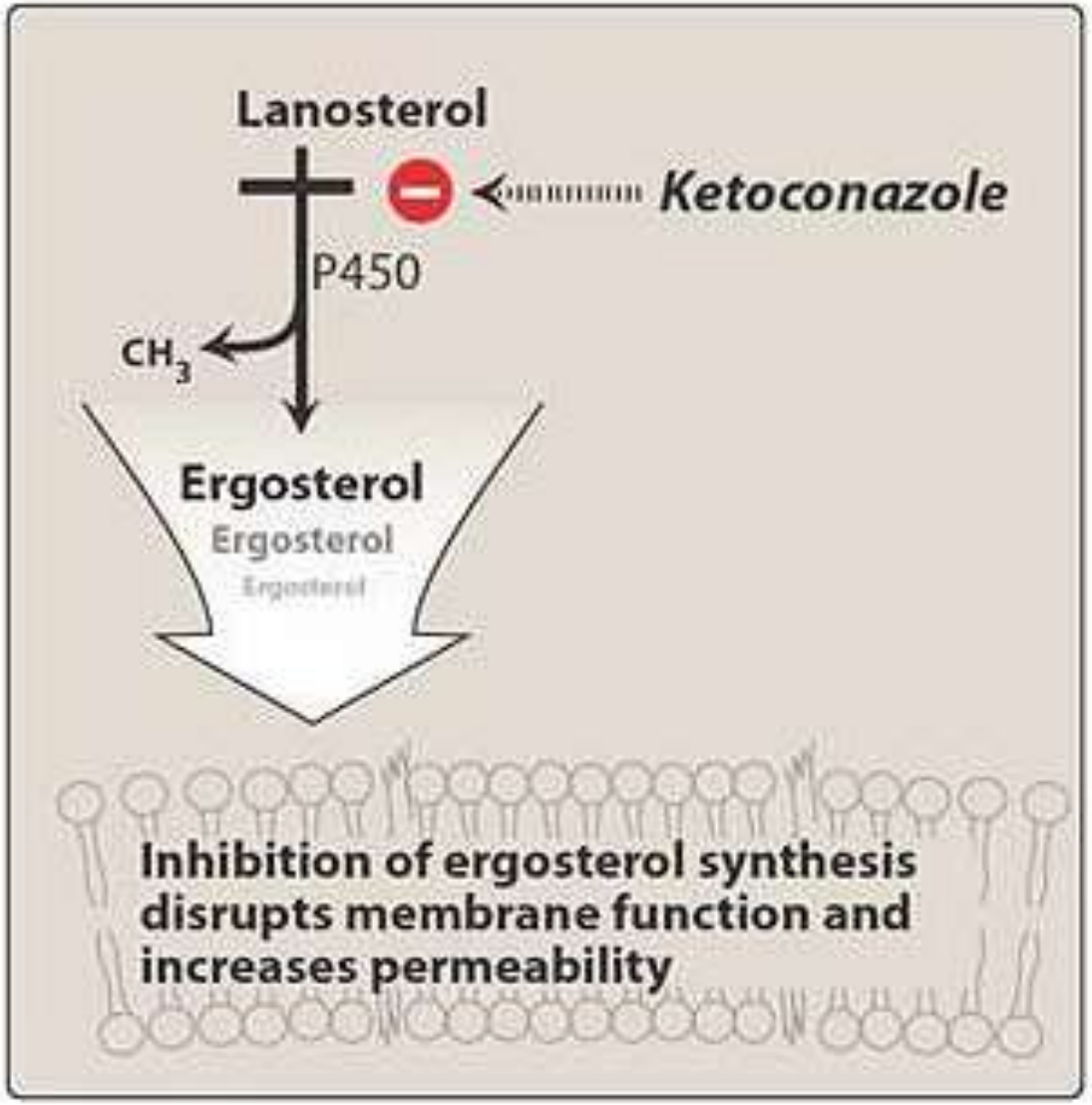
KETOCONAZOLE

- Ketoconazole was the first orally active azole available for the treatment of systemic mycoses.

Mechanism of Action:

- At concentrations achieved following systemic administration, the major effect of imidazoles and triazoles on fungi is inhibition of 14-a-sterol demethylase, a microsomal cytochrome P450 (CYP) enzyme.
- Imidazoles and triazoles thus impair the biosynthesis of ergosterol for the cytoplasmic membrane and lead to the accumulation of 14-a-methylsterols.
- These methylsterols may disrupt the close packing of acyl chains of phospholipids, impairing the functions of certain membrane-bound enzyme systems such as ATPase and enzymes of the electron transport system and thus inhibiting growth of the fungi.

- Some azoles (*e.g.*, clotrimazole) directly increase permeability of the fungal cytoplasmic membrane, but the concentrations required are likely only obtained with topical use.
- Azole resistance has emerged gradually during prolonged azole therapy, causing clinical failure in patients with far-advanced HIV infection and oropharyngeal or esophageal candidiasis.
- The primary mechanism of resistance in *C. albicans* is accumulation of mutations in *ERG11*, the gene coding for the 14-a-sterol demethylase.
- These mutations protect heme in the enzyme pocket from binding to the azole, but allow access of the natural substrate for the enzyme, lanosterol.
- Cross resistance is conferred to all azoles.
- Increased azole efflux by both ATP-binding cassette (ABC) and major facilitator superfamily transporters can add to fluconazole resistance in *C. albicans* and *C. glabrata*. Increased production of 14-a-sterol demethylase is another potential cause of resistance.
- Mutation of the C5,6 sterol reductase gene *ERG3* also can increase azole resistance in some species.



Mechanism of Ketoconazole

ANTIFUNGAL SPECTRUM:

- Ketoconazole is active against many fungi, including *Histoplasma*, *Blastomyces*, *Candida*, and *Coccidioides*, but not *aspergillus* species.
- Although itraconazole has largely replaced ketoconazole in the treatment of most mycoses because of its broader spectrum, greater potency, and fewer adverse effects, ketoconazole, as a second-line drug, is a less expensive alternative for the treatment of mucocutaneous candidiasis.
- Strains of several fungal species that are resistant to ketoconazole have been identified.

RESISTANCE:

- This is becoming a significant clinical problem, particularly in the protracted therapy required for those with advanced HIV infection.
- Identified mechanisms of resistance include mutations in the C-14 Î±-demethylase gene, which cause decreased azole binding.
- Additionally, some strains of fungi have developed the ability to pump the azole out of the cell.

PHARMACOKINETICS:

- Ketoconazole is only administered orally.
- It requires gastric acid for dissolution and is absorbed through the gastric mucosa. Drugs that raise gastric pH, such as antacids, or that interfere with gastric acid secretion, such as H_2-histamine receptor blockers and proton-pump inhibitors, impair absorption.
- Administering acidifying agents, such as cola drinks, before taking the drug can improve absorption in patients with achlorhydria.
- Ketoconazole is extensively bound to plasma proteins.
- Although penetration into tissues is limited, it is effective in the treatment of histoplasmosis in lung, bone, skin, and soft tissues.
- The drug does not enter the CSF.
- Extensive metabolism occurs in the liver, and excretion is primarily through the bile.
- Levels of parent drug in the urine are too low to be effective against mycotic infections of the urinary tract.

ADVERSE EFFECTS:

- Nausea
- Vomiting
- Loss of appetite
- Headache
- Paresthesia
- Rashes
- Hair loss
- Decrease androgen production
- Menstrual irregularities
- Hepatotoxicity

THERAPEUTIC USES:

- Dermatophytosis
- Monilial Vaginitis
- Systemic mycosis
- Leishmaniasis
- Kalaazar
- Cushing's Syndrome

INTERACTIONS:

- H_2 blockers/ proton pump inhibitors/antacids + Ketoconazole = Decrease the oral absorption (by lowering gastric acidity).
- Rifampicin/Phenobarbitone/Carbamazepine/Phenytoin + Ketoconazole = Induces metabolism of ketoconazole and reduce its efficacy.
- Ketoconazole inhibit CYP_{450} as a results of enhance the levels of drugs.
- Terfenadine/Astemizole + Ketoconazole = Polymorphic Ventricular Tachycardia.