ANTIFUNGAL DRUGS

These are drugs used for superficial and deep (systemic) fungal infections. A disquietening trend after 1950s is the rising prevalence of more sinister type of fungal infections which are, to a large extent, iatrogenic. These are associated with the use of broad-spectrum antibiotics, corticosteroids, anticancer immunosuppressant drugs, dentures, indwelling catheters and implants, and emergence of AIDS.

Many topical antifungals have been available since the antiseptic era. Two important antibiotics: amphotericin B-to deal with systemic mycosis, and griseofulvin-to supplement attack on dermatophytes were introduced around 1960.

CLASSIFICATION

1. Antibiotics

A. Polyenes:AmphotericinB (AMB),Nystatin, Hamycin, Natamycin (Pimaricin)

B. Heterocyclic benzofuran: Griseofulvin

2. Antimetabolite Flucytosine (5-FC)

3 Azofes

A. lmidazoles (topical): Clotrimazole,Econazole, Miconazole, Oxiconazole (systemic): Ketoconazole

B. Triazoles (systemic): Fluconazole, Itraconazole, Voriconazole

4. Allylamine Terbinafine

5. Other topical agents Tolnaftate, Undecylenic acid, Benzoic acid, Quiniodochlor, Ciclopirox olamine, Butenafine, Sod. thiosulfate.

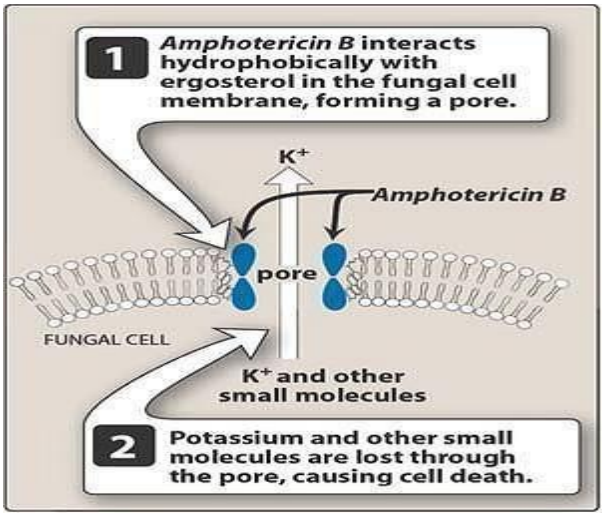
POLYENE ANTIBIOTICS

The name polyene is derived from their highly double-bonded structure. Amphotericin Bis described as the prototype.

Amphotericin B (AMB)

It is obtained from Streptomyces nodosus. Chemistry and mechanism of action The polyenes possess a macrocyclic ring, one side of which has several conjugated double bonds and is highly

lipophilic, while the other side is hydrophilic with many OH groups. Several *amphotericin B* molecules bind to ergosterol in the plasma membranes ofsensitive fungal cells. There, they form pores (channels) that require hydrophobic interactions between the lipophilic segment of the polyene antibiotic and the sterol. The pores disrupt membrane function, allowing electrolytes (particularly potassium) and small molecules to leak from the cell, resulting in cell death.



HETEROCYCLIC BENZOFURAN

Griseofulvin

It was one of the early antibiotics extracted from Penicillium griseofulvum. However, because of lack of antibacterial activity, little attention was paid to it: clinical utility in dermatophytosis was demonstrated only around 1960. Griseofulvin is active against most dermatophytes, including Epidermophyton, Trichophyton, Microsporum.

Griseofulvin interferes with mitosis-multinucleated and stunted fungal hyphae result from its action. It also causes abnormal metaphase configurations. However, unlike the typical mitotic inhibitors (colchicine, vinca alkaloids), it does not cause metaphase arrest; rather the daughter nuclei fail to move apart or move only a short distance.

Flucytosine

Flucytosine [floo-SYE-toe-seen] (*5-FC*) is a synthetic pyrimidine antimetabolite that is often used in combinationwith *amphotericin B.* This combination of drugs is administered for the treatment of systemic mycoses and for meningitis caused by Cryptococcus neoformans and Candida albicans.

Mechanism of action: *5-FC* enters fungal cells via a cytosine-specific permease an enzyme not found in mammalian cells. *5-FC* is then converted by a series of steps to 5 fluorodeoxyuridine 5'-monophosphate. This false *nucleotide inhibits thymidylate synthase*, thus depriving the organism of thymidylic acid an essential DNA component.

Pharmacokinetics: *5-FC* is well absorbed by the oral route. It distributes throughout the body water and penetrates well into the CSF. *5-FU* is detectable in patients and is probably the result of metabolism of *5-FC* by intestinal bacteria. Excretion of both the parent drug and its metabolites is by glomerular filtration, and the dose must be adjusted in patients with compromised renal function.

Adverse effects: *5-FC* causes reversible neutropenia, thrombo-cytopenia, and dose-related bone marrow depression.

Ketoconazole

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

Mechanism of action: Azoles are predominantly fungistatic. They inhibit C-14 ±-demethylase (a cytochrome P450 enzyme), thus blocking the demethylation of lanosterol to ergosterol the principal sterol of fungal membranes *This inhibition disrupts membrane structure and functionand, thereby, inhibits fungal cell growth.*

For example, in addition to blocking fungal ergosterol synthesis, the drug also inhibits human gonadal and adrenal steroid synthesis, leading to decreased testosterone and cortisol production.

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 H2-histamine receptor blockers and proton-pump inhibitors, impair absorption.

Adverse effects: In addition to allergies, dose-dependent gastrointestinal disturbances, including

nausea, anorexia, and vomiting, are the most common adverse effects of *ketoconazole* treatment.

Endocrine effects, such as gynecomastia, decreased libido, impotence, and menstrual irregularities, result from the blocking of androgen and adrenal steroid synthesis by *ketoconazole*