ANTI FUNGAL DRUGS

INTRODUCTION

- **Fungal infections are common throughout much of the natural world.**
- **In humans, fungal infections occur when an invading fungus takes over an area of the body and is too much for the immune system to handle.**
- **Fungi can live in the air, soil, water, and plants. There are also some fungi that live naturally in the human body.**
- **Drugs used in the treatment of fungal infections are called as Anti fungal drugs.**
- **The symptoms of a fungal infection will depend on the type, but common symptoms include the following:**

  - **Redness in the groin, buttocks, or thighs.**
  - **Chafing, irritation, itching, or burning in the infected area.**
  - **A red rash with a circular shape and raised edges.**
  - **Cracking, flaking, or dry peeling of the skin in the infected area.**

Antifungal Drugs- Classification

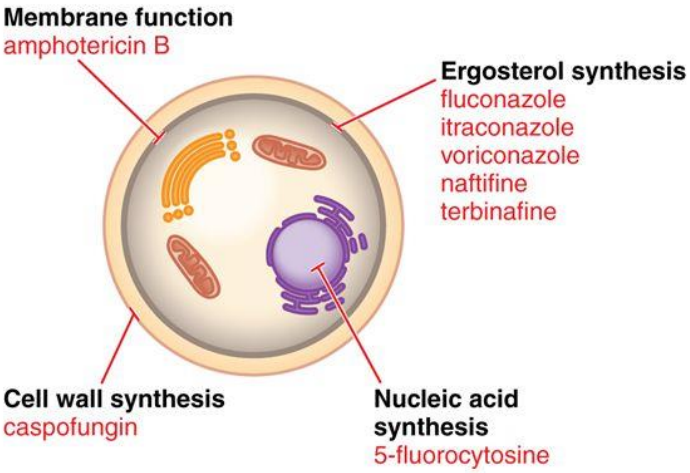
- ***Antibiotics***
  - *Polyenes: AmphotericinB (AMB),Nystatin,Hamycin*
  - *Echinocandins: Caspofungin, Micafungin, Anidulafungin*
  - *Heterocyclic benzofuran: Griseofulvin*
- ***Antimetabolite:*** *Flucytosine (5-FC)*
- ***Azoles***
  - *Imidazoles*
    - topical: Clotrimazole, Econazole, Miconazole, Oxiconazole
    - systemic: Ketoconazole
  - *Triazoles (systemic): Fluconazole, Itraconazole, Voriconazole, Posaconazole*
- ***Allylamine:*** *Terbinafine*
- ***Other topical agents:*** *Tolnaftate, Undecylenic acid, Benzoic acid, Quiniodochlor, Ciclopirox olamine, Butenafine, Sod. thiosulfate.*

ANTIFUNGAL AGENTS

Mechanism of action of Antifungal agents

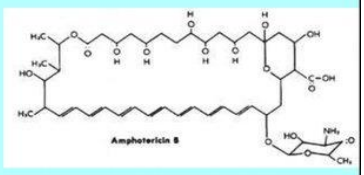
- **Disrupt fungal cell membrane**
  - Polyenes – amphotericin, Nystatin
  - Azoles
    - Imidazole – Ketoconazole, Miconazole, Clotrimazole
    - Triazole – Fluconazole, Itraconazole
  - Allylamines - Terbinafin
  - Echinocandins - Capsofungin
- **Inhibit mitosis** - Gresiofulvin
- **Inhibit DNA synthesis** - Flucytosine
- **Miscellaneous**
  - Tolnaftate
  - Cyclopirox

Sites of Antifungal Activity



Amphotericin B – an antifungal drug, polyene highly toxic antibiotic, produced by *Streptomyces nodosum*.

It is the drug of choice used in the treatment of the **systemic mycoses**.



Adverse effects:

- **Renal Toxicity** - the most serious side effect.
  Some degree of reduction of renal function occurs in > 80% of patients receiving the drug.
- **Hypokalemia** (25%) may require *KCl* supplementation.
- **Hypomagnesaemia**
- **Anaemia, Thrombocytopenia**
- **Impaired hepatic function**
- **Phlebitis** at the site of injection
- **Profound generalized malaise**
- **Anaphylactic reactions**.

Azoles antifungal agents

Ketoconazle :

- **the first oral azoles introduced into clinical use (systemically or topically).**
- **less selective for fungal P450**
- **clinical use has been limited by endocrine side effects, liver toxicity and the drug interactions.**
- **itraconazole or fluconazole has replaced ketoconazle for patients who can afford the more expensive, newer product.**

Itraconazole:

- **antifungal spectrum: broader than kotoconazole**
- **side effects (interact with hepatic microsomal enzymes): less than kotoconazole.**

Antifungal Drugs- Polyene antibiotics

Adverse Effects

- Acute reaction:
  - Acute reaction: Chills, fever, aches, pain all over, nausea, vomiting and dyspnea lasting for 2-5 hours (due to release of cytokines IL, TNF-α)
  - Intensity of reaction decreases with continued medication
  - Injection of hydrocortisone 0.6 mg/kg with the infusion may reduce the intensity of reaction.
  - Thrombophlebitis of the injection vein can occur.
- Long-term reaction:
  - Nephrotoxicity is the most common (it occurs fairly uniformly and is dose-related)
  - manifestations are--azotemia, reduced, g.f.r., acidosis, hypokalemia and inability to concentrate urine. It reverses slowly and often incompletely after stopping of therapy.
  - Anaemia: Most patients develop slowly progressing anaemia which is due to bone marrow depression. It is largely reversible.
  - CNS toxicity: occurs only on intrathecal injection-headache, vomiting, nerve palsies, etc.

Caspofungin acetate

- Semisynthetic antifungal
- MOA: Inhibits B (1,3) D glucan an essential component of fungal cell wall
- Uses: Treatment of invasive aspergillosis & candidiasis (esophageal, intraperitoneal)
- Dose: IV 70 mg slowly then 50 mg daily infusion
- Adverse events:
  - Flushing rashes , nausea, vomiting, phlebitis

Antimetabolite – Flucytosine (5-FC)

- It is a pyrimidine antimetabolite (inactive as such)
- After fungal uptake, it is converted into 5-fluorouracil and then to 5-fluorodeoxyuridylic acid which is an inhibitor of thymidylate synthesis.
- 5-FC is narrow spectrum fungistatic.
- **ADR:** Toxicity of 5-FC is lower than that of AMB. Dose dependent bone marrow depression. Liver dysfunction is mild and reversible.
- Therapy with 5-FC is generally limited to first 2 weeks of AMB regimen to avoid its bone marrow toxicity.