



Antifungal agents

- Most of the fungal infections are **opportunistic**
 - common in DM, cancer, AIDS, pregnancy and inpatients on immunosuppressive therapy (prolonged course of corticosteroids, broad-spectrum antibiotics, anticancer drugs; etc.)
- Treatment of various fungal infections depends on:

- **Patient factors** - Occurs in poorly vascularised tissues – skin, hairs, nails; etc.
- **Drug factors** – Most of the antifungal agents are poorly water soluble.
- **Organism factors** – Fungal organisms multiply very slowly.

Hence, required prolonged therapy.

Fungal Infections – Causative organisms

Superficial mycosis (confined to the skin)

- Dermatophytes
 - Epidermophyton
 - Trichophyton
 - Microsporum
- Candida

Fungal Infections – Causative organisms

- **Deep Mycosis** (involves the lungs, abdominal viscera, bones and or CNS)
 - Aspergillus
 - Blastomyces
 - Cryptococcus
 - Coccidioides
 - Candida
 - Histoplasma
 - Mucormycosis
 - Sporotrichosis

Classification

- **Antifungal antibiotics:** Amphotericin B, Nystatin, Hamycin, Griseofulvin
- **Antimetabolites:** Flucytosine
- **Azoles:** Imidazoles – Ketoconazole, Miconazole, Clotrimazole
Triazoles – Fluconazole, Itraconazole
- **Allylamine:** Terbinafine
- **Echinocandins:** Caspofungin acetate
- **Other topical agents:** Whitfield's ointment, Tolnaftate, Sodium thiosulphate and Selenium sulphide

Polyene antibiotics - Amphotericin B, Nystatin, Hamycin

Amphotericin B

- Amphotericin B (AMB) is a broad spectrum antifungal antibiotic.
- Effective against *Cryptococcus*, *Coccidioides*, *Candida*, *Aspergillus*, *Blastomyces*, *Histoplasma*; *etc.*
- Pharmacokinetics –
 - **Poor absorption** from the gut (**not suitable orally** for systemic infections).
 - Highly bound to plasma proteins and sterols in tissues.
 - Wide distribution, **does not cross BBB.**
 - Metabolized in liver, excreted in urine and bile.

Mechanism

- Fungal cell membrane contains a sterol which resembles cholesterol and is called as **Ergosterol**.
- **Amphotericin B, Nystatin, Hamycin** binds tightly to ergosterol in fungal cell membrane, form pores and channels in the membrane, permeability increases, leakage of the intracellular contents of the fungi.
- Death of the fungi - **FUNGICIDAL**

Formulations

- AMB is poorly water soluble, hence i.v and intrathecal preparations are made with deoxycholate – AMB colloidal deoxycholate complex.

Lipid based formulations of AMB -

- ABCD (AMB Colloidal Dispersion)
- ABLC (AMB Lipid Complex)
- Liposomal AMB

Developed mainly to reduce toxicity, improve tolerability, produce site specific delivery of the drug.

Adverse effects

- Toxic reactions - fever, chills, headache, dyspnoea, phlebitis at the site of injection.
- GI disturbances, anaemia, electrolyte disturbances, etc.
- Nephrotoxicity
- Hepatotoxicity (occasionally)
- Headache and convulsions on intrathecal administration.

Uses

- AMB is highly efficacious, but highly toxic too.
Fluconazole and Itraconazole have replaced AMB in the treatment of fungal diseases.
- Deep mycoses: Mucormycosis, aspergillosis, cryptococcosis and sporotrichosis.
- Deep mycoses in immunocompromised individuals.
- Intrathecally for cryptococcal and coccidioides meningitis.
- Topical AMB for cutaneous candidiasis.
- Lipid based formulations are expensive and less efficacious, hence reserved for patients when they are not tolerating AMB-DOC.

Nystatin

- Poor absorption from skin and mucous membrane.
- Highly toxic for systemic use. Used topically in Candida infections
- Available in ointment, cream, powder, tablet and in combination with corticosteroids / anti-bacterial agents.

Uses:

- Topically for oral, oropharyngeal, corneal, conjunctival and cutaneous candidiasis.
- As oral tablets for intestinal candidiasis and superinfection due to *Candida*.
- Vaginal candidiasis – as vaginal suppositories.

Adverse Effects:

GI disturbances – oral nystatin tablets

Griseofulvin

- Used orally for **dermatophytic** infections.

Mechanism:

Interacts with polymerized microtubules, disrupts the mitotic spindle and acts as a spindle poison. Inhibits fungal mitosis (**FUNGISTATIC**)

- Administered orally. **Bioavailability increased by taking with fatty food and also by using ultrafine preparation.**
- It gets concentrated in keratinized tissues, such as skin, hair, nails; etc. It is an enzyme inducer, thus reduces the effectiveness of warfarin and oral contraceptives.
- It has **disulfiram like reaction**, hence can cause intolerance to alcohol (accumulation of toxic metabolite - Acetaldehyde)

Uses

- Dermatophytic infections.
- Onychomycosis of finger and toe nails.

Adverse effects:

- Headache, peripheral neuritis, confusion, fatigue, vertigo, blurred vision, GI effects such as nausea and vomiting.
- Leukopenia and hepatotoxicity (rare)

Flucytosine

- It is a pro-drug
- Taken up by susceptible fungal cells and converted into 5-fluorouracil (5-FU) that interferes with fungal DNA synthesis by inhibiting thymidylate synthase enzyme, thus producing **FUNGISTATIC** effect.
- Narrow spectrum of activity (*Cryptococcus*, *Chromoblastomyces*, *Candida sp.*)

Uses:

Flucytosine+AMB – Cryptococcal meningitis

Reason for the combination –

- Entry of Flucytosine into the fungal cells is facilitated because of the increased permeability of the membrane due to the action of AMB.
- Reduced toxicity of AMB because of the reduction in the drug dosage.
- Reduced duration of therapy and less chance for emergence of resistance.

Adverse effects:

Bone marrow suppression with anaemia, neutropenia, thrombocytopenia.

Other side effects include nausea, vomiting, diarrhoea, alopecia, skin rashes, itching, hepatitis

Azoles

- **Imidazoles and Triazoles**

- Are structurally related compounds
- Have similar mechanism of action
- Have similar antifungal spectrum

Mechanism:

Impairs ergosterol synthesis by inhibiting the 14^{α} -demethylation of lanosterol to ergosterol conversion using the cytochrome P-450 dependent enzyme 14^{α} -demethylase enzyme
(FUNGISTATIC)

- **Miconazole and Clotrimazole-**

- Dermatophytic and Candida infections (topically)
- Available as cream, gel, lotion, solution, spray, vaginal pessary, etc.

Uses:

- Dermatophytic infections
- Candida infections

Adverse effects

- Local irritation, itching or burning

MICONAZOLE SAFE IN PREGNANCY

- **Ketoconazole (KTZ)**

- **Prototype** among azoles
- Effective orally as well as topically
- Fungal infections like Candidiasis, Dermatophytosis, Deep mycosis
- **MOST TOXIC** among Azoles (hence replaced by Triazoles for systemic use)

Pharmacokinetics:

Orally effective, **acidic environment favours absorption.**

Bioavailability **reduced by drugs like H2 blockers, PPIs.**

Highly bound to plasma proteins.

Adverse effects:

MOST TOXIC among Azoles, but less than AMB.

Anorexia, nausea, vomiting

KTZ reduces adrenal cortical steroids,
testosterone and estrogen synthesis.

Hepatotoxicity, hypersensitivity reactions.

Uses:

Dermatophytosis, Candidiasis

Other uses – Kala azar, Cushing's syndrome.

Fluconazole

Triazoles

- Oral and IV administration
- Broad spectrum
- Topical use in the eye

Pharmacokinetics:

Well absorbed from GI tract, high Bioavailability

Poor protein binding, freely crosses the BBB, high concentration in CSF.

Uses:

Candidiasis, Dermatophytosis

(Cryptococcal meningitis, Coccidioidal meningitis) – **IV Fluconazole**

Blastomycosis, Histoplasmosis, Sporotrichosis

NOT EFFECTIVE in *Aspergillosis* and *Mucormycosis*

Itraconazole

- **Synthetic triazole**
- Orally as well as by IV route
- **Acidity favour the absorption**
- Highly bound to plasma proteins
- Does not cross the BBB
- **Broad spectrum including Aspergillus**

Adverse effects:

Nausea, vomiting, diarrhoea, headache, hepatotoxicity and hypokalemia

Uses:

Histoplasmosis, blastomycosis, sporotrichosis, aspergillosis – **IV Itraconazole** is the drug of choice.

Candidiasis, Dermatophytosis

Onchomycosis – **Oral Itraconazole**

Terbinafine

- An allylamine
- **Inhibits squalene 2,3-epoxide**
- **Blocks ergosterol synthesis**
- Topically and Orally available
- **High concentration in skin, nails and adipose tissues**

Uses:

Dermatophytosis, Candidiasis

Onchomycosis – Preferred drug

Adverse effects:

Nausea, diarrhoea, dyspepsia, skin rashes, hepatitis
(rare)

Caspofungin acetate

- **Semi-synthetic**
- Effective against *Candida* and *Aspergillus*
- **Inhibits the glucans in fungal cell wall.**
- Effective IV
- **Adverse effects**
Nausea, vomiting, flushing, fever, phlebitis at the site of injection.
- **Expensive drug.**

Other topical agents

- **Whitfield's ointment** (6% benzoic acid and 3% salicylic acid) – fungistatic and keratolytic effect – *T. pedis*
- **Undecylenic acid** – Fungistatic drug – *T. pedis*, *T. curis*, Dermatophytoses
- **Selenium sulphide** – *T. versicolor*
- **Sodium thiosulphate** – Fungistatic effect – *T. versicolor*
- **Potassium iodide** – Dermatophytic infection

Thank You...