Antifungal Drugs

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Fungal Infections (mycoses)

- Superficial
- Deep/systemic
Fungal infections (Superficial)

- Dermatomycosis (bcc cup)
  - Tinea pedis (athlete’s foot)
  - Tinea corporis (skin ringworm)
  - Tinea cruris (groin)
  - Tinea capitis (scalp)
  - Tinea unguium (nails)
  - Tinea barbae (beard)
  - Tinea mannum (hand)
- Candidiasis – skin, mouth, vagina oropharynx
Fungal Infection

Fungal Infection
1. ANTIBIOTICS
   Amphotericin B, (AMB), Nystatin, Hamcyin, Natamycin
   Griseofulvin

2. ANTIMETABOLITES:
   5-Fluorocytosine (5-FC)
   inhibition of nucleic acid synthesis
3. AZOLES
   - Imidazoles: (Topical): Clotrimazole, Econazole, Miconazole, Oxiconazole
     (Systemic): Ketoconazole
   - Trizoles: (Systemic) Itraconazole, Fluconazole, Voriconazole

   Inhibition of ergosterol synthesis

4. ALLYLAMINE: Terbinafine

   Inhibition of lanosterol and ergosterol synthesis

5. OTHER TOPICAL AGENTS:
   Tolnaftate, Undecylenic acid, Benzoic acid, Quiniodochlor, Ciclopirox olamine, Sod. thiosulfate.
**Amphotericin B - MOA**

- **In fungi:** ergosterol in membranes: higher affinity than mammalian cholesterol for AmB

- **Ergosterol:** Only present in fungal cell membrane and not in animal cell

- **Ergosterol: Polyenes** combine with it, get inserted into the membrane and several molecules together orient themselves and form a **micropore.**
The Fungal Cell Wall

- Mannoproteins
- β1,6 glucans
- β1,3 glucans
- Cell membrane
- β1,3 glucan synthase
- Chitin
- Ergosterol
Amphotericin B

Fungal cell

K⁺ and other small molecules
Antifungal Spectrum

- Candida albicans, Histoplasma capsulatum, Cryptococcus neoformans, Blastomyces dermatitidis, Coccidioides immitis, Aspergillus, Rhodotorula.
- Resistance is rare and slow to develop
- **Pharmacokinetics**
  - Poorly: crosses cell membranes, absorbed from the gut and penetration into the eye, CSF, and joint capsules
  - **Kidney > liver > spleen > lung > heart > skeletal muscle > brain > bone > CSF > eye**
- For treatment of meningitis, it must be given intrathecally
  - Given only via IV injection or intrathecally Selective distribution into deep tissue sites, with slow release of drug
Classic amphotericin B deoxycholate (Fungizone™) formulation: serious toxic side effects.

Less toxic preparations:

1) Liposomal amphotericin B
2) Amphotericin B colloidal dispersion
3) Amphotericin B lipid complex

- milder acute reaction
- better tolerated
- lower nephrotoxicity
- minimal anaemia
- targeted delivery-liver & Spleen
ADVERSE EFFECTS (AMB)

- **Acute: Infusion-related**
  - Chills, fever, dyspnea, nausea, vomiting, bronchospasm, hypotension, convulsions
- **Chronic**
  - Nephrotoxicity
  - Impaired concentration, impaired urinary acidification, K & Mg wasting with hypokalemia and hypomagnesemia
- Normochromic, normocytic anemia
- (↓ erythropoietin)
Drug interactions

- **FLUCYTOSINE**
  - Synergism
  - AMPHOTERICIN B

- **KETOCONAZOLE**
  - Contraindicated
  - AMPHOTERICIN B
Griseofulvin

- Fungistatic
- A systemic antifungal used to treat topical ringworm infections, e.g., onychomycosis, Tinea capitis, Tinea pedis, etc.
- many *Trichophyton* spp., *Microsporum* spp. and *Epidermophyton* spp. are susceptible
- Dermatophyte infections
- Oral absorption (better with small particle size)
- Enzyme inducer
Mode of Action - Griseofulvin

- disrupts mitotic spindle during metaphase by interacting with fungal microtubules------ (-) fungal mitosis (metaphase arrest)
- sufficient to inhibit growth of fungi (drug is static), preventing them from invading.
Griseofulvin – Mechanism of Action
Griseofulvin-Adverse actions

- GI disturbances
- Allergic reactions
- Skin rash
- Headache
- Photosensitivity
- Angioedema
- Peripheral neuritis
Griseofulvin-Adverse effects (CNS)

- Lethargy
- Mental confusion
- Blurring of vision
- Vertigo
- Being an antimiotic--bone marrow suppression, leucopenia, neutopenia
Griseofulvin - Uses

Dermatophytosis
2. ANTIMETABOLITES:  
5-Flucytosine (5-FC)

- Flucytosine is converted into 5-flurouracil, which inhibits thymidylate synthetase leading to inhibition of DNA synthesis (antimetabolite action)
- All susceptible fungi are capable of deaminating flucytosine to 5-flurouracil
3. AZOLES

- Better CSF penetrability
- High volume of distribution
- Dermatophytes, candida and other deep mycoses
- Triazoles are greater efficacy/lesser side effect and drug interaction
Mechanism of Action:

Acetyl CoA → Squalene → Squalene-2,3 oxide → Lanosterol → Ergosterol → 14-α demethylase → Azoles
Adverse effects of fluconazole include:

- Nausea
- Vomiting
- GI upset
- Hepatotoxicity
- Exfoliative skin rash
Caution:

As these are embryotoxic, they should be avoided in pregnancy.
Effect of azoles on *C. albicans*

Before exposure  
After exposure
Ketoconazole

- Spectrum: yeasts and moulds - poor absorption limits its role for severe infections, generally used in mucosal infections only
- Pharmacokinetics
  - Variable oral absorption, dependent on pH (often given with cola or fruit juice)
  - $T_{1/2}$ 7-10 hours
  - Protein binding > 99%
  - Hepatic, bile and kidney elimination
  - $H_2$ blockers, antacids--- decrease absorption
Adverse effects of Ketoconazole include:

- Hepatotoxicity, which increases liver enzymes (rarely may develop progressive hepatotoxicity, which can be fatal).
- Gynecomastia, loss of libido and oligozoospermia in men (the drug may inhibit androgenic hormones).
- Menstrual abnormalities, which may occur in some women.
- Salt and water retention.

- Hepatotoxicity (2-8%) - increase in transaminases, hepatitis
- Dose related inhibition of CYP P450 - responsible for testosterone synthesis
- Dose-related inhibition of CYP P450 - responsible for adrenal cortisol synthesis
4. ALLYLAMINE: Terbinafine

- It causes non-competitive inhibition of squalene epoxide enzyme, which is involved in the synthesis of ergosterol by fungi.

Squalene-2-3- epoxidase

Acetyl CoA

Farnesyl Pyrophosphate

Erg9

Squalene

Erg1

Squalene Epoxide

Erg7

Lanosterol

Erg11

4,4-dimethylcholesta-8,14,24-trienol

Erg24

4,4-dimethylzymosterol

Erg25
Erg26
Erg27
Erg5

Fecosterol

Erg2

Episterol

Erg3

Ergosta-5,7,24(28)-trienol

Erg5
Erg4

Ergosterol

Allylamines (terbinafine)
Mechanism of Action:

1. Acetyl CoA → Squalene
2. Squalene → Squalene-2,3 oxide
3. Squalene-2,3 oxide → Lanosterol
4. Lanosterol → Ergosterol
5. Ergosterol → Allylamines

Key enzymes:
- Squalene-2,3 epoxidase
- 14-α demethylase
4. ALLYLAMINE: Terbinafine

- A highly lipophilic, keratinophilic
- Effective orally against dermatophytes and candida
- Useful in fungal infections of nails (6-12 weeks)
- Adverse effects: gastric upset, rashes and taste disturbances
- Rarely hepatotoxicity
5. OTHER TOPICAL AGENTS:

- White field’s ointment = Benzoic acid (6%) + Salicylic acid (3%)
- Tolnaftate: Tinea corporis, cruris
- Ciclopirox: Dermatophytes, candida Malassezia furfur
- Selenium Sulfide: Malassezia furfur
- Haloprogin: Dermatophytes, candida
SITES OF ACTION OF ANTIFUNGAL DRUGS

1a. ALLYLAMINES
   block ergosterol formation in cell membrane via inhibition of squalene epoxidase

1b. GRISEOFULVIN
   blocks intracellular microtubules

2. FLUCYTOSINE - active
   uptake via permease
   blocks DNA/RNA synthesis

3. AZOLES
   block ergosterol formation in cell membrane via inhibition of cytochrome P450 dependent
   14α-demethylase

4. POLYENES
   bind to and disrupt cell membranes
What are the targets for antifungal therapy?

**Cell membrane**
Fungi use principally ergosterol instead of cholesterol

**DNA Synthesis**
Some compounds may be selectively activated by fungi, arresting DNA synthesis.

**Cell Wall**
Unlike mammalian cells, fungi have a cell wall

Introduction to Medical Mycology. Merck and Co. 2001
Cell Membrane Active Antifungals

- **Polyene antibiotics**
  - Amphotericin B, lipid formulations
  - Nystatin (topical)

- **Azole antifungals**
  - Ketoconazole
  - Itraconazole
  - Fluconazole
  - Voriconazole
  - Miconazole, clotrimazole (and other topicals)