Antifungal Drugs

Yacoub Irshaid MD, PhD, ABCP
Department of Pharmacology

Antifungal Drugs

Fungal Infections:

1. **Superficial fungal infections:**

A. **Dermatomycosis: Caused by *Trichophyton*, *Microsporum* and *Epidermophyton* and affect skin, nails and hair.**

B. **Candidiasis: affect skin, mucous membranes**

Antifungal Drugs

2. **Systemic fungal infections: affecting deeper tissues and organs.**

- **The incidence and severity have increased since 1970s because of:**

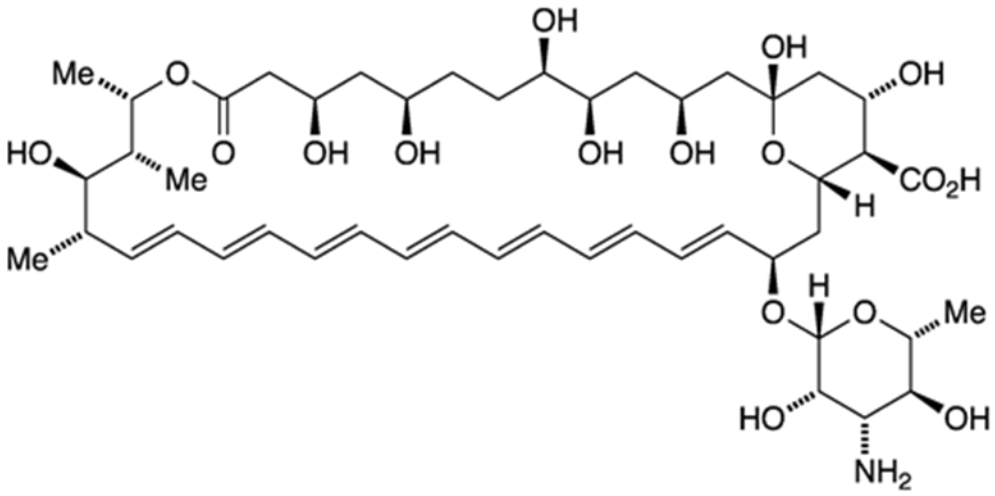
A. **Wide use of broad spectrum antibiotics.**
B. **Immunosuppression: AIDS, Drugs, Chemotherapy**
C. **Older population**
D. **Diabetes mellitus**
E. **Advances in surgery**

Amphotericin B

- **A polyene macrolide antibiotic. It is a broad spectrum antifungal agent.**

Mechanism of Action:

- **Binds ergosterol of fungal cell membrane → formation of amphotericin B associated-pores or transmembrane ion channels by the hydrophilic core of the molecule.**
- **Binding is relatively specific to fungi and the protozoan parasite Leishmania spp.**
- **The pore allows leakage of intracellular ions and macromolecules → cell death.**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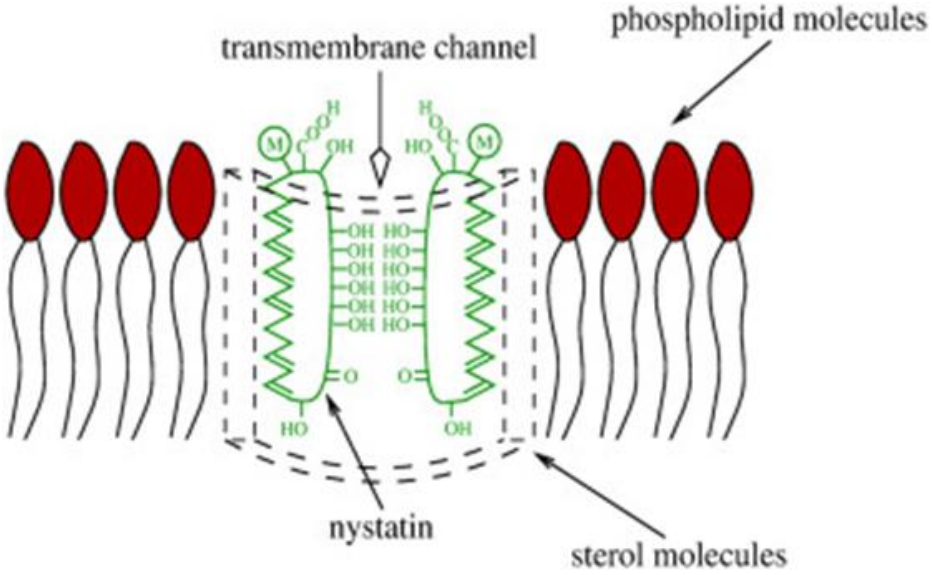
transmembrane channel
phospholipid molecules
nystatin
sterol molecules

Amphotericin B

- **Resistance develops by modifying the sterol target → reduced affinity for the drug.**

Pharmacokinetics:

- **Poor absorption after oral administration.**
- **Can be used PO for fungal infections of GIT (lumen).**
- **It is complexed with deoxycholate as a suspension for slow IV infusion.**

Amphotericin B

- **Liposomal amphotericin B: packaging the drug in lipid delivery vehicles to reduce binding to human cell membranes → reduction of toxicity and permits use of larger doses.**
- **Highly protein bound (>90%)**
- **Crosses BBB poorly, but penetration is improved when meninges are inflamed.**
- **t½ ~ 15 days**

Amphotericin B

Adverse Effects:

A. Infusion-related toxicity:

- Fever, chills, muscle spasm, vomiting, headache and hypotension.
- Can be reduced by slowing the infusion rate.

Amphotericin B

B. Slower cumulative toxicity:

1. **Nephrotoxicity: common (> 80% of patients) and most serious, and constitute:**

a) **Reversible component: represents prerenal failure leading to renal tubular injury.**

Amphotericin B

b) Irreversible component results from prolonged administration (> 4 gram cumulative dose): impaired renal concentrating ability, renal tubular acidosis and severe potassium, sodium and magnesium wasting.
c) Elevation of urea and creatinine.

Amphotericin B

2. **Anemia due to reduced erythropoietin production.**
3. **Others: Hepatic dysfunction, thrombocytopenia, anaphylaxis.**
4. **Seizures and chemical arachnoiditis after intrathecal therapy.**

Amphotericin B

Antifungal Activity:

- **Broad spectrum and fungicidal**
- **Clinically significant yeasts:**

  ***Candida albicans*, *cryptococcus neoformans*.**
- **Endemic mycosis: *Histoplasma capsulatum, Blastomyces dermatitidis, Coccidiodes immitis*.**
- **Pathogenic molds: *Aspergillus fumigatus, Mucor*.**

Nystatin

- **Is similar but more toxic than amphotericin B and only used for fungal infections of the skin & mucous membranes, as creams, ointments suppositories.**

Flucytosine

- **Pyrimidine analog.**
- **Given PO & IV infusion.**
- **Narrow spectrum: effective against yeasts.**
- **It has a synergistic effect when combined with amphotericin B for cryptococcal meningitis due to enhanced penetration through amphotericin B damaged membranes.**

Flucytosine

Mechanism of action:

- **It is taken up by fungal cells via cytosine permease.**
- **It is converted intracellularly to 5-fluorouracil and then to 5-FdUMP and FUTP in fungal cells, which inhibit DNA and RNA synthesis.**
- **Human cells are unable to convert the drug into its active metabolites.**
- **Resistance emerges rapidly during monotherapy, due to altered metabolism of the drug.**

Flucytosine

Pharmacokinetics:

- **Well absorbed after oral administration (> 90%).**
- **Widely distributed throughout body fluids including CNS.**
- **90% excreted unchanged by the kidney by glomerular filtration.**
- **t½ ~3-4 hours.**
- **Dose reduction is needed in renal dysfunction.**

Flucytosine

Adverse Effects:

- **It has a narrow therapeutic window: toxicity develops rapidly at high blood levels, with resistance developing rapidly at subtherapeutic levels.**

1. **GIT disturbances: enterocolitis and hepatitis.**
2. **Bone marrow depression: anemia, neutropenia, thrombocytopenia most common.**
3. **Alopecia.**

Azole Antifungals

Classification:

1. **Imidazoles: Ketoconazole, Miconazole & Clotrimazole**
2. **Triazoles: Itraconazole, Fluconazole & Voriconazole**

- **They are broad spectrum synthetic fungistatic antifungal agents**

Azole Antifungals

Antifungal Spectrum:

- **Many candida, *Cryptococcus neoformans*, the endemic mycoses (blastomycosis, coccidioidmycosis, histoplasmosis), and the dermatophytes.**
- **Itraconazole and voriconazole: *Aspergillus*, and amphotericin-resistant *Pseudallescheria boydii*.**

Azole Antifungals

Mechanism of Action:

- **Inhibition of fungal cytochrome P450 responsible for synthesis of ergosterol of cell membrane → alteration of membrane fluidity and thus, the activity of membrane-associated enzymes.**
- **The net effect is inhibition of replication and growth.**
- **They reduce the formation of amphotericin B binding sites.**

Azole Antifungals

- **Imidazoles also inhibit human P450, leading to a higher incidence of drug interactions and adverse effects.**

Fluconazole

- **Can be given PO (high oral availability) & IV.**
- **Reaches high concentration in CSF and ocular fluid.**
- **Drug of choice for most fungal meningitis (cryptococcal, coccidioidal) and candidemia.**
- **Useful in mucocutaneous candidiasis.**
- **No activity against aspergillus or other filamentous fungi.**

Fluconazole

- **Prophylactic use in bone marrow transplants & AIDS → emergence of resistance.**
- **Fungicidal concentrations can be achieved in vaginal tissue, saliva, skin & nails.**
- **Excreted unchanged mostly in urine.**

Fluconazole

Adverse Effects:

- **Has the widest therapeutic index of azoles.**

1. **Nausea, headache, abdominal pain**
2. **Exfoliative skin lesions (Steven-Johnson syndrome) have been seen in AIDS patients**
3. **Hepatitis**
4. **Does not inhibit drug metabolism and steroidogenesis like ketoconazole → Less drug interactions.**

Itraconazole

- Undergoes extensive first-pass effect.
- Absorption is increased by food and low gastric pH.
- A highly lipid soluble preparation for IV administration is available.
- Bioavailability is reduced by rifamycins.
- Interaction with hepatic microsomal enzymes is less than ketoconazole.
- Excreted in urine.
- Does not penetrate BBB.

Itraconazole

Therapeutic uses:

1. **Drug of choice for dimorphic fungi infections (*Histoplasma, Blastomyces*, & *Sporothrix*).**
2. **Effective against aspergillosis but replaced by voriconazole.**
3. **Used for dermatophytosis and onychomycosis.**

Itraconazole

Adverse Effects:

1. **GIT disturbances , headache, dizziness**
2. **Hepatitis.**
3. **Hypokalemia**
4. **Interacts with P450s (but less than ketoconazole): Impotence, and sexual dysfunction**
5. **Allergic reactions and exfoliative dermatitis.**

Voriconazole

- **Broad spectrum**
- **Can be given PO & IV.**
- **Well absorbed orally.**
- **Eliminated by hepatic metabolism.**
- **Inhibition of mammalian P450 is low.**

Voriconazole

Adverse effects:

1. **Transient visual disturbances (blurring and changes in color vision and brightness). Common, occur in 30% of patients, occur immediately after a dose and resolve in 30 min.**

Voriconazole

Therapeutic uses:

Similar in spectrum to itraconazole:

1. **Excellent activity against candida spp.**
2. **Active against Fluconazole-resistant Candida & Cryptococcus and dimorphic fungi.**
3. **As or more effective than amphotericin B for invasive aspergillosis.**

Topical Azoles

Clotrimazole, Miconazole & Econazole:

- **Used topically for vulvovaginal candidiasis.**
- **Oral clotrimazole troches for oral thrush.**
- **Dermatophytic infections: Creams for tinea corporis, tinea pedis & tinea cruris.**
- **Topical and shampoo forms of ketoconazole for seborrheic dermatitis and pityriasis versicolor.**

Terbinafine

- **Is a synthetic allylamine.**
- **Given PO and is taken up by skin, nails and adipose tissue.**
- **When given topically, it penetrates skin and mucous membranes.**
- **Metabolized by CYPs.**
- **Highly lipophylic and keratinophilic.**
- **Fungicidal for many skin fungi (dermatophytes).**

Terbinafine

Mechanism of action:

- **It inhibits the enzyme squalene epoxidase which is involved in the synthesis of ergosterol in fungal cell wall → accumulation of squalene (toxic) within fungal cell.**

Terbinafine

Therapeutic uses:

1. **Fungal infections of the nails (onychomycosis).**
2. **Topically (creams) for tinea cruris and tinea corporis**

- **Naftifine is similar but only used topically for tinea cruris and tinea corporis.**

Terbinafine

Adverse Effects:

1. **GIT disturbances**
2. **Rash, pruritus**
3. **Headache, dizziness**
4. **Joint and Muscle pain**
5. **Hepatitis**

Echinocandins

- **The newest class of antifungal agents.**
- **They are large cyclic peptides linked to a long-chain fatty acid.**
- **Include: Caspofungin, Micafungin & Anidulafungin.**

Echinocandins

Mechanism of action:

- **Inhibit synthesis of β(1,3)-glucan, a glucose polymer necessary for maintaining the structure of fungal cell wall. The fungus loses integrity → lysis → death.**

Echinocandins

- **Broad spectrum.**
- **Poor absorption after oral administration, available only IV (slow).**
- **Water soluble and highly protein bound.**
- **t½ : caspofungin ~ 10 hours, micafungin ~ 13 hours, anidulafungin ~ 36 hours.**
- **Loading doses are required.**
- **Dosage adjustment is needed in severe hepatic insufficiency.**

Echinocandins

Therapeutic uses:

1. **Candidiasis (mucocutaneous and septicemia).**
2. **Esophageal candidiasis**
3. **Empiric therapy in febrile neutropenia**
4. **Salvage therapy for invasive aspergillosis refractory to amphotericin B.**

Echinocandins

Adverse effects: **well tolerated.**

1. **GIT irritation: abdominal pain, nausea vomiting and diarrhea**
2. **Elevation of liver enzymes when combined with cyclosporine.**
3. **Micafungin has been shown to increase levels of nifedipine, cyclosporine and sirolimus.**

Echinocandins

4. **Anidulafungin releases histamine – flushing, rash, tachycardia.**
5. **Fever, headache.**
6. **Phlebitis/thrombophlebitis**