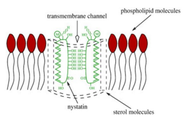
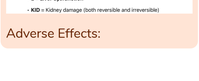
Antifungal Drugs 💊

Amphotericin B

- A polyene macrolide antibiotic. It is a broad spectrum antifungal agent.
- MOA: TEARs 🚽💧
  - Binds ergosterol of fungal cell membrane
    - formation of amphotericin B associated-pores or transmembrane ion channels by the hydrophilic core of the molecule.
  - The pore allows leakage of intracellular ions and macromolecules=>cell death.
  - Binding is relatively specific to fungi and the protozoan parasite **Leishmania spp.**
  - reduced affinity for the drug — Resistance develops by modifying the sterol target
- Route of administration:
  - Can be used PO for fungal infections of GIT (lumen) — Poor absorption after oral administration
  - It is complexed with deoxycholate as a ***suspension for slow IV infusion.***
- Pharmacokinetics:
  - reduction of toxicity and permits use of larger doses. — packaging the drug in lipid delivery vehicles to reduce binding to human cell membranes — Liposomal amphotericin B
  - Highly protein bound (>90%)
  - penetration is improved when meninges are inflamed. — Crosses BBB poorly
  - t1/2 ~ 15 days
- Adverse Effects:
  - A. Infusion-related toxicity: Fever, chills, muscle spasm, vomiting, headache and hypotension — Can be reduced by slowing the infusion rate
  - 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
      - 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.
    - 2. Anemia due to reduced erythropoietin production.
    - 3. Others: Hepatic dysfunction, thrombocytopenia, anaphylaxis.
    - 4. Seizures and chemical arachnoiditis after intrathecal therapy.





- Antifungal Activity:
  - Candida albicans, cryptococcus neoformans. — Clinically significant yeasts:
  - Histoplasma capsulatum, Blastomyces dermatitidis, Coccidiodes immitis. — Endemic mycosis:
  - Aspergillus fumigatus, Mucor. — Pathogenic molds:
  - Broad spectrum and **fungicidal**

Nystatin

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

Terbinafine

- Is a synthetic allylamine.
- **Fungicidal** for many skin fungi (dermatophytes).
- Route of administration:
  - taken up by skin, nails and adipose tissue. — Given PO
  - it penetrates skin and mucous membranes. — given topically
- MOA:
  - 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.
- Pharmacokinetics
  - Metabolized by CYPs.
  - Highly lipophylic and keratinophilic.
- Antifungal activity:
  - Fungal infections of the nails (onychomycosis).
  - Topically (creams) for tinea cruris and tinea corporis — **Naftifine** is similar but only used topically for tinea cruris and tinea corporis
- Adverse Effects:
  - Hepatitis
  - Rash, pruritus
  - Joint and Muscle pain
  - GIT disturbances
  - Headache, dizziness

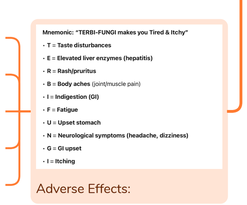


Table summary from ChatGPT

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
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

Flucytosine

- Pyrimidine analog
- MOA:
  - It is taken up by fungal cells via cytosine permease. — It is converted intracellularly to 5-fluorouracil — then to
    - 5-FdUMP — inhibit DNA synthesis
    - FUTP — inhibit RNA synthesis
  - Resistance emerges rapidly during monotherapy, due to altered metabolism of the drug.
- Route of administration: — Given PO & as IV infusion
- Pharmacokinetics:
  - Well absorbed after oral administration (> 90%).
  - Widely distributed throughout body fluids including CNS.
  - Human cells are unable to convert the drug into its active metabolites.
  - 90% excreted unchanged by the kidney by glomerular filtration. — Dose reduction is needed in renal dysfunction.
  - t1/2 ~3-4 hours.
- Adverse Effects:
  - It has a narrow therapeutic window
    - toxicity develops rapidly at high blood levels
    - resistance developing rapidly at subtherapeutic levels.
  - Bone marrow depression: anemia, neutropenia, thrombocytopenia most common.
  - Alopecia
  - GIT disturbances: enterocolitis and hepatitis.

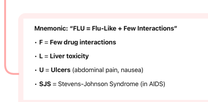
- Antifungal Activity:
  - Narrow spectrum: effective against yeasts.
  - It has a synergistic effect when combined with amphotericin B for cryptococcal meningitis — due to enhanced penetration through amphotericin B damaged membranes.

Azole Antifungals

- There are broad spectrum synthetic **fungistatic** antifungal agents
- Classification:
  1. Imidazoles: Ketoconazole, Miconazole & Clotrimazole
  2. Triazoles: Itraconazole, Fluconazole & Voriconazole
  - Antifungal Spectrum: like amphotericin B
    - Many candida, Cryptococcus neoformans, the endemic mycoses (blastomycosis, coccidioidmycosis, histoplasmosis), and the dermatophytes.
    - **Itraconazole and voriconazole:** Aspergillus, and amphotericin-resistant Pseudallescheria boydii.
- MOA:
  - 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
  - Imidazoles also inhibit human P450 — leading to a higher incidence of drug interactions and adverse effects.

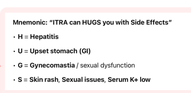
Fluconazole:

- Route of administration: — Can be given PO (high oral availability) & IV.
- Antifungal Activity
  - Drug of choice for most fungal meningitis (cryptococcal, coccidioidal) and candidemia. — NOTE: The doctor said it is EFFECTIVE but not the drug of choice (the drug of choice for cryptococcal meningitis us Amphotericin B with Flucytisine)
  - Useful in mucocutaneous candidiasis.
  - No activity against aspergillus or other filamentous fungi
  - Prophylactic use in bone marrow transplants & AIDS — emergence of resistance
  - **Fungicidal concentrations** can be achieved in vaginal tissue, saliva, skin & nails.
- Pharmacokinetics: Excreted unchanged mostly in urine (Approximately 10% to 20% of fluconazole is metabolized by the CYP3A4 isoenzyme; almost 80% of the agent is excreted unchanged by the kidneys, with the rest excreted as metabolites. *extra*)
  - Reaches high concentration in CSF and ocular fluid.
- Adverse Effects:
  - Has the widest therapeutic index of azoles.
  - Less drug interactions. It Does not inhibit drug metabolism and steroidogenesis like ketoconazole
  - Hepatitis
  - Nausea, headache, abdominal pain
  - Exfoliative skin lesions (Steven-Johnson syndrome) — seen in AIDS patients



Itraconazole

- Route of administration:
  - Orally
  - A highly lipid soluble preparation for IV administration is available
- Pharmacokinetics:
  - Undergoes extensive first-pass effect.
  - Absorption is increased by food and low gastric pH.
  - Bioavailability is reduced by rifamycins.
  - Interaction with hepatic microsomal enzymes is less than ketoconazole.
  - Excreted in urine.
  - Does not penetrate BBB.
- Antifungal Activity:
  - Drug of choice for dimorphic fungi infections (Histoplasma, Blastomyces, & Sporothrix)
  - Effective against aspergillosis but replaced by voriconazole.
  - Used for dermatophytosis and onychomycosis.
- Adverse Effects:



  - Hepatitis.
  - Hypokalemia
  - GIT disturbances , headache, dizziness
  - Interacts with P450s (but less than ketoconazole): Impotence, and sexual dysfunction
  - Allergic reactions and exfoliative dermatitis

Voriconazole

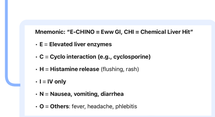
- Broad spectrum
- Route of administration: — Can be given PO & IV.
- Pharmacokinetics:
  - Well absorbed orally.
  - Eliminated by hepatic metabolism.
  - Inhibition of mammalian P450 is low.
- Adverse effects: Transient visual disturbances (Common, occur in 30% of patients, occur immediately after a dose and resolve in 30 min) — blurring and changes in color vision and brightness
- Antifungal Activity: (Similar in spectrum to itraconazole):
  - Excellent activity against candida spp.
  - Active against Fluconazole-resistant Candida & Cryptococcus and dimorphic fungi.
  - As or more effective than amphotericin B for invasive aspergillosis.

Clotrimazole, Miconazole & Econazole (Topical Azoles)

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

Echinocandins (Caspofungin, Micafungin & Anidulafungin)

- Notes 🏏:
  - The newest class of antifungal agents.
  - They are large cyclic peptides linked to a long- chain fatty acid.
  - Broad spectrum
- Route of administration: — Poor absorption after oral administration, available only IV (slow)
- MOA: 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.
- Pharmacokinetics:
  - Water soluble and highly protein bound.
  - Loading doses are required.
  - Dosage adjustment is needed in severe hepatic insufficiency.
  - t1/2 : caspofungin ~ 10 hours, micafungin ~ 13 hours, anidulafungin ~ 36 hours.
- Antifungal activity:
  - Candidiasis (mucocutaneous and septicemia).
  - Esophageal candidiasis
  - Empiric therapy in febrile neutropenia
  - Salvage therapy for invasive aspergillosis refractory to amphotericin B.
- Adverse effects: well tolerated



  - Elevation of liver enzymes when combined with cyclosporine
  - Anidulafungin releases histamine – flushing, rash, tachycardia
  - GIT irritation: abdominal pain, nausea vomiting and diarrhea
  - Fever, headache.
  - Phlebitis/thrombophlebitis
  - Micafungin has been shown to increase levels of nifedipine, cyclosporine and sirolimus.

Presented with xmind