

بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ

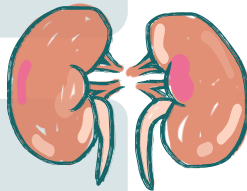


Antifungal Drugs (Pt.2)

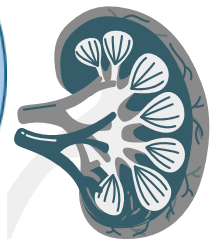
FINAL | Lecture 7

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﴿قُلْ بِفَضْلِ اللَّهِ وَبِرَحْمَتِهِ فَبِذَلِكَ فَلْيَفْرَحُوا هُوَ خَيْرٌ مِّمَّا يَجْمَعُونَ﴾



Voriconazole

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

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). If one of these 3 is resistant to fluconazole, it can be treated with voriconazole .
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 (any part of the body) , tinea pedis (between the toes) & tinea cruris (in perineum and between thighs) .**
 - **Topical and shampoo forms of ketoconazole for seborrheic dermatitis and pityriasis versicolor.**
- ❖ "seborrheic" refers to the **sebaceous (oil-producing) glands** of the skin.
 - ❖ In **seborrheic dermatitis**, it means the condition specifically targets areas of the body that are rich in these glands, such as the scalp, face, ears, and upper chest

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 (Systemic absorption).**
- **Metabolized by CYPs (Cytochrome P450).**
- **Highly lipophilic and keratinophilic.** *Very effective drug for nail fungal infection.*
- **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.
 - ✓ Not only inhibits ergosterol synthesis but also kills fungal cells by accumulation of squalene.

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 $\beta(1,3)$ -glucan, a glucose polymer necessary for maintaining the structure of fungal cell wall.
- **The result:** the fungus loses integrity \rightarrow lysis \rightarrow death.

Echinocandins

- **Broad spectrum of fungi.**
- **Poor absorption after oral administration, available only IV (slow).**
- **Water soluble and highly protein bound.**
- **$t_{1/2}$: caspofungin ~ 10 hours, micafungin ~ 13 hours, anidulafungin ~ 36 hours.**
- **Loading doses (Larger initial doses) are required.** Specifically for anidulafungin but may be needed for caspofungin and micafungin.
- **Dosage adjustment is needed in severe hepatic insufficiency.**
 - ❖ A quick note: unlike renal dysfunction, hepatic dysfunction usually does not require dose adjustment because metabolic function is relatively preserved in mild to moderate hepatic impairment.
 - ❖ However, severe hepatic dysfunction may require dose adjustment.

Echinocandins

Therapeutic uses:

- 1. Candidiasis (mucocutaneous and septicemia).** we give the drug by slow intravenous infusion for septicemia by candida or slow administration
- 2. Esophageal candidiasis** also needs systemic administration.
- 3. Empiric therapy in febrile neutropenia.**
 - ✓ Patients with neutropenia are susceptible to serious infections caused by virulent and multidrug-resistant microorganisms. **Empiric therapy** means that after obtaining a sample (e.g., blood in cases of septicemia) for microbiological identification of bacteria, fungi, or viruses, treatment is initiated according to the most probable causative microorganism before definitive identification.
 - ✓ After identification, the specific drug is given according to the causative organism.
 - ✓ The main problem occurs in **afebrile neutropenia**, which is commonly missed because of the absence of fever.
- 4. Salvage therapy for invasive aspergillosis** (very aggressive type and affects immunocompromised patient) **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.**
 - ✓ Elevation of liver enzymes does not always indicate hepatotoxicity; it may result from enzyme induction (e.g., rifampin) or mild reversible changes (enzyme leakage).
 - ✓ Hepatotoxicity refers to true hepatocellular injury, usually suggested by a significant rise in ALT/AST, especially when associated with clinical or biochemical evidence of liver dysfunction.
 - ✓ Cyclosporine causes immunosuppression and increases susceptibility to infections.
- 3. Micafungin has been shown to increase levels of nifedipine, cyclosporine and sirolimus.**
 - ✓ This suggests that micafungin may act as an inhibitor of cytochrome P450 enzymes, especially CYP3A4.

Echinocandins

4. Anidulafungin releases histamine – flushing, rash, tachycardia.

- ✓ Tachycardia results from hypotension secondary to vasodilation caused by histamine release

5. Fever (drug allergy), headache.

6. Phlebitis/thrombophlebitis.

Phlebitis is the inflammation of a vein without thrombus formation, while thrombophlebitis occurs when that inflammation is caused by—or leads to—a blood clot (thrombus)

الله أكبر، الله أكبر، لا إله إلا الله، الله أكبر، الله أكبر، والله الحمد



PHARMACOLOGY
QUIZ
LECTURE 7

اللهم إن عمر عطية في ذمتك وحبل جوارك، فقه من فتنة القبر وعذاب النار،
أنت أهل الوفاء والحق، فاغفر له وارحمه إنك أنت الغفور الرحيم.

لا إله إلا الله وحده لا شريك له..
له الملك وله الحمد.. وهو على
كل شيء قدير

قال النبي ﷺ: خير الدعاء دعاء يوم عرفة،
وخير ما قلت أنا والنبيون من قبلي: لا إله
إلا الله وحده لا شريك له

Scan the QR code or click it for FEEDBACK



Corrections from previous versions:

Versions	Slide # and Place of Error	Before Correction	After Correction
V0 → V1			
V1 → V2			