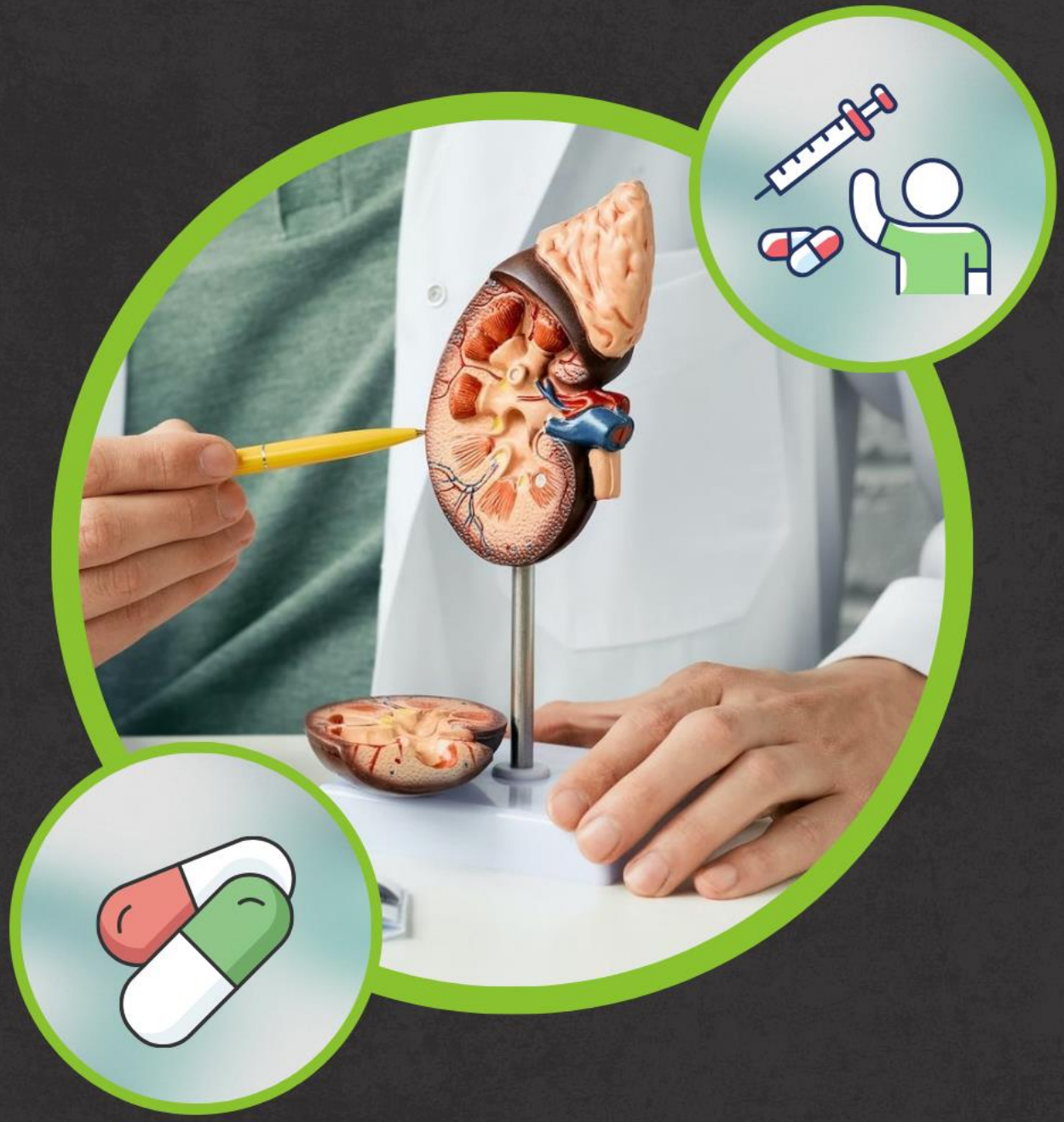


PHARMA

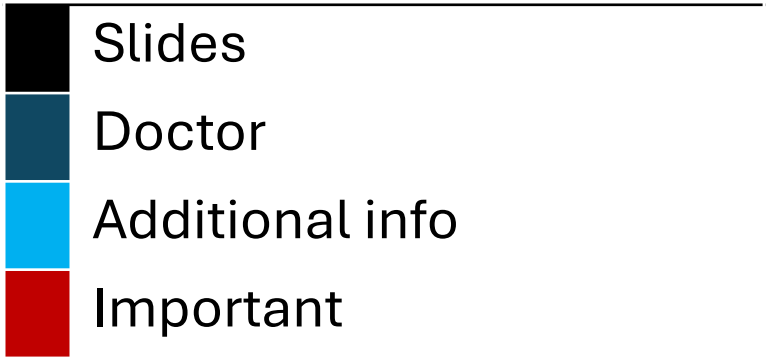
MODIFIED NO. 5

الكُتّاب: حلا صالح وميس سلمان

المدققين: ليث الخزاعلة

الدكتور/ة: يعقوب ارشيد

Color code



Itraconazole

- **Undergoes extensive first-pass effect.** When it passes through the liver the first time after oral administration, most of it will be metabolized.
- **Absorption is increased by food and low gastric pH.** That's because conazoles are acids so they'll be unionized at acidic pH and thus there will be more absorption.
- **A highly lipid soluble preparation for IV administration is available.**
- **Bioavailability is reduced by rifamycins.** Rifamycins, especially rifampicin, causes induction of metabolism of drug metabolizing enzymes, so they increase metabolism of itraconazole which is already high.
- **Interaction with hepatic microsomal enzymes is less than ketoconazole.** It causes less inhibition of CYP450 in comparison to ketoconazole.
- **Excreted in urine.**
- **Does not penetrate BBB. Although it's lipid soluble.**

Itraconazole

Therapeutic uses:

1. **Drug of choice for dimorphic fungi infections (*Histoplasma, Blastomyces*, & *Sporothrix*).**
2. **Effective against aspergillosis but replaced by voriconazole.** Before the development of voriconazole, itraconazole was the drug of choice for aspergillosis, but now it's replaced by voriconazole because it's more effective.
3. **Used for dermatophytosis and onychomycosis.** (Skin and nail infections)

Itraconazole

Adverse Effects:

1. **GIT disturbances , headache, dizziness.** Most drugs cause GI disturbances in particular patients, but here it's a bit different , the patient actually feels those abnormalities.
2. **Hepatitis.**
3. **Hypokalemia**
4. **Interacts with P450s (but less than ketoconazole): Impotence, and sexual dysfunction**; because of inhibition of sex hormone synthesis.
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.**

  In this aspect, it's better than itraconazole and ketoconazole.

Voriconazole

Adverse effects:

1. Transient visual disturbances (blurring and changes in color vision and brightness).changes in color vision is important because when driving you won't be able to discriminate the colors of traffic light and accidents might occur.

Very Common, occur in 30% of patients, occur immediately after a dose and resolve in 30 min. So it's important to tell the patient to take precautions when using this drug.

Voriconazole

Therapeutic uses:

Similar in spectrum to itraconazole: but more effective for invasive aspirgillosis, even more than amphoteracineB.

1. **Excellent activity against candida spp.**
2. **Active against Fluconazole-resistant Candida & Cryptococcus and dimorphic fungi.** So that it can be used for cryptococcal meningitis if there was resistance for fluconazole (not the drug of choice but is effective).
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(trunk), tinea pedis(between toes) & tinea cruris(genitalia). These infections are easily treated.
- Topical and shampoo forms of ketoconazole for seborrheic dermatitis (inflammation of hair roots) and pityriasis versicolor (superficial infection of the skin).

Terbinafine newer

- **Is a synthetic allylamine.**
- **Given PO and is taken up by skin, nails and adipose tissue**

  (it's lipid soluble). When taken orally, the drug will be concentrated in keratin of the skin and nails.
- **When given topically, it penetrates skin and mucous membranes.**
- **Metabolized by CYPs.**
- **Highly lipophylic and keratinophilic.**
- **Fungicidal for many skin fungi (dermatophytes).**

- It was very difficult to treat nail infections in the past, but now it's much better.

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 to the fungus) within fungal cell.**

Terbinafine

Therapeutic uses:

1. **Fungal infections of the nails (onychomycosis).** systemic use, taken orally.
2. **Topically (creams) for tinea cruris and tinea corporis**

- **Naftifine** (belongs to the same group as terbinafine) **is similar but only used topically for tinea cruris and tinea corporis.** It can't be taken systemic for example fungus infections of nails.

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. If β(1,3)-glucan is inhibited The fungus loses integrity → lysis → death. (fungicidal)**

Echinocandins

- **Broad spectrum.**
- **Poor absorption after oral administration, available only IV (slow).**
- **Water soluble and highly protein bound.** So they are poorly absorbed
- **t½** (important for determining the frequency of administration) **: caspofungin ~ 10 hours, micafungin ~ 13 hours, anidulafungin ~ 36 hours.**
  - We do not administer it every two days, but instead, we give a loading dose because it has a long half-life. Then, we administer lower doses to maintain the drug concentration above the therapeutic level.
- **Loading doses are required.**
- **Dosage adjustment is needed in severe hepatic insufficiency.**

If the drug requires dosage adjustment in cases of hepatic insufficiency, it is either metabolized by the liver or causes severe liver tissue damage.

Echinocandins

Therapeutic uses:

1. **Candidiasis (mucocutaneous and septicemia).**
2. **Esophageal candidiasis**
3. **Empiric therapy in febrile neutropenia**

Neutropenia is not always febrile. Sometimes, neutropenic patients do not present with fever, meaning the mechanism for developing a fever may not be functioning properly. As a result, they can develop septicemia. Neutropenia is very dangerous, and if an infection occurs in neutropenic patients, empiric therapy is given immediately to cover the most likely microorganisms causing the infection.

4. **Salvage therapy for invasive aspergillosis refractory to amphotericin B.** if you have invasive aspergillosis and it is sensitive to amphotericin B, but resistance develops after administration, then giving one of the echinocandins will help.

Echinocandins

Adverse effects: **well tolerated.**

1. **GIT irritation: abdominal pain, nausea vomiting and diarrhea**
2. **Elevation of liver enzymes when combined with cyclosporine.**

Cyclosporine is an immunosuppressant given for autoimmune diseases or organ transplants. It suppresses immunity, which can lead to infections. By itself, it can cause liver toxicity and elevate liver enzymes, and this effect is increased when given with echinocandins.

3. **Micafungin has been shown to increase levels of nifedipine, cyclosporine and sirolimus.**

Micafungin is an immunosuppressant. It inhibits CYP3A4 and this cause increase levels of drugs that metabolized by this enzyme like nifedipine, cyclosporine and sirolimus

unlike ketoconazole, which inhibits multiple cytochrome P450 enzymes

- Note related to elevation of liver enzymes :

- The elevation of liver enzymes is not always due to hepatic toxicity. However, if the levels exceed three times the upper limit of the reference range, it is more likely that an infection is present. Another cause of elevated liver enzymes is the use of drugs that induce drug-metabolizing enzymes and liver enzymes, such as rifampicne and anti-TB drugs. These drugs induce drug metabolism and can elevate liver enzymes like ALT, AST, LDH, and alkaline phosphatase. While rifampicine can cause liver toxicity, and distinguishing whether the elevation is due to induction or liver toxicity can be confusing. Therefore, drugs that induce hepatitis are absolutely contraindicated in these patients

4. Anidulafungin releases histamine – flushing, rash, tachycardia

It is not an allergy, as it is not caused by mast cell degranulation. It is a drug-induced histamine release. Histamine release can be triggered by a drug, an allergy, UV light (which causes histamine release from mast cells), or very cold weather.

5. Fever, headache. Drug fever = allergy

6. Phlebitis/thrombophlebitis cause irritation of vein when it is given IV

VERSIONS	SLIDE #	BEFORE CORRECTION	AFTER CORRECTION
V1→ V2			
V2→V3			

امسح الرمز و شاركنا بأفكارك لتحسين أدائنا !!