

بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ

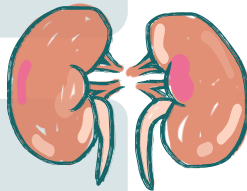


Antifungal Drugs (Pt.1)

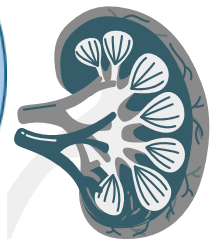
FINAL | Lecture 6

Written by: Abdulrahman Alsaadi

Reviewed by: Ehab Alarakza



﴿قُلْ يَفْضَلُ اللَّهُ وَبِرَحْمَتِهِ ۚ فَبِذَلِكَ فَلْيَفْرَحُوا هُوَ خَيْرٌ مِّمَّا يَجْمَعُونَ﴾



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

Antifungal Drugs

•Yacoub Irshaid MD, PhD, ABCP
Department of Pharmacology

Antifungal Drugs

Most Drugs are **topical** not systemic because infections are not severe .

Fungal Infections:

1. Superficial fungal infections:

- **Dermatomycosis: Caused by *Trichophyton*, *Microsporum* and *Epidermophyton* and affect skin, nails and hair.**
 - ✓ Nails and hair antifungal drugs are not just topical, they also need an antifungal drug to be incorporated into the keratin and has an affinity to reach keratin, which needs to give them **systemically**.
- **Candidiasis: affect skin, mucous membranes** of the mouth, vagina, urinary system, and lumen of the intestine because of taking wide spectrum antibiotics and acid suppression which allow the swallowing fungal organisms to reach intestine causing infection and diarrhea .
 - ✓ All of these are treated with topical drugs; even intestinal candidiasis is treated with poorly absorbable drugs that act locally in the intestine.

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.

- ✓ Superinfection happens because broad-spectrum antibiotics kill the normal flora. Microorganisms that are normally suppressed by the normal flora will then overgrow, causing superinfection, especially with organisms such as Candida or opportunistic infections.
- ✓ Therefore, broad-spectrum antibiotics should be used in multidrug-resistant infections and empirically.

Antifungal Drugs

B. Immunosuppression: AIDS, Immunosuppressant Drugs, Chemotherapy

- ✓ Older cytotoxic anticancer drugs cause direct injury not only to cancer cells, but also to normal cells such as hair follicles, mucosal cells, and immune cells, leading to immunosuppression and decreased WBC count. In contrast, newer anticancer drugs, such as monoclonal antibodies, are mechanism-directed and specifically target cancer cells.
- ✓ Chemotherapy causes immunosuppression mainly with the older type of cytotoxic anticancer drugs, not with the newer targeted anticancer drugs that act specifically on cancer cells.

C. Older population since a lot of functions in the body are low, making the more susceptible to systemic fungal infections

D. Diabetes mellitus causing immunosuppression and high glucose is a rich growth environment for fungi.

E. Advances in surgery (hygiene issues)

Amphotericin B

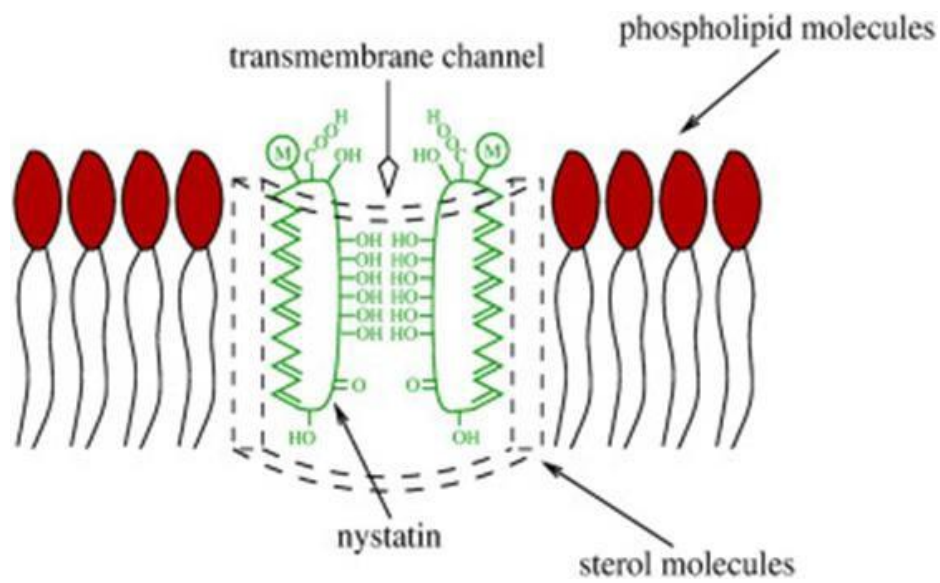
Most important drug in this class (Antifungal drugs)

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

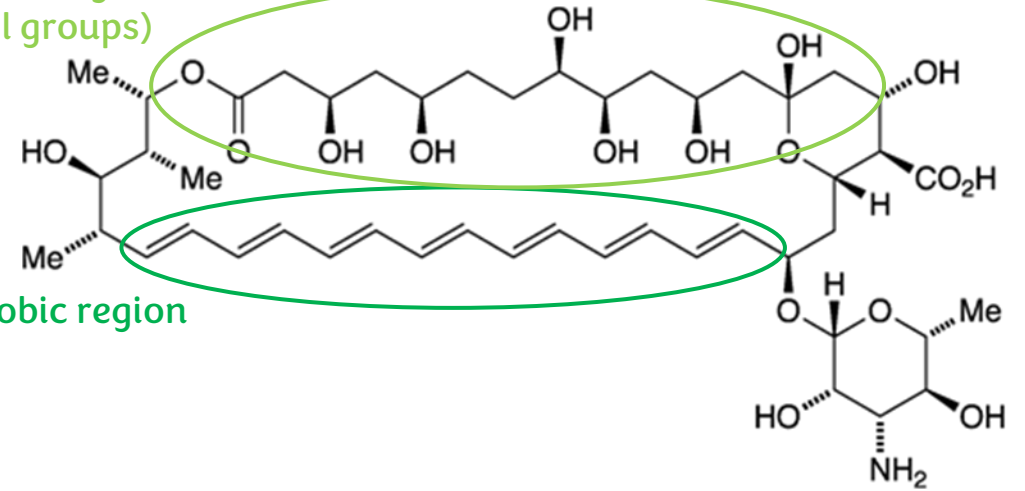
Mechanism of Action:

Ergosterol is the integral part of fungal membrane (like cholesterol in animal).

- Binds ergosterol of fungal cell membrane, more accurately cell wall → formation of amphotericin B associated-pores or transmembrane ion channels by the hydrophilic core of the molecule. See the next slide
- Binding is relatively specific to fungi and the protozoan parasite *Leishmania* spp.
 - ✓ drug of choice for leishmania is amphotericin B .
- The pore allows leakage of intracellular ions and macromolecules → cell death (Fungicidal).



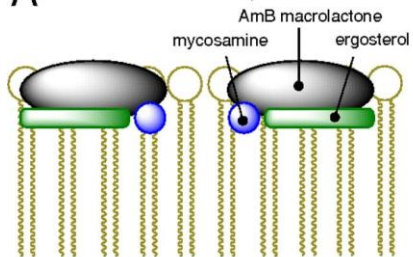
Hydrophilic region
(hydroxyl groups)



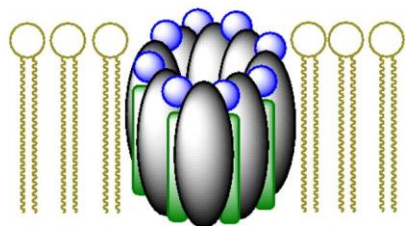
Amphotericin B is an **amphipathic molecule**, meaning that it has both hydrophobic and hydrophilic regions.

- ✓ The green molecule is Amphotericin B .
- ✓ The dotted line are ergosterol .
- ✓ The other are phospholipid .
- ✓ Amphotericin B binds to **ergosterol** in the fungal cell membrane through its hydrophobic region. After binding, multiple amphotericin molecules aggregate and form transmembrane pores (channels). In these pores, the hydrophilic portions of the drug face inward, creating a pathway through which small molecules enter and **leak out of the fungal cell**. This disrupts membrane permeability, leading to cell death.

A mechanism 1: sterol sequestration



B mechanism 2: membrane permeabilization



Additional picture

Amphotericin B

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

Pharmacokinetics:

- **Poor absorption after oral administration.**
 - ✓ It is unusual , but hydroxyl groups power overcome the hydrophobic double bond power which leads to low absorption .
- **Can be used PO for fungal infections of GIT (lumen). (Topical)**
- **It is complexed (added) with deoxycholate (bile acid) as a suspension for slow IV infusion.**
 - ✓ The dose is (1mg/kg of BW) , and when you reach 4grams total (cumulative dose or maximum dose) , you should never add any millimole .

Amphotericin B

- **Liposomal amphotericin B (new)** : packaging the drug in lipid delivery vehicles to reduce binding to human cell membranes
→ reduction of toxicity and permits use of larger doses.
 - ✓ It is nephrotoxic because it binds cholesterol in human cells and makes pores in renal tubules
- **Highly protein bound (>90%)**
 - ✓ It causes lower nephrotoxicity and allow us to give up to (3mg/KG of BW) .
- **Crosses BBB poorly, but penetration is improved when meninges are inflamed.**
 - ✓ It is the drug of choice for **cryptococcus neoformans meningitis** in combination with another drug later will be discussed .
- **$t_{1/2} \sim 15$ days** it takes 2 months (4 half lives) in order to be washed out from the body.

If you want to hear the doctor's discussion focusing on some clinical issues, such as folic acid deficiency in pregnant women and Glucose-6-phosphate dehydrogenase deficiency in females, click [here \[21:32 – 27:00\]](#). (I do not think it will be included in the exam material).

Amphotericin B

Adverse Effects:

A. Infusion-related toxicity:

- Due to release of (TNF- α , IL-1, IL2) proinflammatory cytokines which will cause this type of toxicity allergy like symptoms. This is why slow infusion will reduce these adverse effects.
- Fever, chills, muscle spasm, vomiting, headache and hypotension. *Allergy-like adverse effects but not allergy.*
- Can be reduced by slowing the infusion rate.

Amphotericin B

B. **Slower cumulative toxicity:**

1. **Nephrotoxicity: common (> 80% of patients)** (if the adverse effect reach 1% , it will be considered common, this effect occur in more than 80%) **and most serious, and constitute of:**
 - a) **Reversible component: represents prerenal failure leading to renal tubular injury.**
 - ✓ pores causes loss of water and this what causes the reversible injury which then converts to irreversible one.
 - 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 (Renal Dysfunction).**

Amphotericin B

2. Anemia due to reduced erythropoietin production (kidney is damaged).

❖ the doctor said: Inhibition of erythropoietin is not considered nephrotoxicity; rather, it reflects bone marrow suppression/failure, which lead to anemia. Do your own research

2. Others: Hepatic dysfunction, thrombocytopenia, anaphylaxis.

3. Seizures and chemical arachnoiditis after intrathecal

therapy. (when we give it for meningitis, and the same concept is applied in the use of penicillin G intrathecally for meningitis)

Amphotericin B

Antifungal Activity:

- Broad spectrum and fungicidal
- Clinically significant yeasts:
Candida albicans, cryptococcus neoformans.
- Endemic mycosis: *Histoplasma capsulatum, Blastomyces dermatitidis, Coccidioides immitis.*
- Pathogenic molds: *Aspergillus, fumigatus, Mucor.* (Mucor causes skin necrosis in the face)

Nystatin

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

Flucytosine

(Flu) for **fluoride** , we add it to make the drug more lipid soluble to cross the membranes more easily. Do your own research

- **Pyrimidine analog.**
- **Given PO & IV infusion.**
- **Narrow spectrum: effective against yeasts.** (candida and cryptococcus)
- **It has a synergistic effect when combined with amphotericin B for cryptococcal meningitis due to enhanced penetration through amphotericin B damaged arachnoid membranes in the nervous tissues.**

Flucytosine

Mechanism of action:

- It is taken up by fungal cells via cytosine permease.
- It is converted intracellularly (in the fungal cells) 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.

5-FdUMP: 5-Fluorodeoxyuridine monophosphate

FUTP: Fluorouridine triphosphate

Flucytosine

Pharmacokinetics:

- Well absorbed after oral administration (> 90%).
- Widely distributed throughout body fluids including CNS.
- 90% excreted unchanged (**without metabolism**) by the kidney by glomerular filtration.
- $t_{1/2}$ ~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.
 - ✓ Below therapeutic dose (resistance) , above it (toxicity) .
- 1. **GIT disturbances: enterocolitis and hepatitis.**
- 2. **Bone marrow depression: anemia, neutropenia, thrombocytopenia most common.**
- 3. **Alopecia.**

Azole Antifungal Drugs

They have the azole group

Classification:

- 1. Imidazoles: Ketoconazole** (azole inside it with other chemical characteristics make widespread nonspecific inhibition of cytochromes p450 in the body (increase a lot of drugs concentration), reduce corticosteroids and sex hormones synthesis for this it is not used systemically , it is used topically) ,
Miconazole & Clotrimazole
- 2. Triazoles: Itraconazole, Fluconazole & Voriconazole**
 - They are broad spectrum synthetic fungistatic antifungal agents

Azole Antifungal Drugs

In cryptococcal meningitis, we first use Amphotericin B with Flucytosine. In severe cases, Fluconazole may be added, and later it is used for maintenance therapy.

Antifungal Spectrum:

- **Many candida, *Cryptococcus neoformans*** (for cryptococcal meningitis we use fluconazole specifically, not other azoles), **the endemic mycoses (blastomycosis, coccidioidmycosis, histoplasmosis), and the dermatophytes.**
- **Itraconazole and voriconazole: *Aspergillus*, and amphotericin-resistant *Pseudallescheria boydii*.**

Azole Antifungal Drugs

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 Antifungal Drugs

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

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 (long term 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. High mortality rate
 3. Hepatitis
 4. Does not inhibit drug metabolism and steroidogenesis like ketoconazole → Less drug interactions. It does but less severe than ketoconazole.

Itraconazole

- **Undergoes extensive first-pass effect.**
- **Absorption is increased by food and low gastric pH.**
 - ✓ it needs acidity to be absorbed well.
- **A highly lipid soluble preparation for IV administration is available.**
- **Bioavailability is reduced by rifamycins (induction of drug metabolism).**
- **Interaction with hepatic microsomal enzymes is less than ketoconazole.**
- **Excreted in urine.**
- **Does not penetrate BBB.** Not used for meningitis.

Itraconazole

Therapeutic uses:

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

Itraconazole

Adverse Effects:

1. GIT disturbances , headache, dizziness
2. Hepatitis.
3. Hypokalemia
4. **Interacts with P450s (but less than ketoconazole):** Because of reduction of steroids synthesis which reduce sex steroids , it will cause **Impotence, and sexual dysfunction.** This adverse effects (Impotence, and sexual dysfunction) happen mainly in ketoconazole.
5. **Allergic reactions and exfoliative dermatitis.** Like fluconazole

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



PHARMACOLOGY

QUIZ

LECTURE 6

The quiz was designed in a clinical scenario-based style to make it more useful and practical.
If you answered all questions correctly, you are truly exceptional!

انشر

قال رسول الله ﷺ :

**ما من أيام أعظم عند الله
ولا أحب إليه العمل فيهن، من:
هذه الأيام العشر، فأكثرُوا فيهن
من التهليل والتكبير والتحميد**

تفسير:

من عمل صالحا في هذه الأيام (العشر من ذي الحجة) يضاعف له بما لا يضاعف للأعمال الصالحات في الأيام الأخرى، فهن العشر المباركات وهن الأيام المعلومات، فينبغي على المسلم أن يستفتح هذه العشر بتوبة نصوح إلى الله ﷻ وأن يجتنب المعاصي، ويستكثر من الطاعات والأعمال الصالحة، والذكر والتهليل والتكبير والتحميد.

- حديث صحيح -

الراوي: عبدالله بن عمر / المصدر: مسند أحمد: ٤ / ٩



Talam.Hadith



@Talam_Hadith



gplus.to/TalamHadith

#تعلم_حديث

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			