Athar Batch

Pharmacology

Lecture: 34

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Antifungals

Pharmacology and Toxicology
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Fungal infections →mycoses/ common infections especially skin infections.

Mycotic infections may involve only the skin (cutaneous mycoses extending into the epidermis), or may cause subcutaneous or systemic infections.

The same principles that apply to how we treat bacterial infections are applied to fungal infections also which means antifungal chemotherapy agents are designed to kill fungal cells

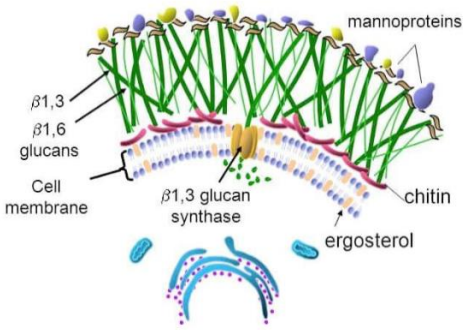
And the process of developing antibiotics was that we understand how bacteria function and their growth, proliferation, synthesizing their proteins, DNA and we target these processes.

The same thing will be done with fungal.

Overview

- Mycoses (mycotic infections) are often chronic.
- Can be cutaneous, subcutaneous or systemic.
- Relevant structural characteristics of fungi:

A. Eukaryotic
B. Rigid cell walls (chitin not peptidoglycan)
C. Cell membrane contains ergosterol not cholesterol

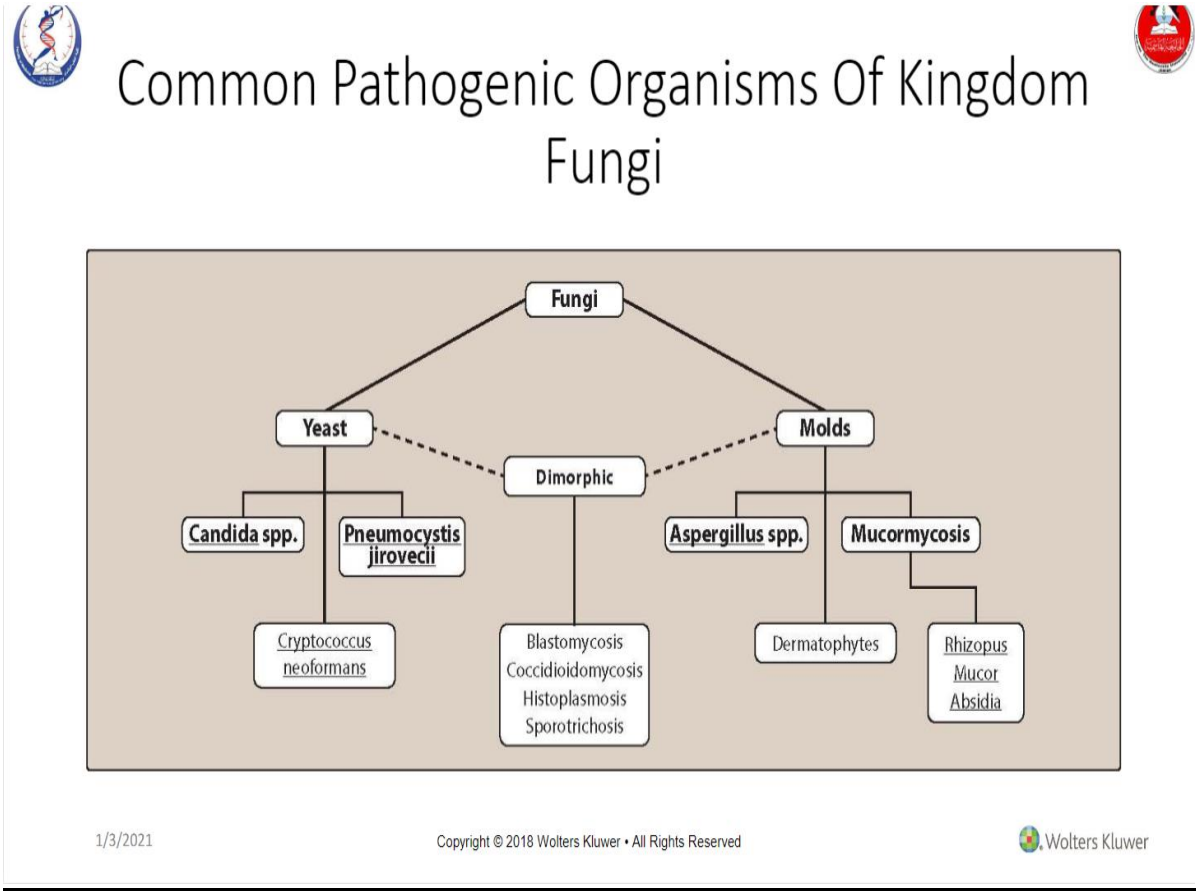


There are differences between bacterial and fungal cells

- Bacterial cells are prokaryotic / fungal cells are eukaryotic. (True nucleus) which means they are closer <u>but not completely the same</u> to humans and this is a challenge point in treatment of fungal infections → so we want to design drugs that is highly selective to fungal cells without causing damage to humans' cells.
- The fungal cells have cell walls but human do not have (*difference between fungal and humans*). <u>They share this feature with bacteria.</u>
- <u>Bacterial cell wall is composed of peptidoglycans **but** cell wall of fungal cell is consist of chitin.</u> → this is the reason why cell wall inhibitors of bacteria do not work on fungal cell walls.
- Plasma membrane of the fungal cell is more similar to human cell.
  - Cholesterol within the phospholipid bilayer makes the membrane more fluid-like structure.
  - Fungal cells have lipid in their cell membrane similar to cholesterol which is ergosterol as a main component of plasma

membrane. (*one of Differences between humans and fungal cells that can be used to design selective antifungal drugs)*.

- Not all fungi cause infections .



Candida spp. → -from yeast family

- The common type of candida spp. Is candida albicans which causes wide variety od infections from simple skin infections which is common to sever systemic infections that can lead to meningitis, pneumonia and JIROVECII PNEUMONIA which is opportunistic infection usually do not effect healthy individual it effects patients with AIDs. (Cotrimoxazole is drug of choice in this case).
- The problem of fungal infections that is become more systemic (severe infections).

جهاز المناعة تبعنا ذو كفاءة عالية بالتخلص من العدوى اذا كان المسبب فطريات يعني ما رح يوصلو لمرحلة انو ياثرو على اجهزة الجسم ولكن بالوقت الحالي زادت نسبة وفرصة انو الفطريات تسبب امراض خطيرة لانو صار في عنا علاج كيماوي مثلا لعلاج السرطان وصار عنا عمليات زراعة اعضاء الي بتتطلب انو تستخدم ادوية لتثبيط المناعة وكمان صار عنا مرض مناعي منتشر الي هو مرض الايدز الي بلش بالسبعينات والي هو اصلا مرض يستهدف الجهاز المناعي وبدمرو ف بصير الجسم عرضة لكل انواع العدوى .

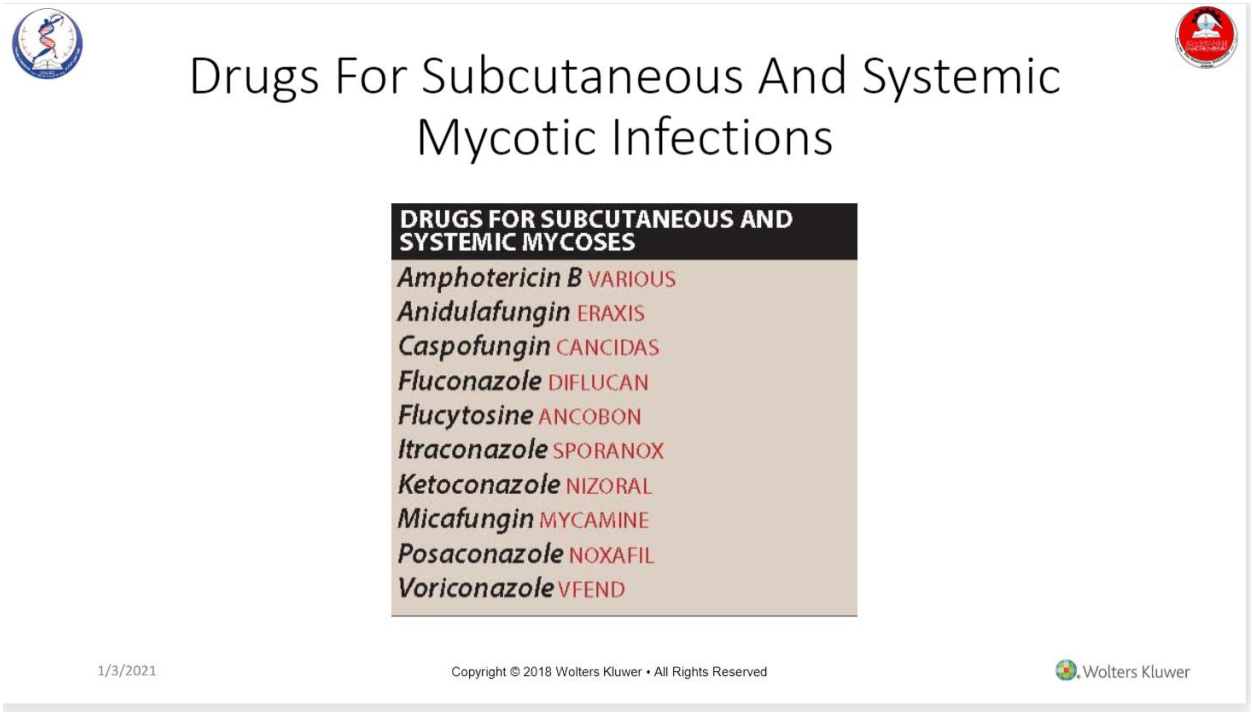
SO, IN THIS CASE WE NEED AGGRESSIVE ANTIFUNGAL DRUGS.

-Dimorphic category cause systemic infections.

-molds such as aspergillus spp. Can cause sever pneumonia.

-dermatophytes cause skin infections.

<u>- In this part of the lecture we will talk about systemic fungal infections.</u>

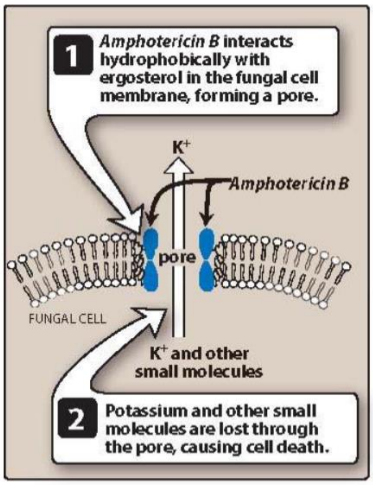


Amphotericin B

Amphotericin B

Mechanism of action

- Natural, produced by *Streptomyces nodosus*
- Binds to ergosterol forming pores that disrupts the membrane function
- Results in electrolyte leakage and cell death
- **Resistance**: decreased ergosterol content of the fungal membrane.



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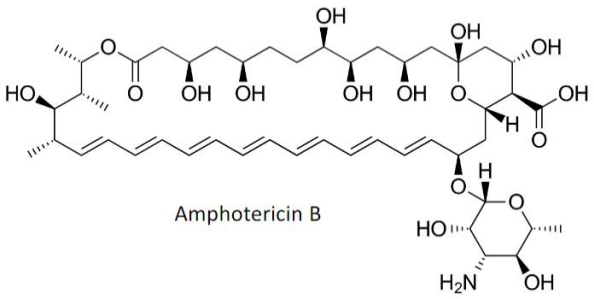
Amphotericin B

Antifungal spectrum

- Fungicidal/fungistatic
- Effective against a wide range:
- *Candida albicans*
- *Histoplasma capsulatum*
- *Cryptococcus neoformans*
- *Coccidioides immitis*
- *Blastomyces dermatitidis*
- *Aspergillus*



Amphotericin B

- Large bulky compound that is usually hydrophobic that interact with other lipids.
- Amphotericin B binds to ergosterol in the plasma membranes of fungal cells.
- it forms pores (channels) that require hydrophobic interactions between the lipophilic segments and the pores disrupt membrane function→allowing electrolytes (particularly potassium) and small molecules to leak from the cell
- Unfortunately, one of the most important things to describe that the cell is alive is the integrity of the membrane, once you lose the integrity of the membrane the cell will defiantly undergo one of the cell death pathways.
- The fungal cell can reduce it content of ergosterol as a way to resist this antifungal drug.

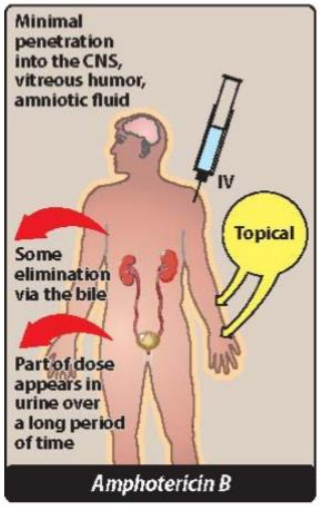
-Amphotericin B is a broad spectrum.

-the problem with this drug that is associated with toxicity so it transfer from the first drug of choice for the treatment of several life-threatening mycoses to the 2nd line drug.

Amphotericin B

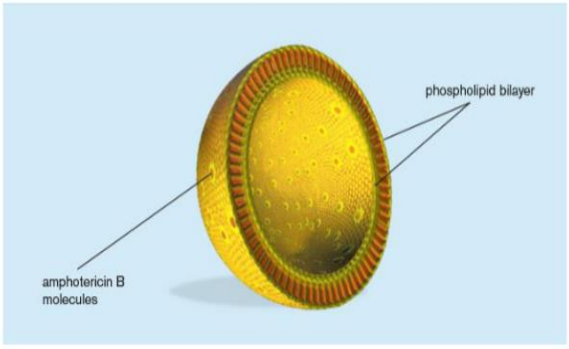
Pharmacokinetics

- Slow IV infusion
- Provided in liposomal preparations due to low water solubility (not cheap)
- Extensively protein-bound
- Well distributed but little into CSF
- Low levels of drug/metabolites are excreted in urine



-Amphotericin B is insoluble in water and must be co-formulated with sodium deoxycholate (conventional) or artificial lipids to form liposoms.

Amphotericin Liposome



Amphotericin B

Adverse effects

- Fever and chills

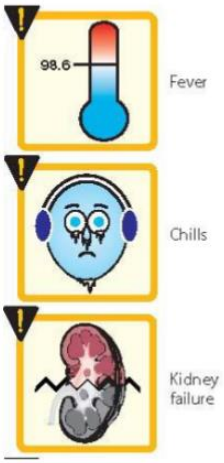
-1-3 hours after IV administration, might require corticosteroids/antipyretics

- Renal impairment

-glomerular/tubular injury

-azotemia can be worsened by other nephrotoxic agents. Like?

-liposome prep and infusions with saline lower the risk



Very common →fever and chills happen very fast after IV administration → inflammatory reaction in response to amphotericin injection and after 3 fever and chills will appear on the patient.

So, we use corticosteroid to treat them (anti-inflammatory) and antipyretics.

-patients may exhibit a decrease in glomerular filtration rate and renal tubular function because of this drug and the situation well be worsen if we use nephrotoxic drugs with this drug.

-nephrotoxic drugs such as aminoglycosides.

Amphotericin B

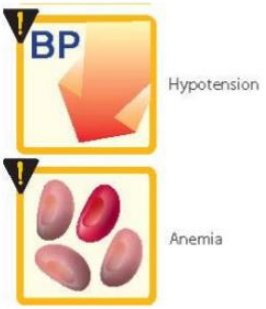
Adverse effects

- Hypotension

-accompanied with hypokalemia

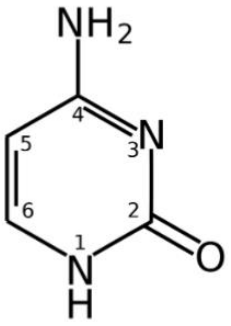
- Thrombophlebitis

-adding heparin might help

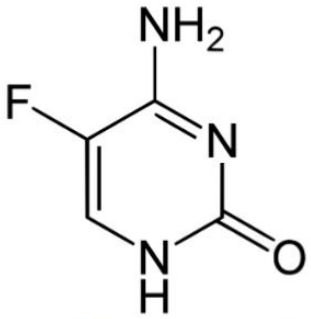


Antimetabolite Antifungals

Flucytosine (5-FC)



cytosine



Flucytosine (5-FC)

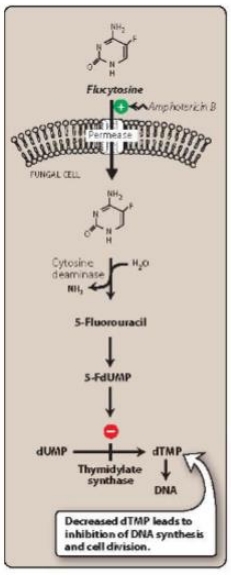
- This drug has the simplest structure.
- Flucytosine is a synthetic pyrimidine antimetabolite that is often used in combination with other antifungal agents

Flucytosine (5-FC)

- Often used in combination with amphotericin B for systemic mycoses and meningitis

Mechanism of action:

- Enters the cell through cytosine-specific permease
- Converted into 5-fluorouracil and 5-fuorodeoxyuridine 5'-monophosphate
- Disrupt nucleic acid and protein synthesis



- cytosine specific permease, an enzyme not found in mammalian cells.
- 5-florouracil alone is anticancer drug.

Flucytosine (5-FC)

Antifungal spectrum

- Fungistatic
- In combination with itraconazole for chromoblastomycosis
- In combination with amphotericin B for candidiasis and cryptococcosis
- Alternative to fluconazole for urinary candidiasis

-This drug is weak antifungal.

-not used as a first line drug and we don't use It alone because of high resistance.

-Amphotericin B increases cell permeability, allowing more 5-FCto penetrate the cell leading to synergistic effects.

Flucytosine (5-FC)

Mechanisms of resistance

- Decreased levels of any of the enzymes in the conversion of 5-FC to 5-FU
- Increased synthesis of cytosine
- Best if always used in combination

Oral absorption	complete
Plasma half-life	3-6 hrs
Volume of distribution	0.7-1l/kg (low)
Plasma protein binding	~12%

Pharmacokinetics

- Administered orally
- Excreted renally

Thinking Question

Homework: After the oral administration of 5-flucytosine, can levels of 5-FU be detected in the plasma of the patient? And why?

5-FU is detectable in patients and is probably the result of metabolism of 5-FC by intestinal bacteria.

Flucytosine (5-FC)

Adverse effects

- Reversible neutropenia, thrombocytopenia, bone marrow suppression
- Reversible hepatic dysfunction
- Gastrointestinal upset

❑N/V/D

❑Severe enterocolitis

The adverse effect is the same to the adv. Effect of 5-florouracil (chemotherapy).

Azole Antifungals

- Triazole Antifungals
- Imidazole Antifungals

Triazole antifungals → used to treat systemic fungal infections

Imidazole antifungals→ are applied topically for cutaneous infections.

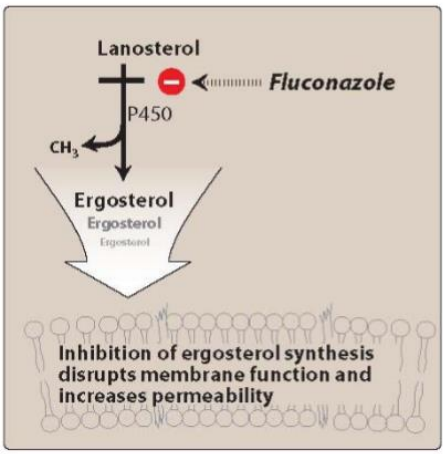
These drugs are most commonly used .

Triazole Antifungals

Drugs: fluconazole, itraconazole, posaconazole, voriconazole, isavuconazole

Mechanism of action

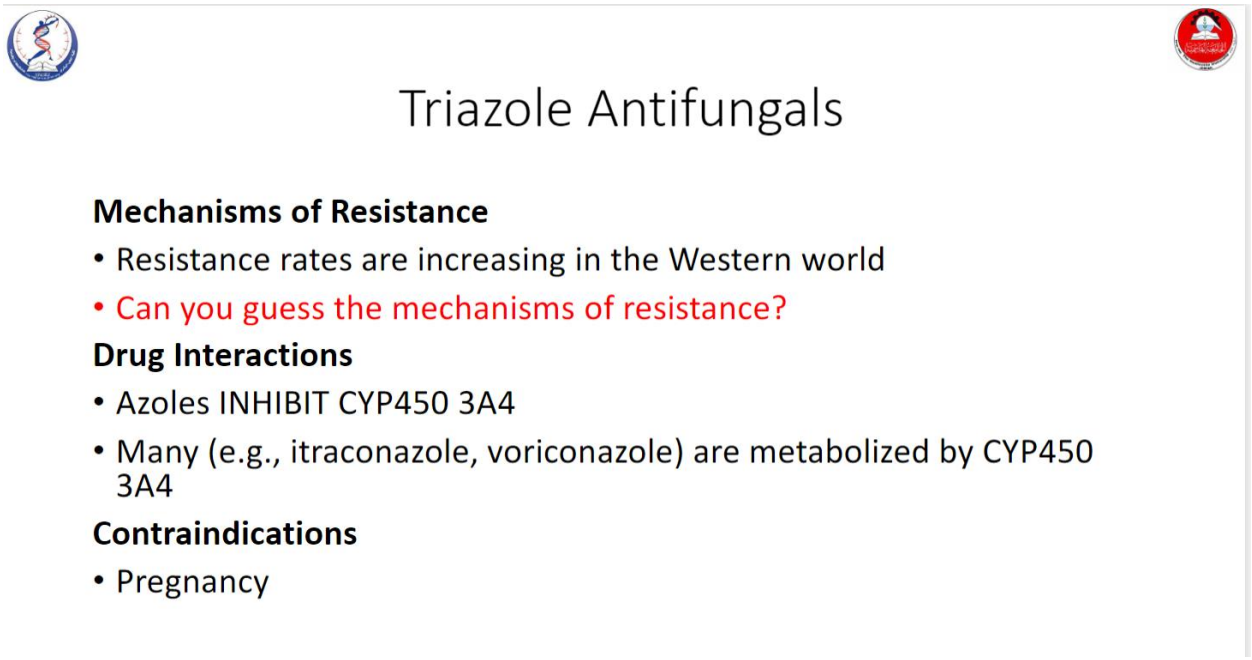
- Inhibit *14 α-demethylase* (a cytochrome P450 [CYP450] enzyme)
- Block the demethylation of lanosterol to ergosterol
- Disrupt cell membrane structure/function
- Disrupt fungal growth



-they interfere with ergosterol by targeting the synthesis of ergosterol.

The last step in ergosterol synthesis is catalyzed by 14 a-demethylase which is part of cyp450 family of fungi → when this enzyme is inhibited → the conversion of lanosterol to ergosterol will be blocked.

-cyp450 system in our liver can be effected by this drug.



The mechanisms of resistance:

- Efflux pumps
- Altering the target
- Increasing the 14 a-demethylase (substrate).

شرح النقطة الثانية بتفاعلات الادوية .. مع انو هاي الادوية بصير الها ميتابوليزم بالسيستم هاد الا انها ممكن تعمل تثبيط لشغل السيستم كيف طيب؟ يعني هلا لازم نعرف انو هاي الادوية وكمان ادوية اخرى بصيرلها عمليات ايض عنفس هاد السيستم ف بتنافسو مع بعض هاي الادوية ف ممكن الادوية الي بنحكي عنها هلا بهاد السلايد تثبط عمل السيستم للادوية الاخرى اذا كان تركيزها اعلى .. يارب تكونو فهمتو 😊

Fluconazole

- Least active amongst the group
- Spectrum limited to yeast and dimorphic fungi
- Used for the prophylaxis against invasive fungal infections in transplant patients
- Second drug of choice for *Cryptococcus neoformans* after amphotericin B and 5-FC
- Effective against most forms of mucocutaneous candidiasis
- Given as a single-dose oral treatment vulvovaginal candidiasis

-its spectrum limited to yeasts and some dimorphic fungi.

Itraconazole

- Synthetic triazole
- Broader antifungal spectrum than fluconazole
- Drug of choice for the treatment of blastomycosis, sporotrichosis, paracoccidioidomycosis, and histoplasmosis
- Rarely used for candida
- Given as two oral doses
- Hepatic metabolism
- **Adverse effects:** N/V, rash, hypokalemia, hypertension, edema, hepatotoxicity, negative inotropic effect

Posaconazole

- synthetic triazole
- Broad-spectrum antifungal
- Available orally and IV
- Used for the treatment of candida and aspergillus infections in severely immunocompromised patients
- Used for invasive systemic fungal infections
- Not metabolized by CYP450, instead via glucuronidation
- **Adverse effects:** gastrointestinal upset, drug-drug interactions (potent inhibitor of CYP3A4)

Comparison of Different Triazoles

	FLUCONAZOLE	*ITRACONAZOLE*	*VORICONAZOLE*	*POSACONAZOLE*
SPECTRUM OF ACTIVITY	+	++	+++	++++
ROUTE(S) OF ADMINISTRATION	Oral, IV	Oral	Oral, IV	Oral, IV
ORAL BIOAVAILABILITY (%)	95	55 (solution)	96	Variable
DRUG LEVELS AFFECTED BY FOOD OR GASTRIC PH	No	Yes	No	Yes
PROTEIN BINDING (%)	10	99	58	99
PRIMARY ROUTE OF ELIMINATION	Renal	Hepatic CYP3A4	Hepatic CYP2C19, 2C9, 3A4	Hepatic Glucuronidation
CYTOCHROME P450 ENZYMES INHIBITED	CYP3A4, 2C9, 2C19	CYP3A4, 2C9	CYP2C19, 2C9, 3A4	CYP3A4
HALF-LIFE ($t_{1/2}$)	25 hours	30–40 hours	Dose Dependent	20–66 hours
CSF PENETRATION	Yes	No	Yes	Yes
RENAL EXCRETION OF ACTIVE DRUG (%)	> 90	< 2	< 2	< 2
TDM RECOMMENDED (RATIONALE)	No	Yes (Efficacy)	Yes (Efficacy and Safety)	Yes (Efficacy)

Summary of Triazoles Uses

Fluconazole

- Limited use
- Second drug of choice for cryptococcus neoformans
- Also for mucocutaneus candidiasis

Itraconazole

- Drug of choice for blastomycosis, histoplasmosis and paracoccidioidomycosis
- Not for candida

Voriconazole

- Drug of choice for aspergillosis