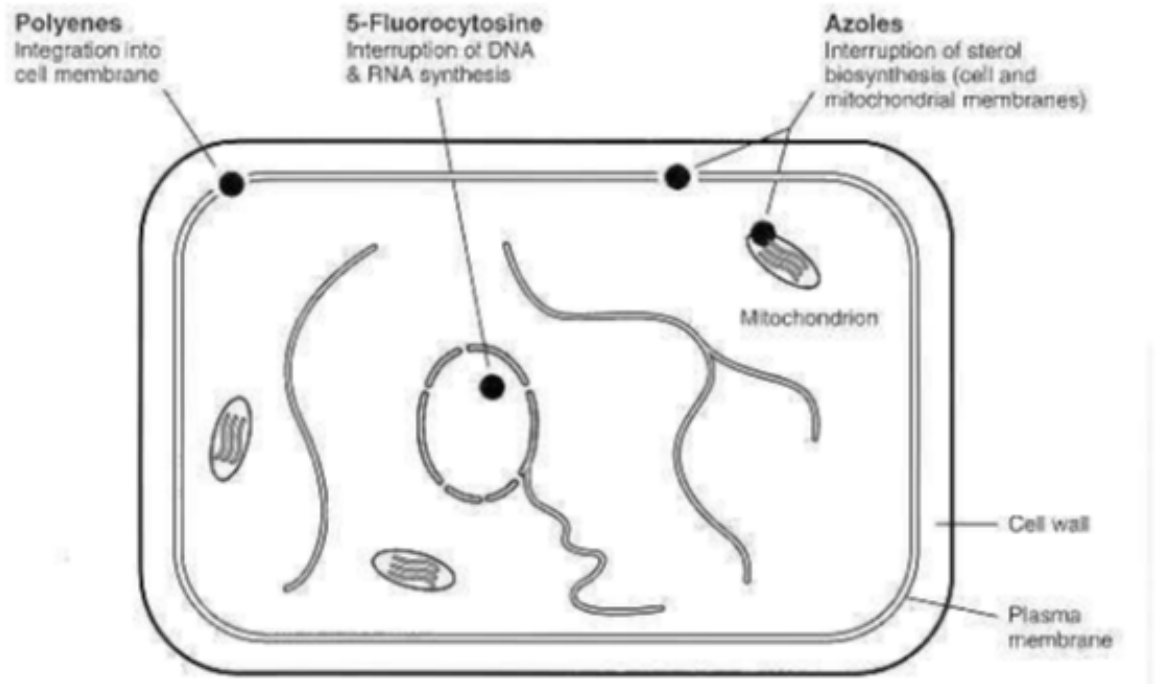
Pharmacology – Antifungals

Fungal Characteristics

- Rigid cell wall composed of Chitin (N Acetylglucosamine) (Bacterial cell wall is composed of peptidoglycan)
- Plasma or cell membrane which contains ergosterol (Human cell membrane is composed of cholesterol) (Selectivity of some anti-fungal agents)
- Fungi are eukaryotic organisms that live as saprobes or parasites, they have nucleus, well-defined nuclear membrane, and chromosomes.

Fungi vs Bacteria

- They are complex organisms in comparison to bacteria (Prokaryotic cells have no nuclear membranes and no mitochondria)
- Therefore, Anti-Bacterial agents are not effective in fungal infections and vice versa.



Infections: (Mycoses), these infections (whether superficial or systemic) are common in patients with weak immune system, examples include:

1) Patients with AIDS

2) Debilitated patients

3) Patients underwent organ transplantation and on immunosuppressants

4) Patients under anti-cancerous therapy

Fungal Infections are either **Superficial / Systemic**:

Superficial Infections: affecting skin, nails, scalp, or mucous membranes. They can be further classified into:

1) **Dermatomycoses**: infections of the skin, hair, and nails, caused by dermatophytes. The most common dermatomycoses are due to Tinea organisms which are also known as ringworms.

2) **Superficial candidiasis** (Candida is a common normal flora of the mouth, skin, intestines, and vagina), in this type, the fungus candida infects the mucous membranes of the mouth (Oral thrush), or the vagina (Vaginal thrush) or the skin.

Systemic Infections: affecting deeper tissues and organs. They include:

1) Systemic candidiases

2) Cryptoccocal meningitis or endocarditis

3) Pulmonary aspergillosis

4) Blastomycosis

5) Histoplasmosis

6) Coccidioidomycosis

7) Paracoccidioidomycosis and more!

Drug Family	MOA	MOR/NOTES	Examples
Polyenes	Bind to ergosterol in fungal plasma membrane leading to formation of pores and hence increase permeability of the membrane. This allows leakage of intracellular ions and enzymes especially loss of intracellular k causing death to the fungus. They bind selectively to ergosterol in fungus but not to cholesterol in mammalian plasma membranes.	**1) Decreased ergosterol content of the fungal membrane.** **2) Impaired binding to ergosterol**	**Amphotericin B** **Nystatin** **Natamycin**
Azoles	They inhibit cytochrome P450 demethylase enzyme, which is important for formation of ergosterol, this inhibition disrupts membrane structure and function, thereby inhibiting fungal growth (Fungistatic)	**Mutation in the gene encoding for demethylase**	1) Imidazole (contain2nitrogen's): - **Ketoconazole**, - **Miconazole**, - **Clotrimazole** 2) Triazoles (contain3nitrogen's): - **Itraconazole**, - **Fluconazole**
Allylamines	Inhibit fungal squalene epoxidase, thereby. decreasing the synthesis of ergosterol. This plus the accumulation of toxic amounts of squalene result in the death of the fungal cell. For this to happen to human squalene epoxidase, it requires much larger doses (This provides selectivity to fungi)	**NOT LISTED**	**Terbinafine** **Naftifine** **Butenafine**
Echinocandins	Interfere with the synthesis of the fungal cell wall by inhibiting the synthesis of D-Glucan, leading to lysis and fungal cell death.	**NOT LISTED**	**Caspofungin** **Micafungin** **Anidulafungin**
Mitosis Inhibitors	It inhibits fungal mitosis by inhibiting mitotic spindle formation. It binds to tubulin, interfering with microtubule function, thus inhibiting mitosis.	**NOT LISTED**	**Griseofulvin**
DNA Synthesis Inibitors (Antimetabolites)	It enters fungal cells by permease (an enzyme not found in mammalian cells) and is then converted by a series of steps to (5-fluorodeoxyuridine 5-monophosphate). This false nucleotide inhibits thymidylate synthase, thus depriving the fungus of thymidylic acid; an essential DNA component.	**Note*: Amphotericin B increases cell permeability thus allowing more Flucytosine to penetrate the cell (Synergism)**	**Flucytosine**

Tables time ☹️

Drug	Amphotericin B	Nystatin	Natamycin	Flucytosine
Notes	*A **macrolide antibiotic** *Poorly absorbed orally, thus useful for fungal infection of the GI tract. ***Drug of choice** for **most systemic infections**, given as **slow IV infusion** *Locally used in corneal ulcers (ophthalmic oint), arthritis (intra articular) and bladder irrigation. ***Penetration through BBB is poor** but increases in inflamed meninges ***Excreted slowly via kidneys**, traces found in urine for months after cessation of drug *t1/2= 15 days.	*It is a **polyene macrolide**, similar in structure to Amphotericin B and with same MOA ***Too toxic for systemic use** *Not absorbed from GIT, skin or vagina, therefore **administered orally to prevent or treat superficial candidiasis of mouth, esophagus or intestinal tract**.	*It is a **macrolide polyene antifungal** *Not absorbed when given orally *Available in cream and **ophthalmic eye drops**	*It is **synthetic pyrimidine antimetabolite** that is often used in **combination with Amphotericin B** *As we said earlier, it is **fungistatic** ***It is absorbed rapidly and well from GIT *Widely distributed in body and **penetrates well into CSF**
Clinical Uses	*Effective in **Candida infection** and **cutaneous leishmaniasis** Available in Cream, Lotion, Ointment and Vaginal Suppository dosage forms	*Effective in **Candida albicans infection** and available in cream, ointment, powder forms (Cutaneous) , oral suspension and tablets (GIT colonization with candida) and vaginal tablets (Vaginal candidiasis).	*Especially effective in treating keratitis, an **infection of the eye.** *Effective against **Aspergillus** and **Fusarium corneal infections** *Also effective in Candida, Cephalosporium and Penicillium	*Has useful activity against **Candida and Cryptococcus** *Effective in **combination with Itraconazole** for treating **chromoblastomycosis** and **with Amphotericin B** for treating **cryptococcosis** ***Highly effective in **cryptococcal meningitis in AIDS patients**
Side effects	***Most serious is renal toxicity** , which occurs in 80 % of patients. *Hypokalaemia in 25 % of patients *Hypomagnesaemia *Anemia & thrombocytopenia *Impaired hepatic function *Anaphylactic shock *New formolations~(Liposomal preparations) were found to reduce toxicity * N/V/weight loss/fever/joint muscle pain	NOT MENTIONED	NOT MENTIONED	***Reversible neutropenia**, **thrombocytopenia,** and **occasional bone marrow depression** *N/V, diarrhea, **severe enterocolitis** *Reversible hepatic enzyme elevation in 5% of patients

Drug	Ketoconazole	Fluconazole	Itraconazole	Voriconazole
Notes	*The first orally active **narrow spectrum** azole available for the treatment of **systemic mycoses** *Well absorbed orally (only way of administration) **as acidic environment favors its dissolution** *Bioavailability is decreased with H2 Blocker, proton pump inhibitors and antacids and absorption is impaired with food *84% bound to plasma proteins ***Doesn't enter CSF** *Metabolized **extensively in liver by cyp450** and the inactive metabolites are excreted in **bile** *Induction of microsomal enzymes by other drugs like **Rifampin reduces its concentration** *Potentiates the toxicity of Cyclosporine's, phenytoin, Tolbutamide, warfarin. *Warfarin and Rifampin increase its metabolism and hence decrease concentration (shorten its DOA) *H2 blockers, antacids, proton pump inhibitors and Sucralfate decrease its absorption *decreases ergosterol in the fungal membrane, **thus reduces the fungicidal action of Amphotericin B**	*A **Triazole**, damages the fungal cell membrane by inhibiting the enzyme **demethylase** ***Selective, cause less endocrine disturbances, **penetrate to CNS** ***Completely absorbed from GIT, thus great bioavailability orally (equals IV!) **Not altered** by **food** or **gastric acidity** *Great bioavailability in CSF *Has the least effect on hepatic microsomal enzymes (Less common drug interactions) *Renally excreted *Safe prophylactically in bone marrow transplant patients *Resistance is not a problem **except in AIDS patients.**	*A Triazole, damages the fungal cell membrane by inhibiting the enzyme demethylase *Selective, cause less endocrine disturbances, **penetrate to CNS** ***Administered orally as well as IV *Food increases its absorption *It is **highly lipid soluble**, it is well distributed to bone, sputum and adipose tissue *Itraconazole is **extensively metabolized** in liver by **cytochrome P450** (CYP 3A4) *Highly **bound to plasma proteins** ***Does not penetrate CSF** adequately as compared to Fluconazole *Large loading dose recommended in deep mycosis (steady state takes 4 days)	*A Triazole, damages the fungal cell membrane by inhibiting the enzyme demethylase *Selective, cause fewer endocrine disturbances, **penetrate to CNS** ***A new drug available in oral and IV dosage forms ***It is similar to Itraconazole but more potent ***High biological availability when given orally ***Hepatic metabolism predominant** ***Inhibition of P450 is less**
Clinical Uses	*Active against many fungi, including Histoplasma, Blastomyces, Candida, and Coccidioides, but **not aspergillus species.** *Available in oral tablets, cream, and shampoo (highly effective in treating seborrheic dermatitis) *Could be used in the management of Cushing's syndrome and cancer of prostate	***Drug of choice in cryptococcal meningitis and Coccidioidomycosis** ***Drug of choice in coccidial meningitis** ***Candidiasis, cryptococcosis *It has also activity against histoplasmosis, blastomycosis, Sporotrichosis and ring worm **but Itraconazole is better in the same dose** ***Not effective in Aspergillosis** ***Effective in systemic mycosis, mucocutaneous candidiasis, and other cutaneous infections**	*Less useful against meningeal infections (Lower CSF concentrations) *Intravenously reserved only in serious infections. ***Effective in systemic mycosis, mucocutaneous candidiasis, and other cutaneous infections**	***Effective in systemic mycosis, mucocutaneous candidiasis, and other cutaneous infections**
Side effects	*Inhibits adrenal and gonadal steroidogenesis (Cortisol, progesterone, estrogens, testosterone) which leads to menstrual irregularities in females, loss of libido, impotency, gynecomastia ***Main toxicity is Liver - may prove FATAL!** *N/V/anorexia/**hair loss** ***Teratogenic**, contraindicated in pregnancy just like all azoles. *Cyclosporin and Phenytoin increase its toxicity	*N/V/headache/**Skin rash**/ abdominal pain/ diarrhea *Reversible alopecia *Hepatic failure that may lead to death *Teratogenic	*N/V *hypertriglyceridemia, *hypokalemia *increased aminotransferase, *hepatotoxicity and rash (leads to drug discontinuation)	***Reversible visual disturbances**

Drug	Posaconazole	Caspofungin	Tolnaftate	Terbinafine	Griseofulvin
Notes	*Is a new oral, broad spectrum antifungal agent similar to Itraconazole *Given orally and well tolerated *Like Ketoconazole, Posaconazole can cause an elevation of liver function tests and it inhibits cytochrome P 450 system	*It is a member of the Echinocandin class of antifungal drugs *Not active orally, **given IV** ***Highly bound to serum proteins *Slowly metabolized by hydrolysis and N acetylation *Eliminated equally by urinary and fecal route	*Available in as cream, gel, powder and topical solution.	*A synthetic allylamine *Fungicidal with limited activity (Only candida albicans and dermatophytes) *As compared to Griseofulvin it is **better tolerated** and **requires shorter duration of therapy** *Protein binding more than 99 % in plasma and metabolized by P450 system *Well absorbed orally, bioavailability affected by first pass metabolism *Slowly released from tissues, 200-400hrs half-life compared to an initial of 12! (As it accumulated in the skin, nails and fat) *Accumulates in breast milk, ****should not be given to lactating mothers** *Metabolites excreted in urine and its clearance is reduced in moderate renal and hepatic impairment; **Not recommended in azotemia or hepatic failure** *** **Rifampicin decreases** and **Cimetidine increases** its blood concentrations	*Remember, it's a mitotic inhibitor *Very insoluble in water *It has largely been **replaced by Terbinafine** for treatment of **dermatophytic infections of the nails** because of toxicity *It is fungistatic and has narrow spectrum. *It's absorption **increases with fatty meal** *Extensively metabolized in liver and **induces CYP 450** ***Barbiturates decrease the absorption from GIT *The drug has to deposit first in keratin of growing skin, nail and hair to get rid of disease (doesn't heal the already formed nail) *It is ineffective topically it has to be given orally
Clinical uses	*It was approved to prevent Candida and Aspergillus infections in severely immunocompromised patients and for the treatment of oropharyngeal candidiasis *Could be used in the treatment of fungal infections caused by Mucor species and other zygomycetes	***Especially useful for aspergillus and candida**	*Effective in **most cutaneous mycosis** ***Ineffective against Candida** *In **Tinea pedis** cure rate is around 80%	***Drug of choice for treating dermatophytes** ***Effective for the **treatment of onychomycosis** (fungal infections of the nail) - 6 weeks for fingernail, 12 weeks for toenail	*It is useful for dermatophytes *Mycotic diseases of skin, hair (particularly for scalp) and nail *It is also highly effective in athletes' foot *Not effective in subcutaneous or deep mycoses *1 month for scalp, 6-9 months for nails, at least a year for toenails.
Side effects	*The most common side effects observed were gastrointestinal symptoms (nausea, vomiting, diarrhea, and abdominal pain) and headaches	*Adverse effects include nausea, vomiting, flushing and liver dysfunction ***Very expensive**	****	***The drug accumulates in skin, nails, and fat** ***Severely hepatotoxic (liver failure may lead to death) *The drug accumulates in skin, nails and fat ***GIT disturbances** ***Taste and visual disturbance** ***Severe allergic reactions** ***Transient rise in serum liver enzymes**	*Headache ***Peripheral neuritis, lethargy, mental confusion, impairment in performance of routine task** *Fatigue, **vertigo**, syncope, **blurred vision**

Miscellaneous and some notes:

***Ciclopirox Olamine**: An effective drug in Tinea versicolor (cream, lotion, solution, shampoo)

* **Naftifine** (cream; gel) and **Terbinafine** (cream, oint, gel, spray, solution) Effective in **Tinea pedis** (Athlete's foot), **Tinea cruris**, and **Tinea corporis**

***Topical Azoles**: (**Miconazole**, **Clotrimazole**, **Butoconazole** and (*finally*) **Terconazole**)
Are topically active drugs that are only rarely administered parenterally because of their SEVERE toxicity. Their mechanism of action and antifungal spectrum are the same as those of Ketoconazole.

- Topical use of azoles is associated with **contact dermatitis**, **vulvar irritation**, and **edema**
- Miconazole is a potent **inhibitor of Warfarin metabolism** and has produced bleeding in Warfarin treated patients **even when it is applied topically**. No significant difference in clinical outcomes is associated with any azole or Nystatin in the treatment of vulvar candidiasis.

Dr really wants us to focus on the special things for each drug, such as the nephrotoxicity of Amphotericin B, hepatotoxicity that's the common side effect of most antifungals, doses and numbers are not required, yellow is important (What's yellow in the slides is yellow here too)

Good luck!
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