Antifungal Drugs

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Fungi are eukaryotic and have rigid cell walls composed largely of chitin rather than peptidoglycan, which is a characteristic component of most bacterial cell walls. The fungal cell membrane contains ergosterol rather than the cholesterol found in mammalian membranes. Fungal infections are generally resistant to antibiotics, and, conversely, bacteria are resistant to antifungal agents. Fungal infection is termed mycosis.

Types of fungal infections:

■ **Mucocutaneous** (superficial) infections

- Dermatophytes: cause infection of skin, hair, and nails: eg. tinea capitis (scalp), tinea cruris (grain), tinea pedis (foot), onychomycosis (nails).

- Yeasts cause infections of moist skin and mucous membranes: e.g. Candida albicans causing oral, pharyngeal, vaginal, & bladder Infections.

■ **Systemic mycoses**: are fungal infections affecting internal organs. It occurs in immune-compromised patients e.g. cryptococcosis, and aspergillosis (Lung).

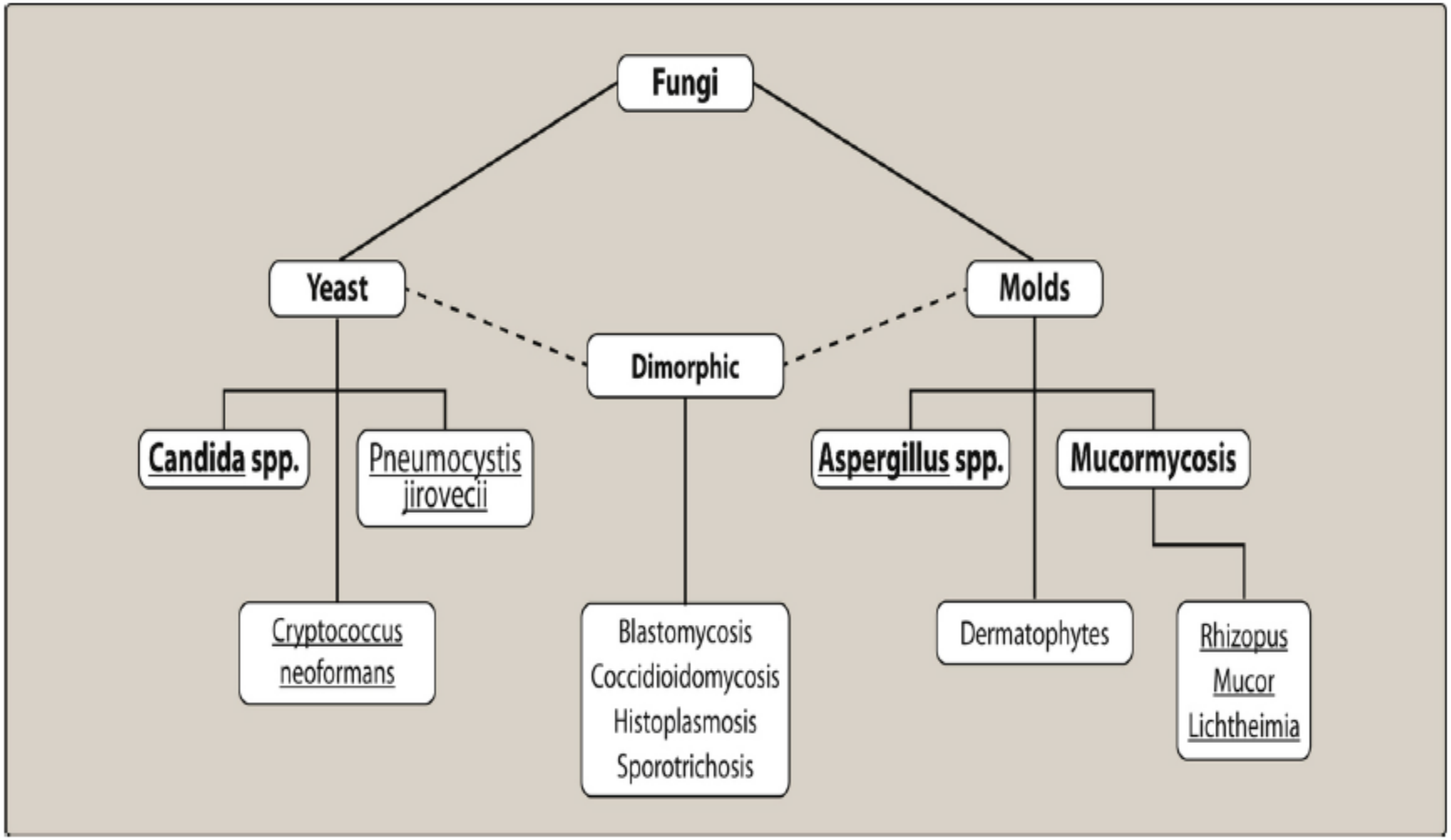

Figure-1 The common pathogenic organisms of the Kingdom Fungi

Classification of antifungal drugs

Antifungals can be grouped into three classes based on their site of action:

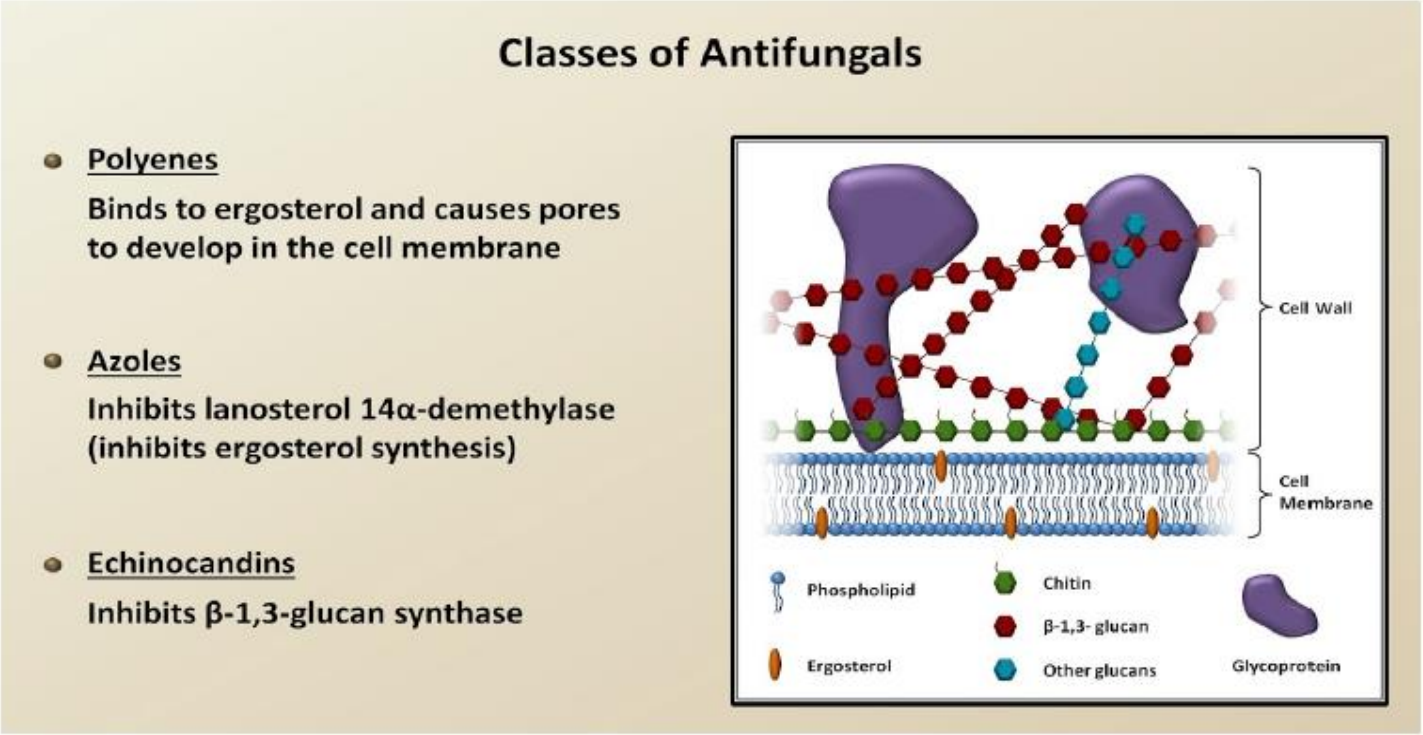

Figure 2: Classification of antifungal drugs (Polyenes such as amphotericin B bind to ergosterol in the fungal membrane causing disruption of membrane structure and function. Azoles inhibit the synthesis of ergosterol in the endoplasmic reticulum of the fungal cell. Flucytosine is converted within the fungal cell to 5-fluorouracil which inhibits DNA synthesis.)

Drugs for Subcutaneous and Systemic Mycotic Infections

A. Amphotericin B

Amphotericin B, a naturally occurring polyene antifungal, is derived from Streptomyces nodosus. Drug for life-threatening mycoses.

The mechanism of action involves binding to ergosterol in fungal cell membranes, forming pores that disrupt membrane function, leading to the leakage of electrolytes and small molecules and ultimately causing cell death. Amphotericin B exhibits both fungicidal and fungistatic properties , It is effective against a broad spectrum of fungi, including Candida albicans, Histoplasma capsulatum, Cryptococcus neoformans, Coccidioides immitis, Blastomyces dermatitidis, and various strains of Aspergillus. Additionally, it is utilized in treating leishmaniasis.

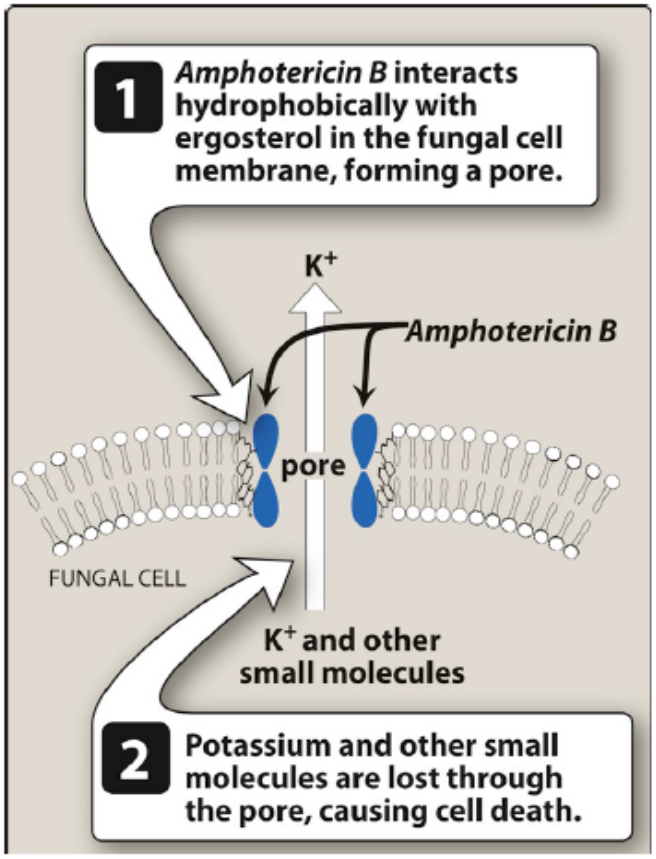

Figure-3-(Amphotericin B) mechanism of action

Resistance: Reduced ergosterol content in the fungal membrane.

Pharmacokinetics:

Administered through slow IV infusion, amphotericin B is insoluble in water and requires co-formulation with sodium deoxycholate or artificial lipids. The drug is extensively bound to plasma proteins, distributed throughout the body, and excreted primarily in the urine over an extended period, with limited penetration into certain body fluids.

Adverse Effect

low therapeutic index. Fever and chills: These occur most commonly 1-3 hours after starting the IV administration to mitigate these effects, premedication with a corticosteroid or antipyretic is recommended. Renal impairment: Azotemia is exacerbated by other nephrotoxic drugs, such as aminoglycosides, cyclosporine, and vancomycin, although adequate hydration can decrease its severity. Hypotension companied by hypokalemia; potassium fluctuations may occur in patients taking digoxin requiring potassium supplementation. Thrombophlebitis: Adding *heparin* to the infusion can alleviate this problem.

B. Antimetabolite antifungals

Flucytosine (5-FC) is a synthetic pyrimidine antimetabolite that is often used in combination with other antifungal agents.

Mechanism of action: 5-FC enters the fungal cell via a cytosine-specific permease, an enzyme not found in mammalian cells. It is subsequently converted to a series of compounds, including 5-fluorouracil (5-FU) and 5-fluorodeoxyuridine 5′-monophosphate, which disrupt nucleic acid and protein synthesis **([Note: Amphotericin increases cell permeability, allowing more 5-FC to penetrate the cell leading to synergistic effects**.].

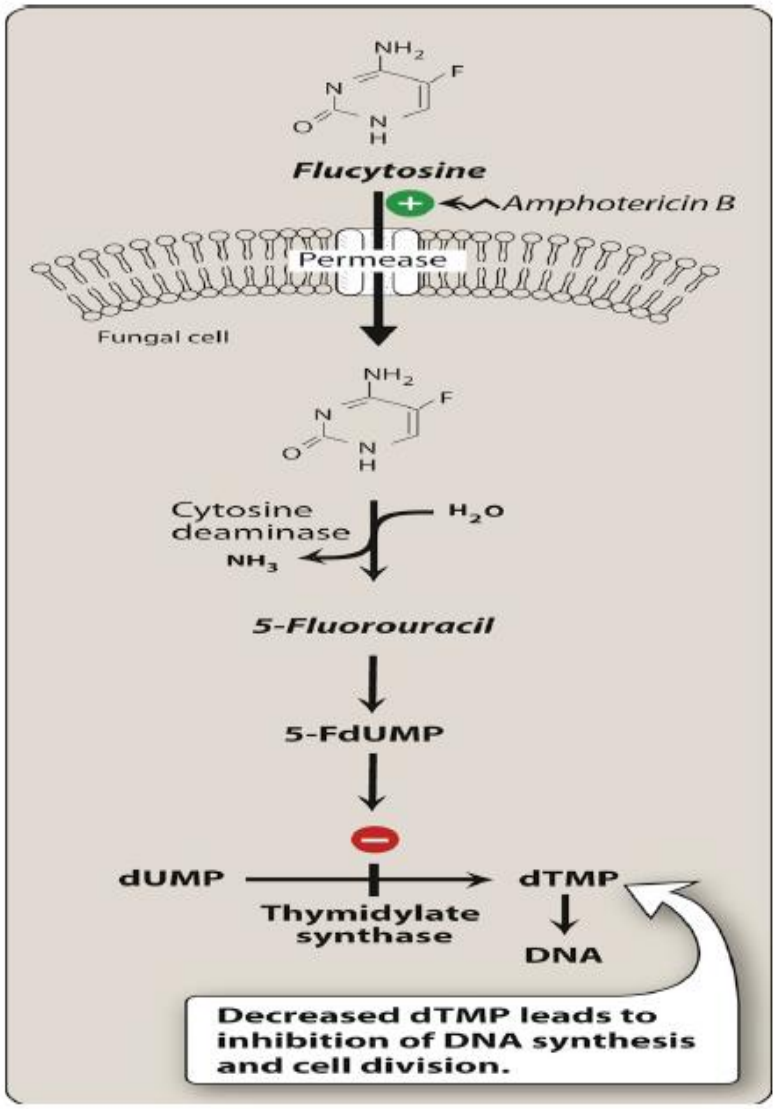

Figure-4- Flucytosine mechanism of action

Antifungal spectrum: 5-FC is fungistatic. It is effective in combination with itraconazole for treating chromoblastomycosis. It is also used in combination with amphotericin B for the treatment of systemic mycoses and for meningitis caused by C. neoformans and C. lbicans

Flucytosine is an alternative treatment for Candida urinary tract infections when fluconazole is not suitable, although resistance may develop with repeated use. Resistance is linked to decreased enzyme levels in the conversion of flucytosine to active metabolites. Combining flucytosine with another antifungal agent lowers the emergence of resistant fungal cells, emphasizing that it is not employed as a standalone antifungal drug.

Pharmacokinetics: 5-FC is efficiently absorbed orally and widely distributed in the body water, with good penetration into the cerebrospinal fluid (CSF). The presence of 5-FU in patients is likely due to the metabolism of 5-FC by intestinal bacteria. Both the parent drug and its metabolites are excreted through glomerular filtration, necessitating dose adjustments in individuals with impaired renal function.

Adverse effects: *5-FC* causes reversible neutropenia, thrombocytopenia, and dose-related bone marrow depression. Reversible hepatic dysfunction with elevation of serum transaminases has been observed. Nausea, vomiting, and diarrhea are common, and severe enterocolitis may occur.

C. Azole antifungals

Azole antifungals consist of two classes—imidazoles and triazoles—with similar mechanisms of action and spectra of activity. However, their pharmacokinetics and therapeutic uses differ. Imidazoles are typically used topically for cutaneous infections, while triazoles are administered systemically for treating or preventing both cutaneous and systemic mycoses. The systemic triazole antifungals include *fluconazole*, *itraconazole*, *posaconazole*, *voriconazole*, and *isavuconazole*.

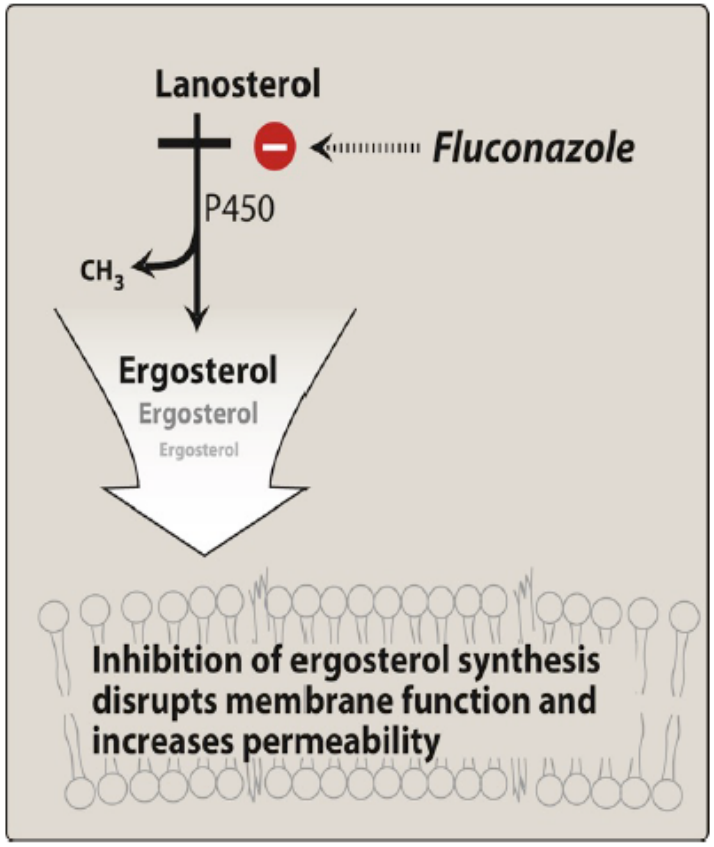

Figure 5: ***Mode of action of azole antifungals.***

Mechanism of action: Azoles function as fungistatic agents by inhibiting 14-α-demethylase, a cytochrome P450 enzyme. This inhibition prevents the demethylation of lanosterol to ergosterol, disrupting the biosynthesis of ergosterol. Consequently, this disruption compromises the structure and function of the fungal membrane, leading to the inhibition of fungal cell growth.

Resistance

Mutations in the14-α-demethylase gene that lead to decreased azole binding and efficacy. efflux pumps that pump the drug out of the cell or have reduced ergosterol in the cell wall.

Contraindications: Azoles are considered teratogenic, and they should be avoided in pregnancy unless the potential benefit outweighs the risk to the fetus.

D. Fluconazole

Fluconazole, the initial triazole antifungal, exhibits the lowest activity among its counterparts, primarily targeting yeasts and certain dimorphic fungi. Notably, it is ineffective against aspergillosis or mucormycosis. The drug demonstrates high efficacy against C. neoformans and specific Candida species like C. albicans and Candida parapsilosis. Nevertheless, resistance is a concern, particularly with other species such as Candida krusei and Candida glabrata.

Uses: Fluconazole is employed in bone marrow transplant recipients to prevent invasive fungal infections. It is the preferred treatment for C. neoformans following initial therapy with amphotericin B and flucytosine. Additionally, fluconazole is utilized for treating candidemia, coccidioidomycosis, and various forms of mucocutaneous candidiasis. For vulvovaginal candidiasis, it is commonly administered as a single oral dose.

Fluconazole is available in oral and IV dosage formulations. It is well absorbed after oral administration and distributes widely to body fluids and tissues. The majority of the drug is excreted in urine, and doses must be reduced in patients with renal dysfunction.

Adverse effects: nausea, vomiting, headache, and skin rashes.

E. Itraconazole

Itraconazole, a synthetic triazole, exhibits a broad antifungal spectrum compared to fluconazole. It is the preferred treatment for blastomycosis, sporotrichosis, paracoccidioidomycosis, and histoplasmosis. Available in capsule or oral solution form, the capsule is best taken with food and an acidic beverage for enhanced absorption, while the solution is more effective on an empty stomach. The drug distributes well in various tissues, including bone and adipose tissues. Extensively metabolized by the liver, both the drug and its inactive metabolites are excreted in urine and feces.

Itraconazole: potent inhibitor of CYP3A4 and coadministration of other agents metabolized by CYP3A4 should be avoided, if possible.

Adverse effects

Nausea, vomiting, diarrhea, rash (more pronounced in immunocompromised patients), hypokalemia, hypertension, edema, and headache. Liver toxicity is a concern, particularly when administered concurrently with other hepatotoxic drugs. Itraconazole has a negative inotropic effect, making it unsuitable for patients with evidence of ventricular dysfunction, such as those with heart failure.

F. Posaconazole

Posaconazole, a synthetic triazole similar to itraconazole, is a broad-spectrum antifungal available in oral suspension, tablet, and IV formulations. Treating and preventing invasive Candida and Aspergillus infections in severely immunocompromised patients, it also demonstrates efficacy against infections caused by Scedosporium and Mucorales due to its broad spectrum. **Posaconazole** has low oral bioavailability and requires administration with food. Unlike other azoles, it is not metabolized by CYP450 but is eliminated via glucuronidation. Drugs that increase gastric pH (for example, proton pump inhibitors) may decrease the absorption of oral posaconazole and should be avoided. Concomitant use of posaconazole with various agents, including ergot alkaloids, atorvastatin, alprazolam, citalopram, and risperidone, is contraindicated due to posaconazole's potent inhibition of CYP450 3A4.

G. Voriconazole

Voriconazole, a synthetic triazole related to fluconazole, serves as a broad-spectrum antifungal agent available in IV and oral forms. It has replaced amphotericin B as the preferred treatment for invasive aspergillosis and is approved for invasive candidiasis, as well as serious infections caused by Scedosporium and Fusarium species. **Voriconazole** exhibits high oral bioavailability, effective tissue penetration, and undergoes extensive metabolism by CYP2C19, CYP2C9, and CYP3A4 isoenzymes, with the metabolites primarily excreted via urine.

Side Effect

High concentrations of the drug have been linked to adverse effects such as visual and auditory hallucinations, an increased risk of hepatotoxicity, hypokalemia, and reversible visual impairment upon discontinuation. Voriconazole is **contraindicated** with many drugs that are inducers of CYP450 (for example, *rifampin*, *rifabutin* and carbamazepine,

H. Isavuconazole

Isavuconazole is a broad-spectrum antifungal agent available in both intravenous and oral forms, supplied as the prodrug isavuconazonium. The prodrug rapidly converts to isavuconazole in the blood. Isavuconazole is effective against invasive aspergillosis and invasive mucormycosis, sharing a similar spectrum of activity with voriconazole. It exhibits high bioavailability orally and distributes well into tissues. Metabolism involves CYP3A4, CYP3A5, and uridine-diphosphate-glucuronosyltransferases. Coadministration with potent CYP3A4 inhibitors and inducers is contraindicated due to drug interactions. Additionally, Isavuconazole inhibits the CYP3A4 isoenzyme, leading to increased concentrations of drugs that are substrates of CYP3A4.

Side Effect: Nausea, vomiting, diarrhea, and hypokalemia.

	Fluconazole	*Itraconazole*	*Isavuconazole*	*Voriconazole*	*Posaconazole*
Spectrum of activity	+	++	+++	+++	++++
Route(s) of administration	Oral, IV	Oral	Oral, IV	Oral, IV	Oral, IV
Oral bioavailability (%)	95	55 (solution)	98	96	Variable
Drug levels affected by food or gastric pH	No	Yes	No	No	Yes
Protein binding (%)	10	99	99	58	99
Primary route of elimination	Renal	Hepatic CYP3A4	Hepatic CYP3A4, UGT	Hepatic CYP2C19, 2C9, 3A4	Hepatic glucuronidation
Cytochrome P450 enzymes inhibited	CYP3A4, 2C9, 2C19	CYP3A4	CYP3A4	CYP2C19, 2C9, 3A4	CYP3A4
Half-life ($t_{1/2}$)	25 h	30–40 h	130 h	Dose dependent	20–66 h
CSF penetration	Yes	No	Yes	Yes	Yes
Renal excretion of active drug (%)	>90	<2	45	<2	<2
TDM recommended (rationale)	No	Yes (efficacy)	No	Yes (efficacy and safety)	Yes (efficacy)

Figure 6: Major different between azole drugs.

I. Echinocandins (*Caspofungin*, *micafungin*, and *anidulafungin*)

Echinocandins, such as caspofungin, micafungin, and anidulafungin, disrupt fungal cell wall synthesis by inhibiting β(1,3)-d-glucan synthesis, leading to cell lysis and death. These drugs, administered intravenously once daily, are particularly effective against Aspergillus and various Candida species, even those resistant to azoles. Micafungin stands out for not requiring a loading dose. Despite minimal activity against other fungi, they can induce adverse effects like fever, rash, nausea, and phlebitis. Slow IV infusion is recommended to prevent histamine-like reactions, especially flushing, associated with rapid administration.

1. Caspofungin: is a first-line treatment for invasive candidiasis, including candidemia, and a second-line option for invasive aspergillosis in patients unable to tolerate amphotericin B or an azole. Dosing adjustments are necessary for moderate hepatic dysfunction, and caution is advised when co-administering with CYP450 enzyme inducers. Concurrent use with cyclosporine is discouraged due to a high risk of elevated hepatic transaminases.

2. Micafungin and anidulafungin:

Micafungin and anidulafungin are recommended as first-line treatments for invasive candidiasis, including candidemia. Micafungin also serves for prophylaxis against invasive Candida infections in patients undergoing hematopoietic stem cell transplantation. Notably, both drugs are not substrates for CYP450 enzymes and do not pose any associated drug interactions.

DRUGS FOR CUTANEOUSMYCOTIC INFECTIONS

Cutaneous infections caused by mold-like fungi are known as dermatophytes or tinea. These infections, classified by the affected site (e.g., tinea pedis for feet infections), are commonly referred to as "ringworm" when presenting as round red patches with clear centers. The primary fungi responsible for cutaneous infections are Trichophyton, Microsporum, and Epidermophyton. Additionally, skin infections can be caused by yeasts such as Malassezia and Candida.

A. Squalene epoxidase inhibitors

These agents act by inhibiting squalene epoxidase, thereby blocking the biosynthesis of ergosterol, an essential component of the fungal cell membrane (Figure-7). Accumulation of toxic amounts of squalene results in increased membrane permeability and death of the fungal cell.

A. Squalene epoxidase inhibitors

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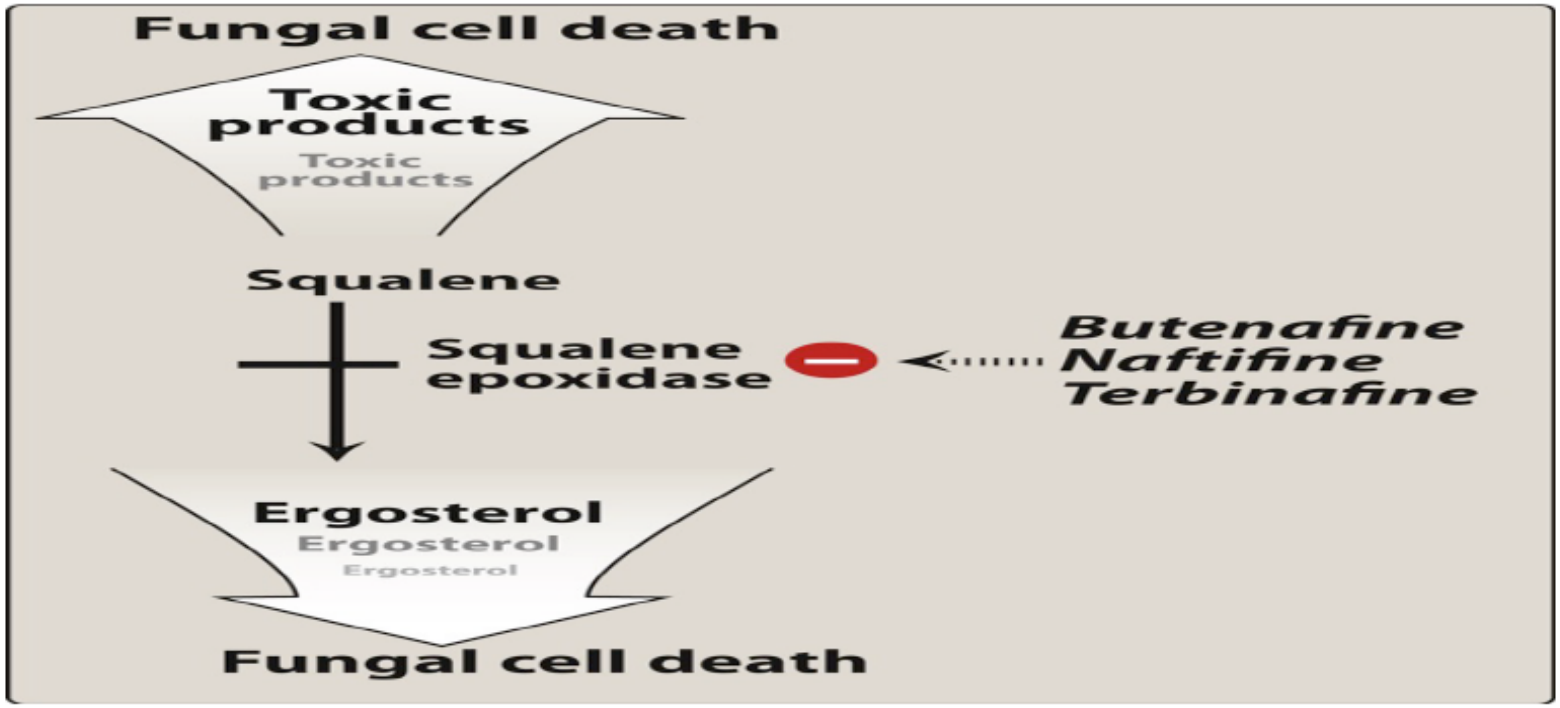

Figure-7- Mode of action of squalene epoxidase inhibitors.

1. Terbinafine:

Oral terbinafine is the preferred treatment for dermatophyte onychomycoses (nail fungal infections), offering better tolerance, shorter therapy duration (usually around 3 months), and increased effectiveness compared to itraconazole or griseofulvin, particularly against Trichophyton. This oral antifungal is also applicable for tinea capitis (scalp infection), requiring systemic therapy. Conversely, topical terbinafine in various forms is employed for treating tinea pedis, tinea corporis, tinea cruris, and tinea versicolor caused by Malassezia furfur, with a typical treatment duration of 1 week.

Antifungal spectrum

Terbinafine is effective against Trichophyton and Malassezia. While it may potentially work against Candida, Epidermophyton, and Scopulariopsis.

Pharmacokinetics:

Terbinafine, available for oral and topical use, exhibits 40% bioavailability orally due to first-pass metabolism. It is highly protein-bound and accumulates in the skin, nails, and adipose tissue, leading to a prolonged half-life of 200 to 400 hours. Metabolized by various CYP450 isoenzymes, primarily excreted through urine, it should be avoided in patients with significant renal or hepatic impairment. Terbinafine inhibits CYP2D6 isoenzyme, posing a risk of adverse effects when used concurrently with CYP2D6 substrates.

Adverse effects:

The oral formulation of the medication is associated with common adverse effects such as diarrhea, dyspepsia, nausea, headache, and rash. Additionally, taste and visual disturbances may occur, along with elevated levels of serum hepatic transaminases. On the other hand, the topical formulations are generally well tolerated.

2. Naftifine:

Naftifine is effective against Trichophyton, Microsporum, and Epidermophyton. It is utilized topically in the form of cream and gel for treating tinea corporis, tinea cruris, and tinea pedis, with a typical treatment duration of 2 to 4 weeks.

3. Butenafine:

Butenafine is effective against Trichophyton rubrum, Epidermophyton, and Malassezia. It is employed topically, in cream form, similar to naftifine, for the treatment of tinea infections.

B. Griseofulvin

Griseofulvin disrupts the mitotic spindle and inhibits fungal mitosis, making it effective for dermatophytosis of the scalp and hair. However, it has been largely replaced by oral terbinafine for onychomycosis treatment. Griseofulvin is fungistatic, necessitating a prolonged treatment duration (e.g., 6-12 months for onychomycosis), determined by the rate of healthy skin and nail replacement. The drug is absorbed well with high-fat meals, concentrating in skin, hair, nails, and adipose tissue. Griseofulvin induces hepatic CYP450 activity, impacting drug metabolism, contraindicating its use in pregnancy and porphyria patients.

C. Nystatin

Nystatin, a polyene antifungal similar to amphotericin B in structure, chemistry, mechanism of action, and resistance profile, is employed for treating cutaneous and oral Candida infections. Due to minimal absorption from the gastrointestinal tract and potential systemic toxicity, it is not administered parenterally. Instead, it is given orally for oropharyngeal candidiasis, intravaginally for vulvovaginal candidiasis, or topically for cutaneous candidiasis, using methods such as "swish and swallow" or "swish and spit."

D. Imidazoles,

Imidazoles a class of azole derivatives, includes various agents like butoconazole, clotrimazole, econazole, ketoconazole, miconazole, oxiconazole, sertaconazole, sulconazole, terconazole, and tioconazole. These topical agents exhibit

broad activity against Epidermophyton, Microsporum, Trichophyton, Candida, and Malassezia. They are utilized for treating conditions such as tinea corporis, tinea cruris, tinea pedis, oropharyngeal and vulvovaginal candidiasis. However, their topical use may lead to contact dermatitis, vulvar irritation (with vaginal preparations), and edema. Clotrimazole and miconazole are available in troche and buccal tablet forms, respectively, for treating thrush. While oral ketoconazole is rarely used due to severe side effects, topical formulations are effective against conditions like tinea versicolor and seborrheic dermatitis.

E. Efinaconazole

Efinaconazole is a topical triazole antifungal agent designed for treating toenail onychomycosis caused by T. rubrum and Trichophyton mentagrophytes, with a prescribed treatment duration of 48 weeks.

F. Ciclopirox

Ciclopirox, a pyridine antimycotic, disrupts the synthesis of DNA, RNA, and proteins by inhibiting the transport of essential elements in fungal cells. Ciclopirox exhibits activity against various fungi, including Trichophyton, Epidermophyton, Microsporum, Candida, and Malassezia. It comes in multiple formulations, such as shampoo for seborrheic dermatitis, and cream, gel, or suspension for conditions like tinea pedis, tinea corporis, tinea cruris, cutaneous candidiasis, and tinea versicolor. Additionally, onychomycosis can be addressed with the nail lacquer formulation of ciclopirox.

G. Tavaborole

Tavaborole is a topical solution used to treat toenail onychomycosis by inhibiting an aminoacyl-transfer ribonucleic acid synthetase, thereby preventing fungal protein synthesis. It is effective against T. rubrum and T. mentagrophytes, requiring a 48-week treatment period.

H. Tolnaftate

Tolnaftate, a topical thiocarbamate, disrupts hyphae and inhibits mycelial growth in susceptible fungi, specifically targeting Epidermophyton, Microsporum, and Malassezia furfur. However, it is not effective against Candida. Tolnaftate is employed in the treatment of conditions such as tinea pedis, tinea cruris, and tinea corporis, and is available in solution, cream, and powder forms.