Al-Mustaqbal University

Pharmacology I

3rd stage

Antifungal Drugs (179- 190)

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Antifungal Drugs

- 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: e.g. 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).

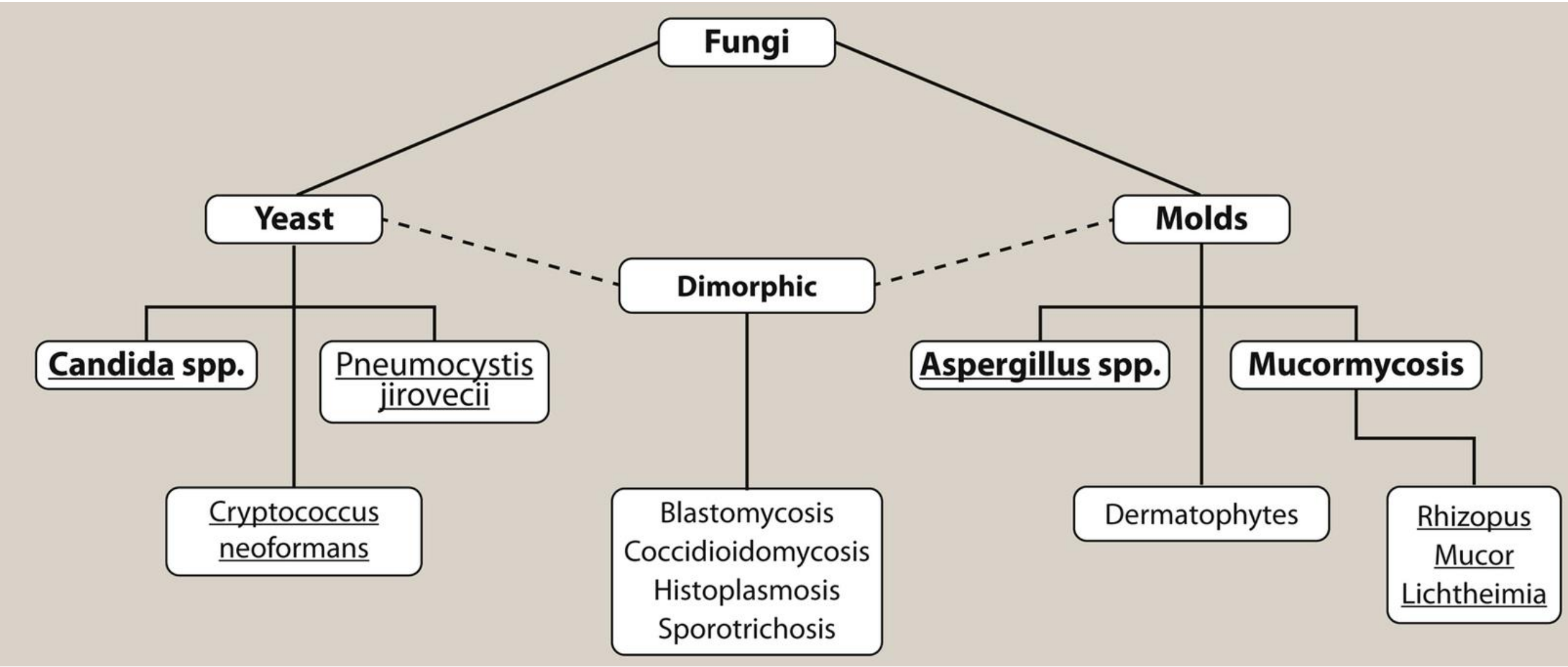


Figure-1 The common pathogenic organisms of the Kingdom Fungi

Classification of antifungal drugs

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

1- (Polyenes: such as amphotericin B bind to ergosterol in the fungal membrane causing disruption of membrane structure and function.

2- 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.)

3- Echinocandins: inhibits β-1,3-glucan synthase.

Antifungal Drugs

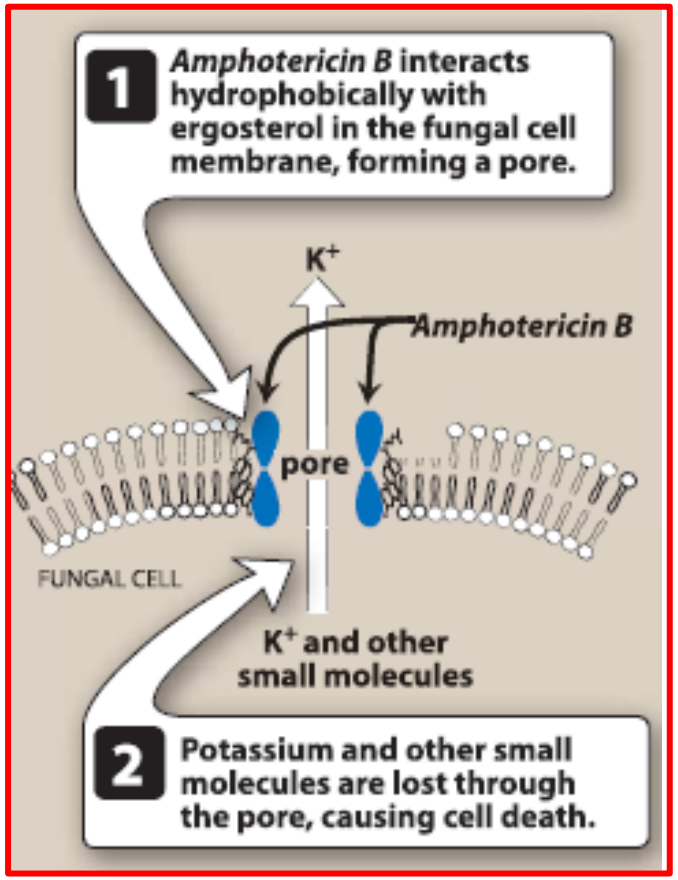
• DRUGS FOR SUBCUTANEOUS AND SYSTEMIC MYCOTIC INFECTIONS

I- Amphotericin B is a naturally occurring polyene antifungal produced by Streptomyces nodosus.

In spite of its toxic potential, amphotericin B remains the drug of choice for the treatment of several life-threatening mycoses.

MOA: as right figure.

Resistance: by decreased ergosterol content of the fungal membrane.



Antifungal spectrum:

- 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 Aspergillus.
- Additionally, it is utilized in treating leishmaniasis.

Pharmacokinetics:

- Administered through slow IV infusion,
- It 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 effects: Amphotericin B has a low therapeutic index.

1. Fever and chills: 1-3 hours after starting IV administration but can be prevented by corticosteroid or an antipyretic.

2. Renal impairment: Azotemia is exacerbated by other nephrotoxic drugs, such as aminoglycosides, cyclosporine, and vancomycin, although adequate hydration can decrease its severity.

3. Hypotension: Hypotension companied by hypokalemia; potassium fluctuations may occur in patients taking digoxin requiring potassium supplementation..

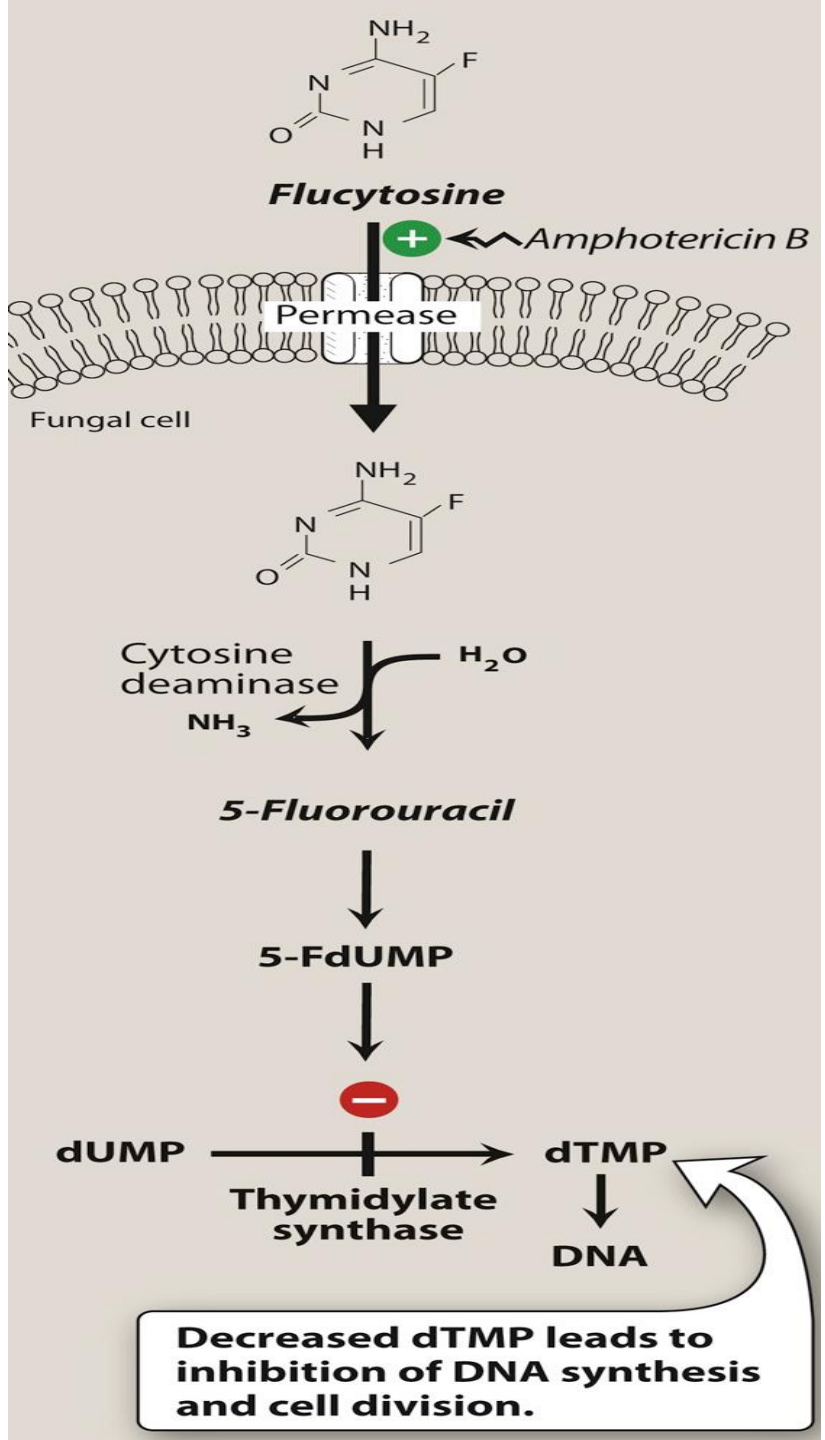
4. Thrombophlebitis: Adding heparin to the infusion can alleviate this problem.

II- Antimetabolite antifungals

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

MOA: 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 B increases cell permeability, allowing more 5-FC to penetrate the cell leading to synergistic effects.



Antifungal spectrum:

- 5-FC is fungistatic.
- It is used in combination with amphotericin B for the treatment of systemic mycoses and for meningitis caused by C. neoformans and C. albicans.
- It is effective in combination with itraconazole for treating chromoblastomycosis.
- Flucytosine is an alternative treatment for Candida urinary tract infections when fluconazole is not suitable,

Resistance: Resistance may occur due to decreased levels of any of the enzymes in the conversion of 5-FC to 5-FU and other metabolites.
Resistance decrease with combination with another antifungal. emphasizing that it is not employed as a standalone antifungal drug.

Pharmacokinetics:

- 5-FC is well oral absorption,
- widely distributed in the body water,
- it penetrates well into the 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.

III- Azole antifungals

There are two different classes of azole, imidazoles and triazoles. with similar mechanisms of action and spectra of activity.

imidazoles are applied topically for cutaneous infections, whereas triazoles are administered systemically for the treatment or prophylaxis of cutaneous and systemic mycoses.

The systemic triazole antifungals include: fluconazole, itraconazole, posaconazole, voriconazole, and isavuconazole.

MOA: Azoles are predominantly fungistatic. They inhibit 14 α demethylase (a cytochrome P450) thereby blocking the demethylation of lanosterol to ergosterol . The inhibition of ergosterol biosynthesis disrupts fungal membrane structure and function, which, in turn, inhibits fungal cell growth.

Resistance:

1- mutations in the 14-α demethylase gene that lead to decreased azole binding and efficacy.

2- fungi develop efflux pumps.

3- 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.

a- Fluconazole:

It is the least active of all triazoles, with most of its spectrum limited to yeasts and some dimorphic fungi.

It is highly active against Cryptococcus neoformans and Candida albicans and Candida parapsilosis.

Fluconazole is used for prophylaxis against invasive fungal infections in recipients of bone marrow transplants.

It is the drug of choice for Cryptococcus neoformans after induction therapy with amphotericin B and flucytosine and is used for the treatment of candidemia and coccidioidomycosis.

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.
Its doses must be reduced in patients with renal dysfunction.
Adverse effects: nausea, vomiting, headache, and skin rashes.

b- Itraconazole (broad antifungal spectrum compared to fluconazole)

Itraconazole is a drug of choice for the treatment of blastomycosis, sporotrichosis, paracoccidioidomycosis, and histoplasmosis.

Capsule and tablet of itraconazole should be taken with food, and ideally an acidic beverage, to increase absorption. While oral solution should be taken on an empty stomach, as food decreases the absorption.

The drug distributes well in most tissues, including bone and adipose tissues. Itraconazole is extensively metabolized by the liver, and the drug and inactive metabolites are excreted in the 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, rash, hypokalemia, hypertension, edema, and headache. Liver toxicity can also occur, especially when given with other hepatotoxic drugs. Itraconazole has a negative inotropic effect and should be avoided in patients with evidence of ventricular dysfunction, such as heart failure.

c- Posaconazole (broadspectrum antifungal structurally similar to itraconazole)
It is available as an oral suspension, oral tablet, or IV formulation.
- Treating and preventing invasive Candida, and Aspergillus infections in severely immunocompromised patients also against Scedosporium, Mucorales.

The drug has low oral bioavailability and should be given with food.
Unlike other azoles, posaconazole 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.

Due to its potent inhibition of CYP450 3A4, concomitant use of posaconazole with a number of agents (for example, ergot alkaloids, atorvastatin, citalopram, and risperidone) is contraindicated.

d- Voriconazole, a synthetic triazole related to fluconazole, is a broad-spectrum antifungal agent that is available in both IV and oral dosage forms.

Voriconazole has replaced amphotericin B as the drug of choice for invasive aspergillosis and invasive candidiasis as well as Scedosporium and Fusarium.

Voriconazole exhibits high oral bioavailability, effective tissue penetration.

It is extensively metabolized by CYP450 2C19, 2C9, and 3A4 isoenzymes, and the metabolites are primarily excreted via the 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.

Because of significant interactions, use of voriconazole is contraindicated with many drugs (for example, rifampin, rifabutin and carbamazepine).

e- Isavuconazole is a broad-spectrum antifungal agent, which is supplied as the prodrug isavuconazonium in IV and oral dosage forms.

Isavuconazonium is rapidly convert to isavuconazole in the blood.

Spectrum: similar to voriconazole and is approved for invasive aspergillosis and invasive mucormycosis (similar spectrum of activity with voriconazole).
lsavuconazonium has high bioavailability after oral administration and distributes well into tissues.
The drug is metabolized by CYP450 3A4/5 and uridine diphosphate-glucuronosyl transferases. Coadministration of isavuconazole with potent CYP450 3A4 inhibitors and inducers is contraindicated.
Isavuconazole is also an inhibitor of the CYP450 3A4 isoenzyme, thereby increasing the concentrations of drugs that are substrates of CYP450 3A4.
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)

Major different between azole drugs.

IV- Echinocandins (Caspofungin, micafungin, and anidulafungin)
Echinocandins interfere with the synthesis of the fungal cell wall by inhibiting the synthesis of β (1 ,3)-d-glucan, leading to cell lysis and death.

Caspofungin, micafungin, and anidulafungin are available for IV administration once daily. Micafungin is the only echinocandin that does not require a loading dose.

The echinocandins have potent activity against Aspergillus and most Candida species, including those species resistant to azoles.

However, they have minimal activity against other fungi.
The most common adverse effects are fever, rash, nausea, and phlebitis at the infusion site.
Slow IV infusion is recommended to prevent histamine-like reactions, especially flushing, associated with rapid administration.

a- Caspofungin: is a first-line option for patients with invasive candidiasis, including candidemia, and a second-line option for invasive aspergillosis in patients who have failed or cannot tolerate amphotericin B or an azole.

The dose of caspofungin should be adjusted with moderate hepatic dysfunction.

Concomitant administration of caspofungin with CYP450 enzyme inducers (for example, rifampin) may require an increase in caspofungin dose.

Caspofungin should not be coadministered with cyclosporine due to a high incidence of elevated hepatic transaminases with concurrent use.

b. Micafungin and anidulafungin: Micafungin [mi-ka-FUN-jin] and anidulafungin are:

first-line options for the treatment of invasive candidiasis, including candidemia.

Micafungin is also indicated for the prophylaxis of invasive Candida infections in patients who are undergoing hematopoietic stem cell transplantation.

These agents are not substrates for CYP450 enzymes and do not have any associated drug interactions.

A 30-year patient with tuberculosis and he takes rifampin. Recently he is diagnosed with invasive candidiasis. Which of the following is most appropriate antifungal drug for him?

a- Caspofungin.
b- Itraconazole
c- Micafungin.
d- Griseofulvin.
e- Terbinafine.

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.

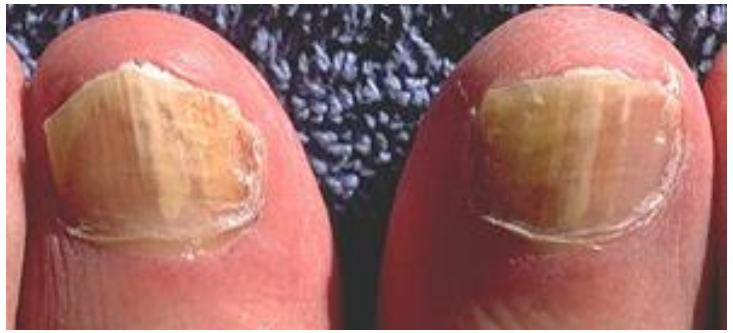
I- Squalene epoxidase inhibitors

These agents blocking the biosynthesis of ergosterol by inhibiting squalene epoxidase. Accumulation of toxic amounts of squalene results in increased membrane permeability and death of the fungal cell.

1- Terbinafine: Oral terbinafine is the drug of choice for treating (fungal infections of nails).

This oral antifungal is also applicable for tinea capitis (scalp infection), requiring systemic therapy.

It is better tolerated, requires a shorter duration of therapy, and is more effective than either itraconazole or griseofulvin for Trichophyton. (usually about 3 months)



Topical terbinafine is used to treat tinea pedis, tinea corporis, tinea cruris, and tinea versicolor caused by Malassezia furfur (treatment duration of 1 week).

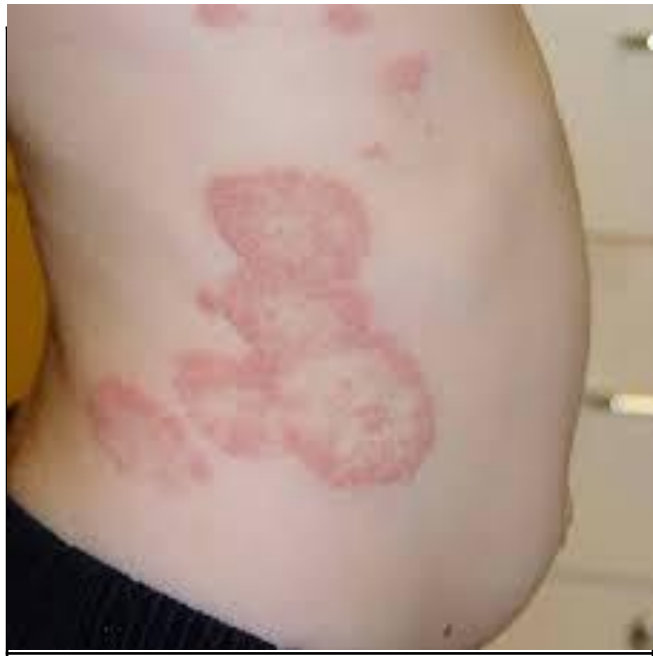
Spectrum: Terbinafine is effective against Trichophyton and Malassezia. While it may potentially work against Candida, Epidermophyton, and Scopulariopsis.

Pharmacokinetics:

40% bioavailability orally due to first-pass metabolism.

Terbinafine is highly protein bound and is deposited in the skin, nails, and adipose tissue, leadfing to prolonged terminal half-life of 200 to 400 hours may reflect the slow release from these tissues.

avoided in patients with moderate to severe renal impairment or hepatic dysfunction.



tinea corporis (ringworm)

Terbinafine is an inhibitor of the CYP450 2D6

Adverse effects: Common adverse effects include diarrhea, dyspepsia, nausea, headache, and rash.
Taste and visual disturbances and elevations in serum hepatic transaminases.

2- Naftifine: is active against Trichophyton, Microsporum, and Epidermophyton. Naftifine cream and gel are used for topical treatment of tinea corporis, tinea cruris, and tinea pedis. Duration of treatment is usually 2 to 4 weeks.

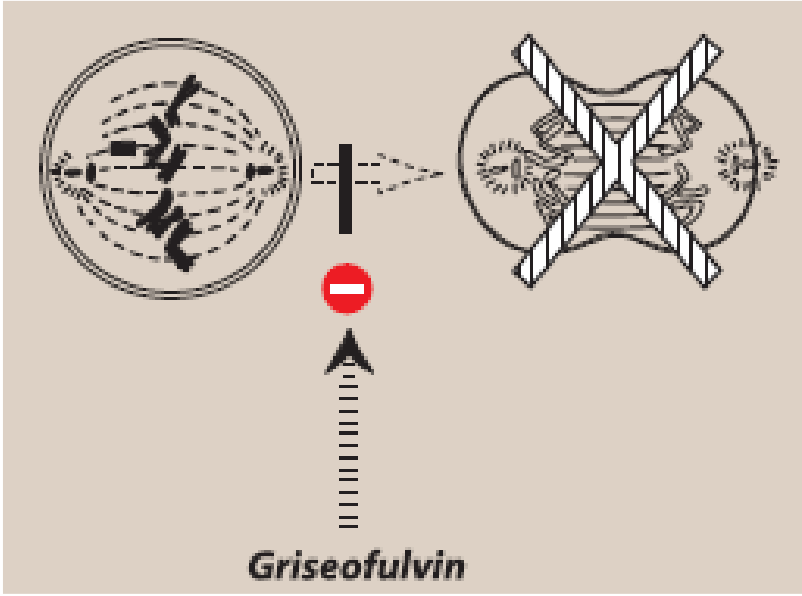
3. Butenafine: Butenafine is effective against Trichophyton rubrum, Epidermophyton, and Malassezia. It is employed topically, in cream form, similar to naftifine, for the treatment of tinea infections.

II- Griseofulvin

Griseofulvin [gris-ee-oh-FUL-vin] causes disruption of the mitotic spindle and inhibition of fungal mitosis.

It has been largely replaced by oral terbinafine, although it is still used for dermatophytosis of the scalp and hair.

Griseofulvin is fungistatic and requires a long duration of treatment (for example, 6 to 12 months).



gastrointestinal tract, and absorption is enhanced by high-fat meals.
The drug concentrates in skin, hair, nails, and adipose tissue.

Griseofulvin induces hepatic CYP450 activity.

Griseofulvin is contraindicated in pregnancy and patients with porphyria.

III- Nystatin

Nystatin, a polyene antifungal similar to amphotericin B in structure, chemistry, mechanism of action, and resistance profile.

It is used for the treatment of cutaneous and oral Candida infections.

The drug is negligibly absorbed from the gastrointestinal tract, and it is not used parenterally due to systemic toxicity (nephrotoxicity).

It is administered as an oral agent for the treatment of oropharyngeal candidiasis (thrush), intravaginally for vulvovaginal candidiasis, or topically for cutaneous candidiasis, using methods such as "swish and swallow" or "swish and spit."

IV- 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.

Topical use is associated with contact dermatitis, vulvar irritation, and edema.

• Clotrimazole is also available as a troche (lozenge).

• Miconazole is available as a buccal tablet for the treatment of thrush.

• While oral ketoconazole is rarely used due to severe side effects, topical formulations are effective against conditions like tinea versicolor and seborrheic dermatitis.

V- Efinaconazole

Efinaconazole [eff-in-a-KON-a-zole] is a topical triazole antifungal agent approved for the treatment of toenail onychomycosis. Duration of treatment is 48 weeks.

VI- Ciclopirox

Ciclopirox, a pyridine antimycotic, inhibits the transport of essential elements in the fungal cell, disrupting the synthesis of DNA, RNA, and proteins.

Ciclopirox shampoo is used for treatment of seborrheic dermatitis.
Tinea (fungal infections) may be treated with the cream, gel, or suspension.
Onychomycosis can be treated with the nail lacquer formulation.

VII- Tavaborole

Tavaborole [tav-a-BOOR-ole] inhibits an aminoacyl-transfer ribonucleic acid synthetase, preventing fungal protein synthesis.

A topical solution is approved for the treatment of toenail onychomycosis, requiring 48 weeks of treatment.

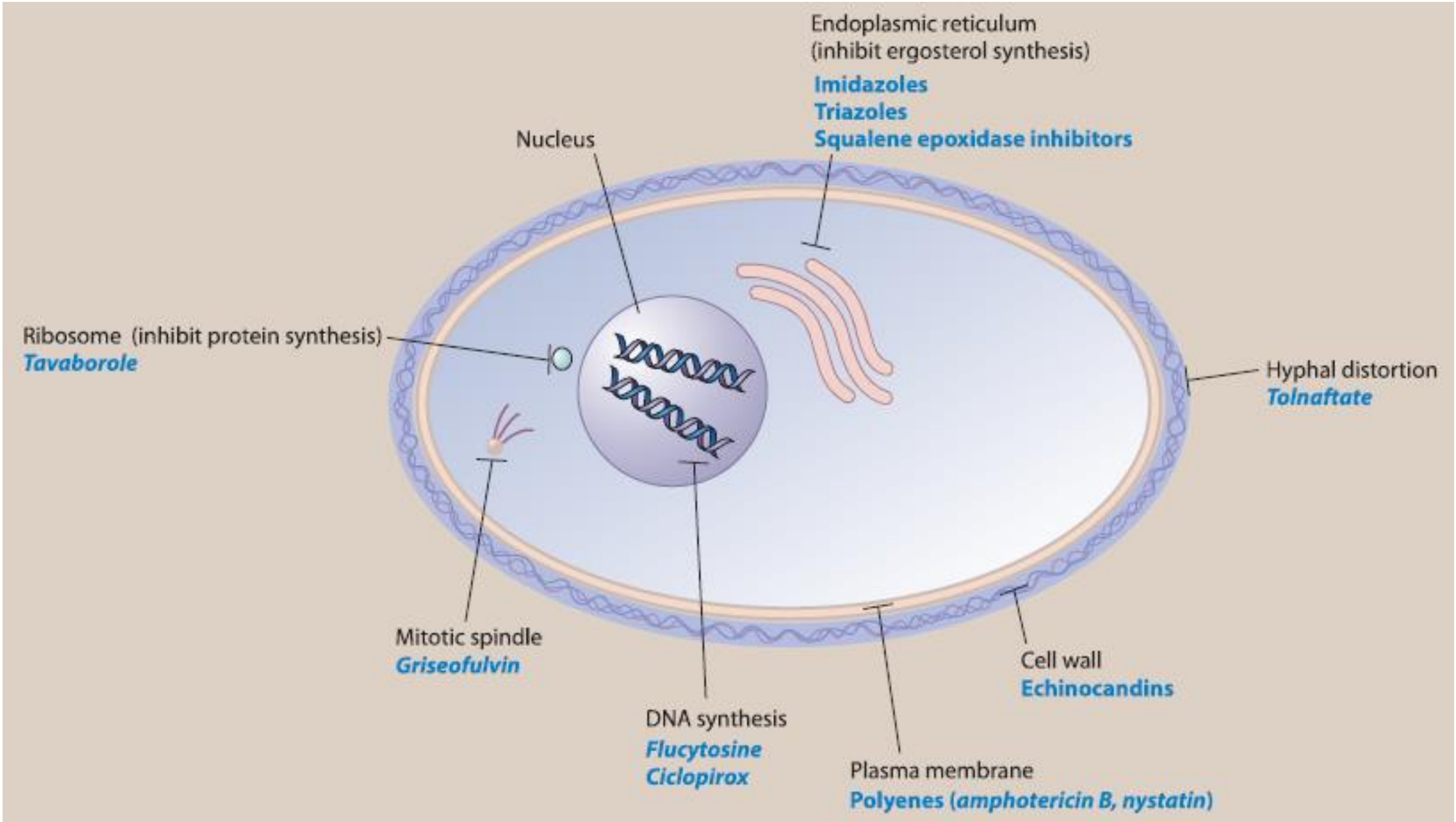
VIII- Tolnaftate

Tolnaftate, a topical thiocarbamate, distorts the hyphae and inhibits mycelial growth in susceptible fungi. specifically targeting Epidermophyton, Microsporum, and Malassezia furfur.

It is available as a solution, cream, and powder.

Tolnaftate is used to treat tinea pedis, tinea cruris, and tinea corporis.

Tolnaftate is not effective against Candida.


Endoplasmic reticulum
(inhibit ergosterol synthesis)
Imidazoles
Triazoles
Squalene epoxidase inhibitors
Nucleus
Ribosome (inhibit protein synthesis)
Tavaborole
Hyphal distortion
Tolnaftate
Mitotic spindle
Griseofulvin
DNA synthesis
Flucytosine
Ciclopirox
Plasma membrane
Polyenes (amphotericin B, nystatin)
Cell wall
Echinocandins

References

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Thank you