ANTIFUNGAL AGENTS

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CONTENTS

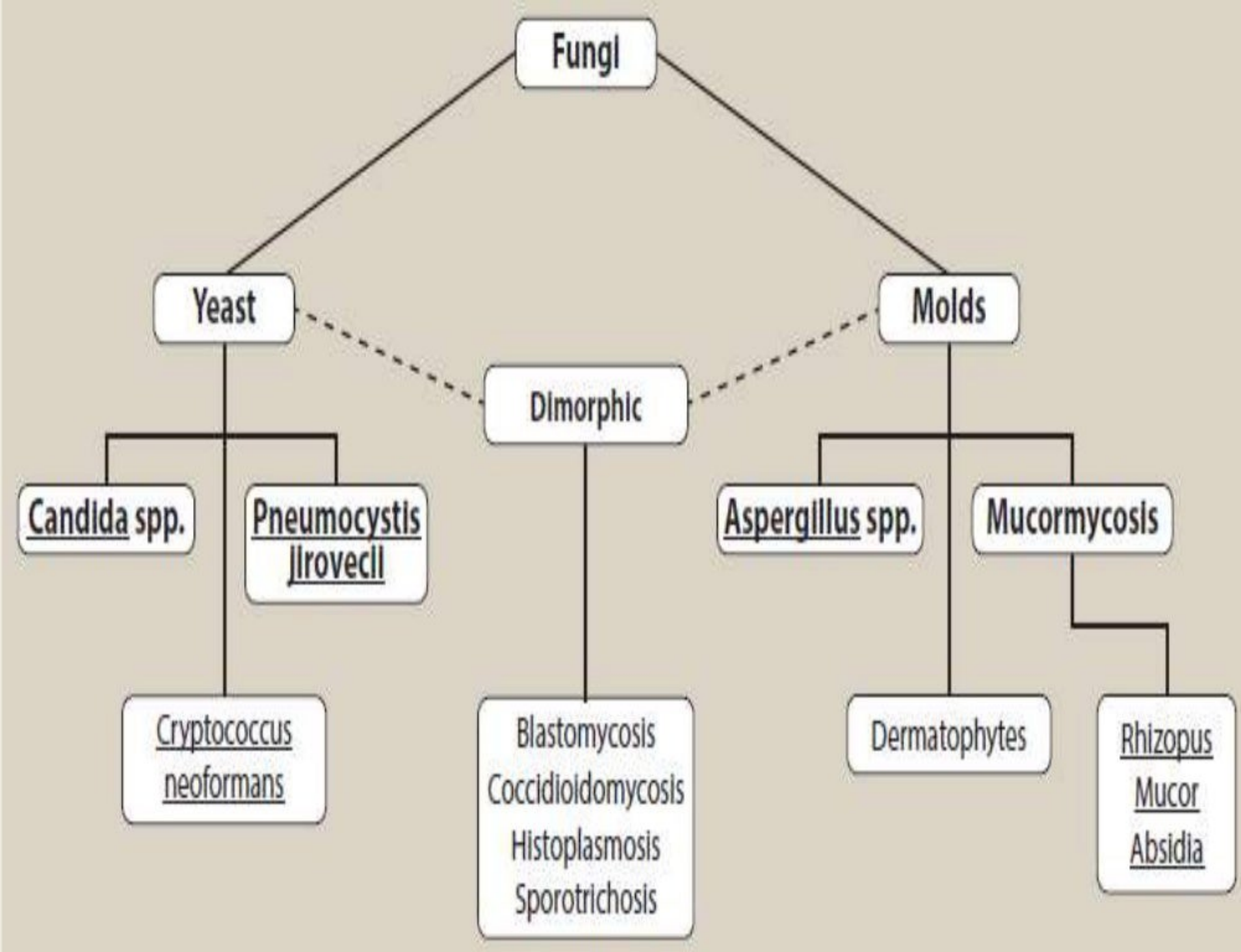
- Introduction
- Types of fungal organisms
- Difference between bacteria and fungi
- Classification of fungal infections
- Classification of antifungal agents
- Pharmacology of antifungal agents
- Drug of choice for various fungal infections

- Fungi are also called mycoses
- They are eukaryotic organisms & possess cell wall
- Fungal cell wall is made up of ***chitin*** (NAG)
- Cell membrane is made up of ***Ergosterol***.
- In 1950s the incidence of fungal infections were predominant
- Fungal infections are iatrogenic/ drug induced
- Infections majorly occur in immunocompromised people receiving immunosuppressants

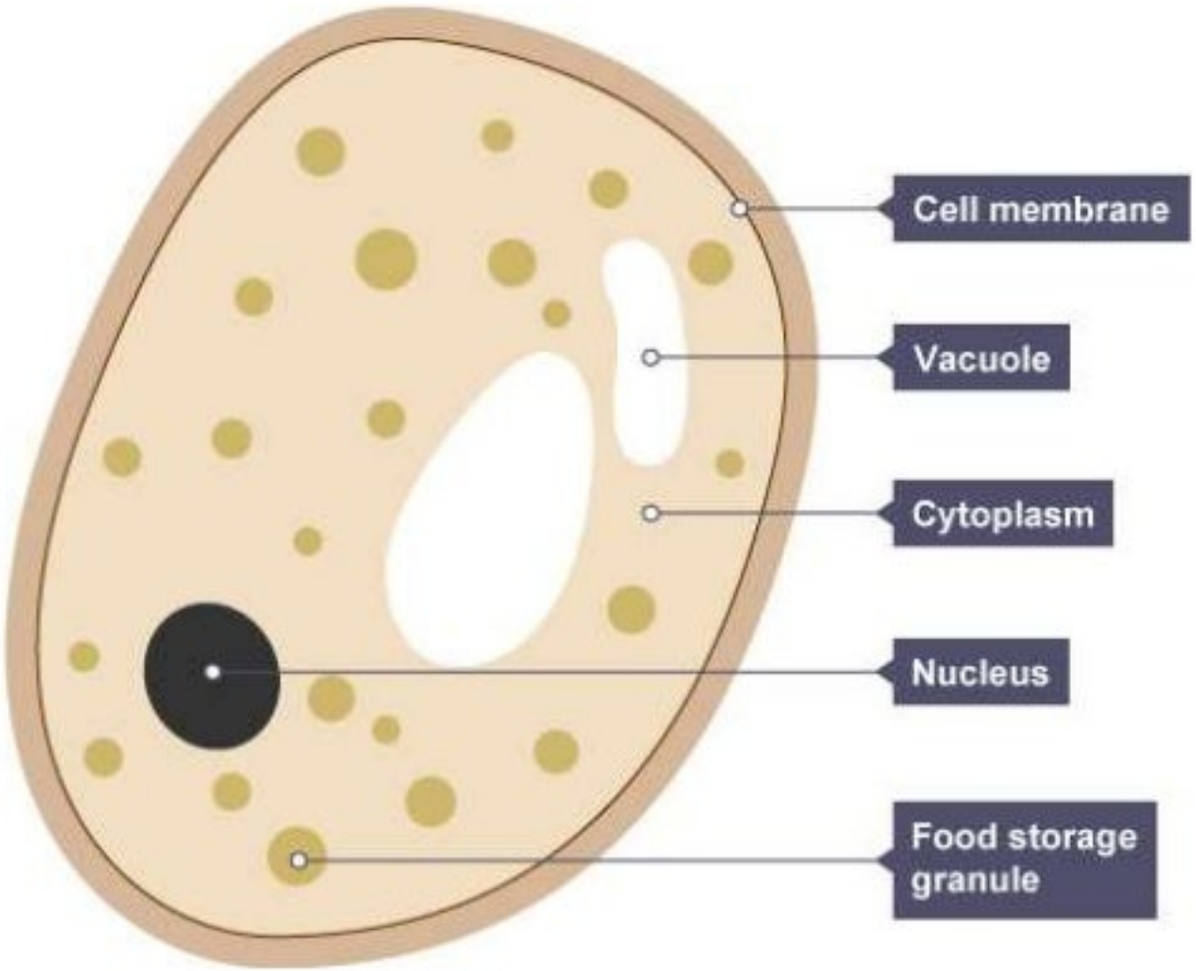
- ✓ Similar to animals, fungi are **heterotrophs**, that is, they acquire their food by absorbing dissolved molecules, typically by secreting **digestive enzymes** into their environment.

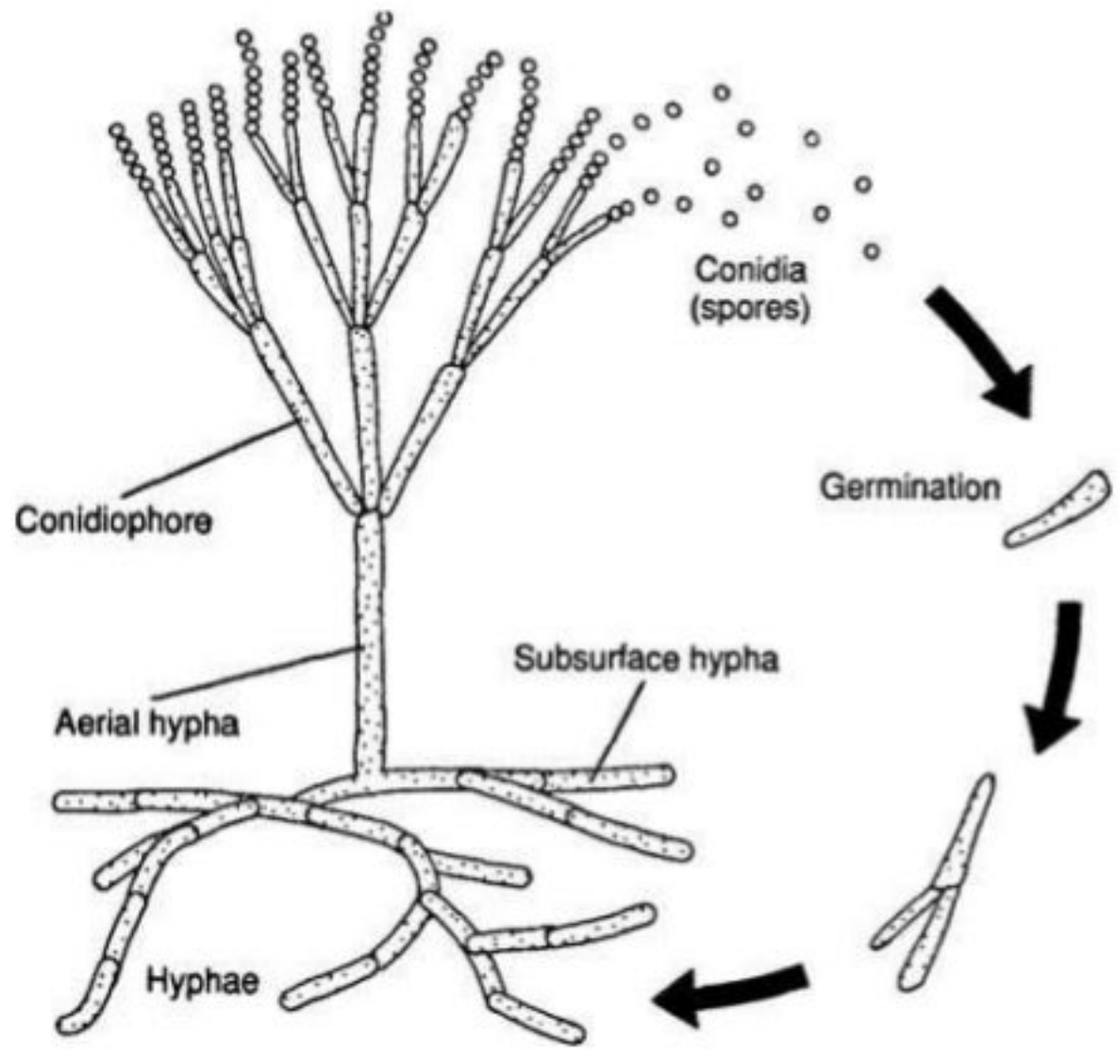
- ✓ The discipline of **biology** devoted to the study of fungi is known as **mycology.**

- ✓ Fungal cells contain membrane-bound **nuclei** with chromosomes that contain DNA with noncoding regions called introns and coding regions called exons. Fungi have membrane-bound cytoplasmic organelles such as mitochondria, sterol-containing membranes, and ribosomes of the **80S** type.
- ✓ Fungi lack chloroplasts.
- ✓ Fungi **have a cell wall and vacuoles**. They reproduce by both **sexual and asexual** means, and like basal plant groups (such as ferns and mosses) produce spores.


Fungi
Yeast
Molds
Dimorphic
Candida spp.
Pneumocystis jirovecii
Aspergillus spp.
Mucormycosis
Cryptococcus neoformans
Blastomycosis
Coccidioidomycosis
Histoplasmosis
Sporotrichosis
Dermatophytes
Rhizopus
Mucor
Absidia

- ✓ A **mold** or **mould** is a fungus that grows in the form of **multicellular** filaments called *hyphae*. In contrast, fungi that can adopt a **single-celled growth** habit are called **yeasts.**





TYPES OF FUNGAL ORGANISMS

CLASS	MODE OF TRANSMISSION	SPECIES INVOVLVED	DISEASE CAUSED
YEASTS	Budding	Cryptococcus neoformans	Meningitis
YEAST LIKE FUNGI	Partly grows like yeast and partly as filaments (hyphae)	Candida albicans	Oral thrush Vaginal thrush Systemic Candidiasis
		Pityrosporom orbiculare	Pityriasis versicolor Tinea versicolor
MOULDS	Filamentous fungi reproduce by forming spores	Dermatophytes (pathogenic moulds) Trichophyton sp., Microsporum sp., Epidermophyton sp.,	Skin/ nail infections

TYPES OF FUNGAL ORGANISMS

CLASS	MODE OF TRANSMISSION	SPECIES INVOVLVED	DISEASE CAUSED
MOULDS	Filamentous fungi reproduce by forming spores	Dermatophytoses/Tinea infections *Tinea barbe* *T. capitis* *T. corporis* *T. Cruris* *T. manum* *T. pedis* *T. unguium* *Aspergillus fumigans*	 Infection of Beard Scalp Body Groin Hand Athelete foot Nails Pulmonary aspergillosis
DIMORPHIC FUNGI	Grow as filaments or as yeast	*Histoplasma capsulatum* *Coccidiodes immitis* *Blastomyces deramtides* *Sporothrix sp.,*	Histoplasmosis Coccidiomycosis Blastomycoses Sporotrichosis

- ✓ *Cryptococcus neoformans* and *Cryptococcus gattii* are significant pathogens of immunocompromised people. They are the species primarily responsible for **cryptococcosis**, a fungal disease that occurs in about one million HIV/AIDS patients, causing over 600,000 deaths annually.
- ✓ The cells of these yeast are surrounded by a rigid polysaccharide capsule, which helps to prevent them from being recognized and engulfed by white blood cells in the human body.

- ✓ Yeasts of the *Candida* genus, another group of opportunistic pathogens, cause **oral and vaginal** infections in humans, known as **candidiasis.**

- ✓ *Candida* is commonly found as a commensal yeast in the **mucous membranes** of humans and other warm-blooded animals.

- ✓ **Aspergillosis** is the group of diseases caused by *Aspergillus*. The most common subtype among **paranasal sinus infections** associated with aspergillosis is *A. fumigatus*.
- ✓ The symptoms include fever, cough, chest pain, or breathlessness, which also occur in many other illnesses, so diagnosis can be difficult. Usually, only patients with already **weakened immune systems** or who suffer other lung conditions are susceptible.

USEFUL & HARMFUL FUNGI

ORGANISM	USES
Saccharomyces cerviciae	▪ Manufacturer of beverages and bread ▪ Majorly used in fermentation processes
Penicllium notatum *Penicillium crysogenum*	▪ Produce PENICILLIN
Streptomyces griseofulvin	▪ Griseofulvin
	HARMS
Claviceps purpurea	▪ Produces mycotoxins causing food poisoning
Aspergillus	▪ Produces Alfatoxin that is carcinogenic

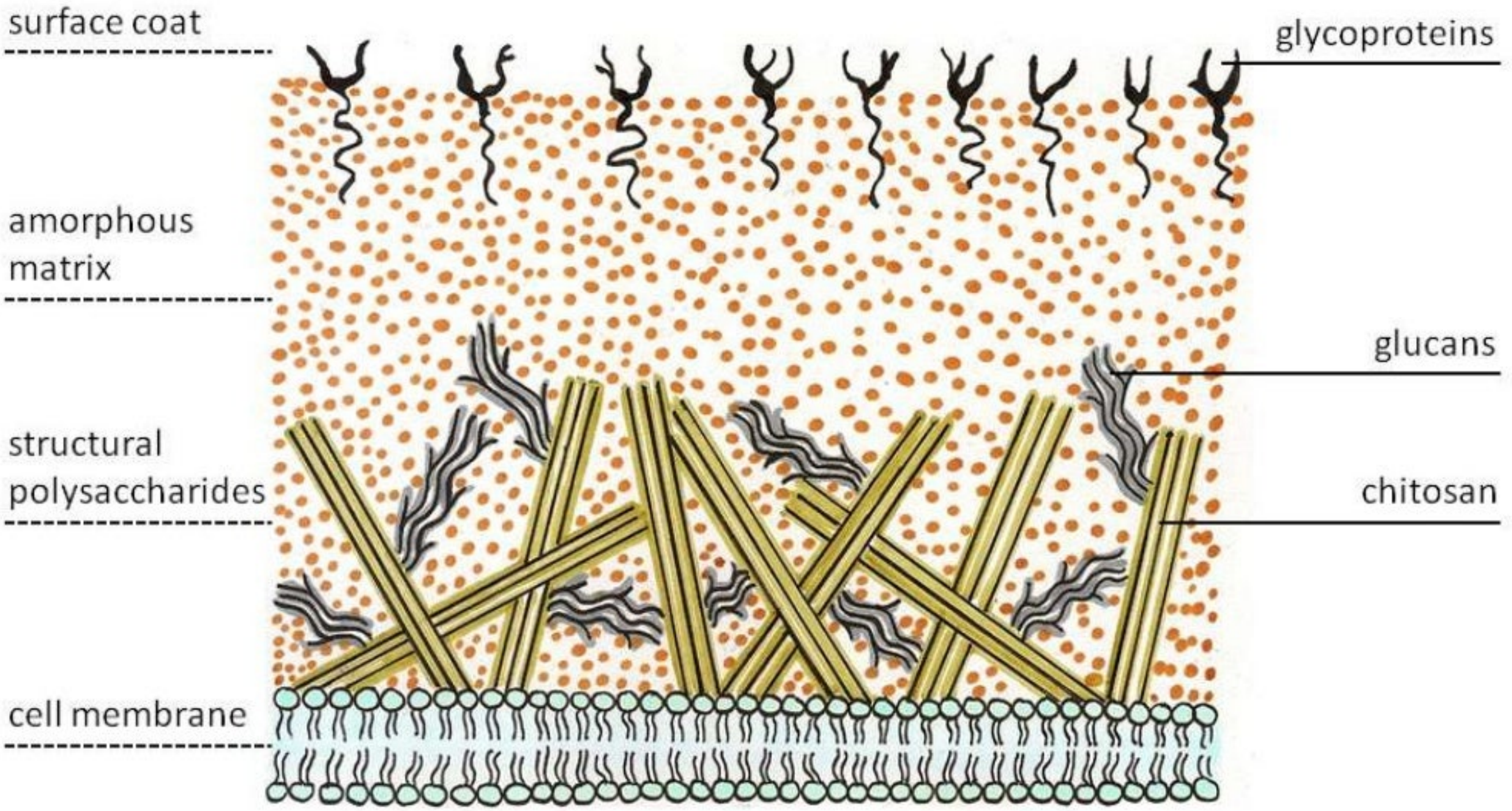
DIFFERENCE BETWEEN BACTERIA AND FUNGI

BACTERIA

- Peptidoglycan layer is present in the cell and consists of NAGA & NAMA
- Cell wall is composed of proteins
- Lipids present in the cell membrane are made of cholesterol

FUNGI

- Consists of polysaccharides both **simple** (*β – glucans 1,3 & 1,6*) and **complex** polysaccharides (*Chitin – NAG*) constituting 80% of the cell wall
- Cell membrane is made of ergosterol


surface coat
glycoproteins
amorphous matrix
glucans
structural polysaccharides
chitosan
cell membrane

CLASSIFICATION OF FUNGAL INFECTIONS

FUNGAL INFECTIONS

SUPERFICIAL INFECTIONS

On the surface of the skin

CUTANEOUS INFECTIONS

Dermatophytes

Ringworm infections

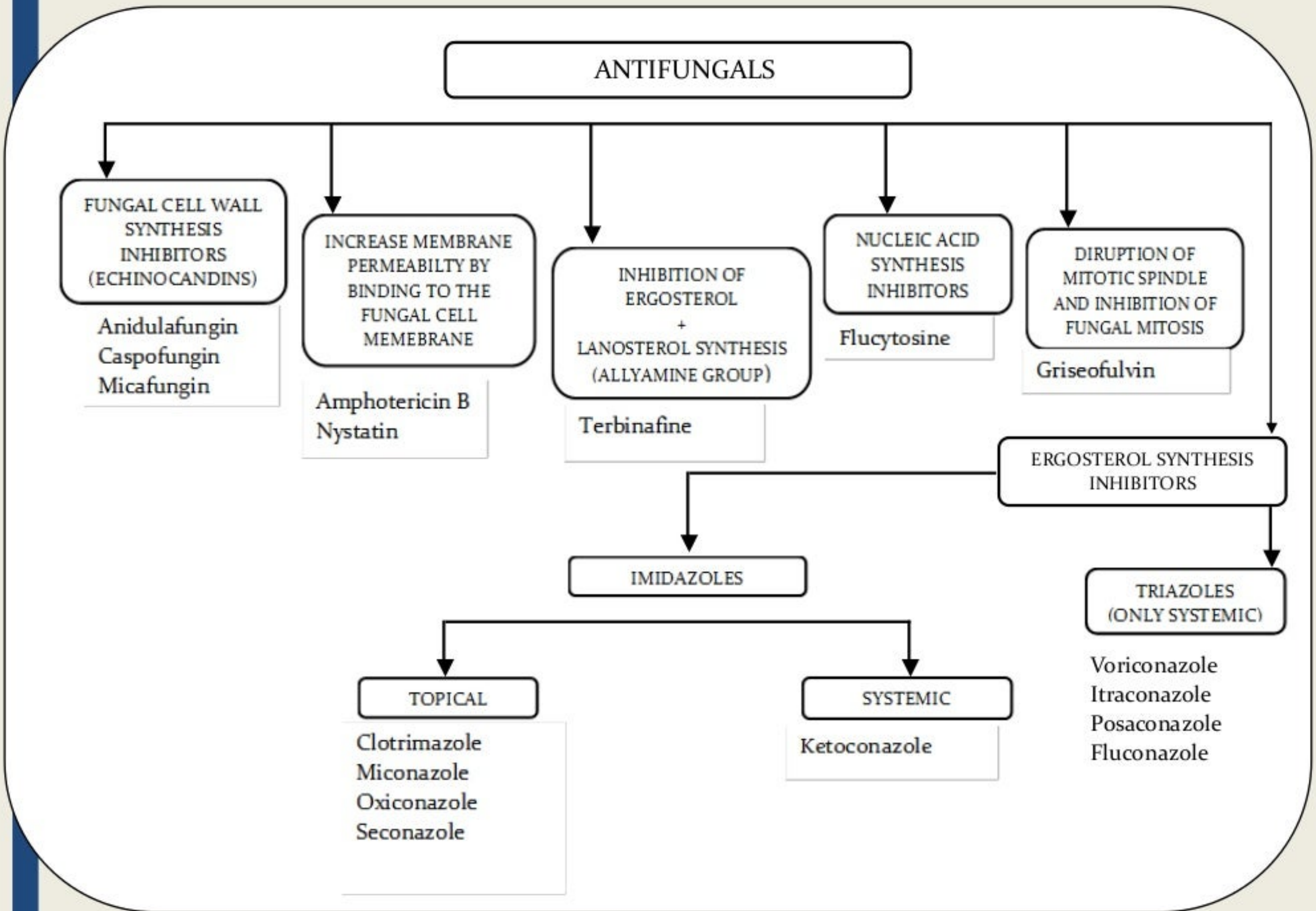
All Tinea sps

Candida sps

SUB CUTANEOUS INFECTIONS

DEEP MYCOSAL INFECTIONS OR SYSTEMIC MYCOSAL INFECTIONS

CLASSIFICATION OF ANTIFUNGAL AGENTS



CLASSIFICATION OF ANTIFUNGAL AGENTS

BASED ON CHEMICAL NATURE

POLYENES

AMPHOTERICIN B
NYSTATIN

ECHINOCANDINS

MICAFUNGIN
CASPOFUNGIN
ANIDULAFUNGIN

ANTIMETABOLITES

FLUCYTSOINE

ALLYLAMINES

NAFTIFINE
TERBINAFINE
BUTENIFINE

MISCELLANEOUS

GRISEOFULIVIN
BENZOIC ACID
UNDECYCLINIC ACID
SODIUM METBISULPHATE

AZOLES

IMIDAZOLES

TOPICAL
CLOTRIMAZOLE
SECONAZOLE
OXICONAZOLE
MOCONAZOLE
ECONAZOLE

SYSTEMIC
KETOCONAZOLE

TRIAZOLES

VORICONAZOLE
ITRACONAZOLE
POSACONAZOLE
FLUCONAZOLE

CLASSIFICATION OF ANTIFUNGAL AGENTS

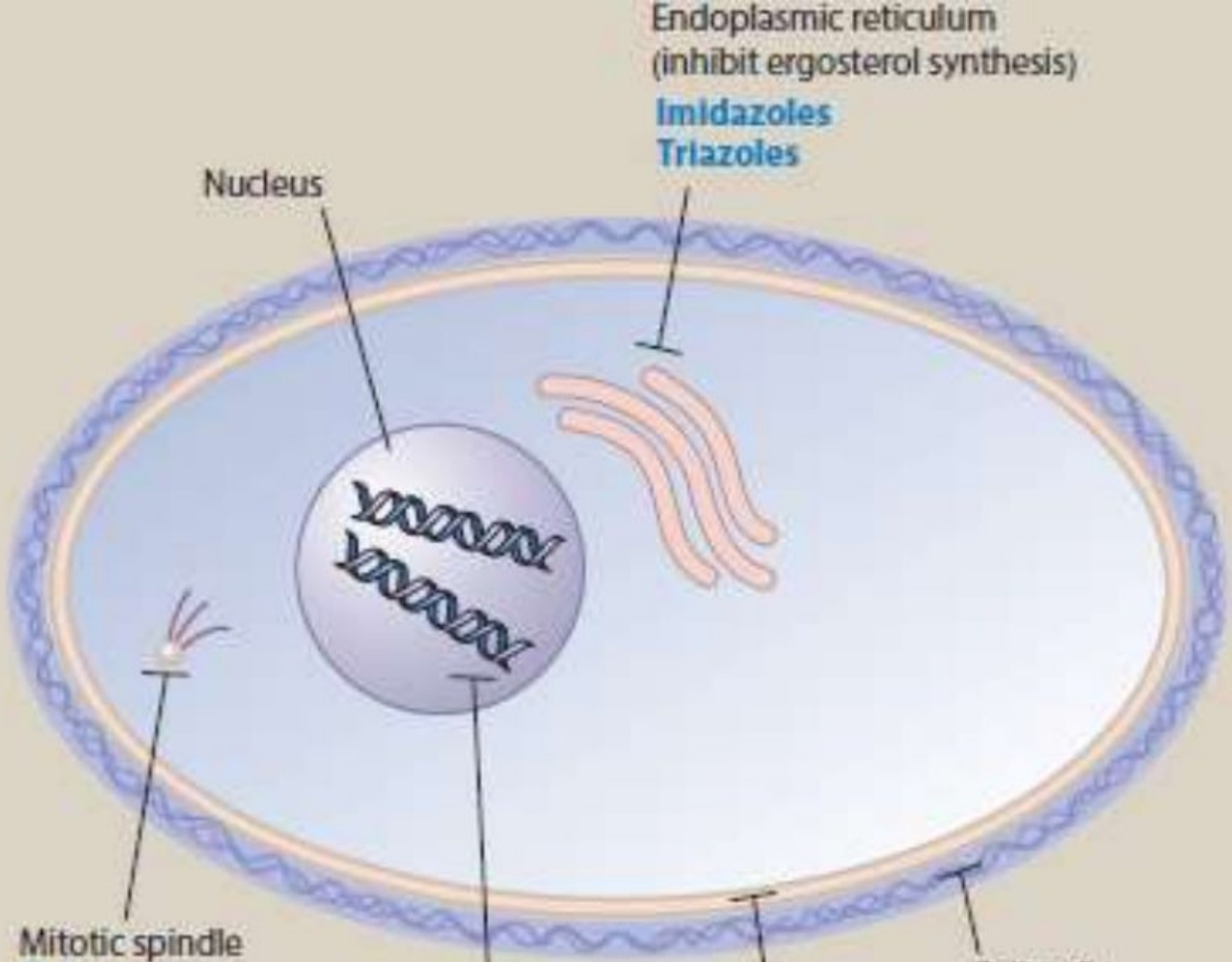
BASED ON SITE OF INFECTION

CUTANEOUS/TOPICAL INFECTIONS

- NYSTATIN
- GRISEOFULVIN
- CLOTRIMAZOLE
- SECONAZOLE
- OXICONAZOLE
- MECONAZOLE
- BENZOIC ACID
- UNDECYCLINIC ACID
- SODIUM METABISULPHATE

SYSTEMIC/ SUB CUTANEOUS INFECTIONS

- AMPHOTERICIN B
- KETOCONAZOLE
- VORICONAZOLE
- ITRACONAZOLE
- POSACONAZOLE
- MICAFUNGIN
- CASPOFUNGIN
- FLUCONAZOLE


Endoplasmic reticulum
(inhibit ergosterol synthesis)
Imidazoles
Triazoles
Nucleus
Mitotic spindle
Griseofulvin
DNA synthesis
Flucytosine
Plasma membrane
Polyenes (amphotericin B)
Cell wall
Echinocandins

POLYENE ANTIBIOTICS
AMPHOTERICIN B

- *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.

- It is a macromolecule and consists of both lipophilic and hydrophilic groups i.e., it is amphiphilic in nature

- Conjugated nature is responsible for lipophilicity and OH group is responsible for hydrophilicity

- The amphiphilicity of the drug is responsible for its unique mechanism of action

PHARMACOKINETICS

- Yellowish colour powder
- Unstable in aqueous solutions
- Given through IV route in salt form along with AMPHOTERICIN DESOXYCHOLATE
  - Metabolised in liver
  - $t_{1/2}$ - 15 days

- It is extensively bound to plasma proteins and is distributed throughout the body.

- Inflammation favors penetration into various body fluids, but little of the drug is found in the CSF, vitreous humor, or amniotic fluid. However, amphotericin B does cross the placenta.

- Accumulates in renal cells causing nephrotoxicity leading to Azotemia characterized by decreased GFR, Urinary output, Cr_{cl} and increased Scr and BUN

MECHANISM OF ACTION

AMPHOTERICIN B

HYDROPHILIC PART

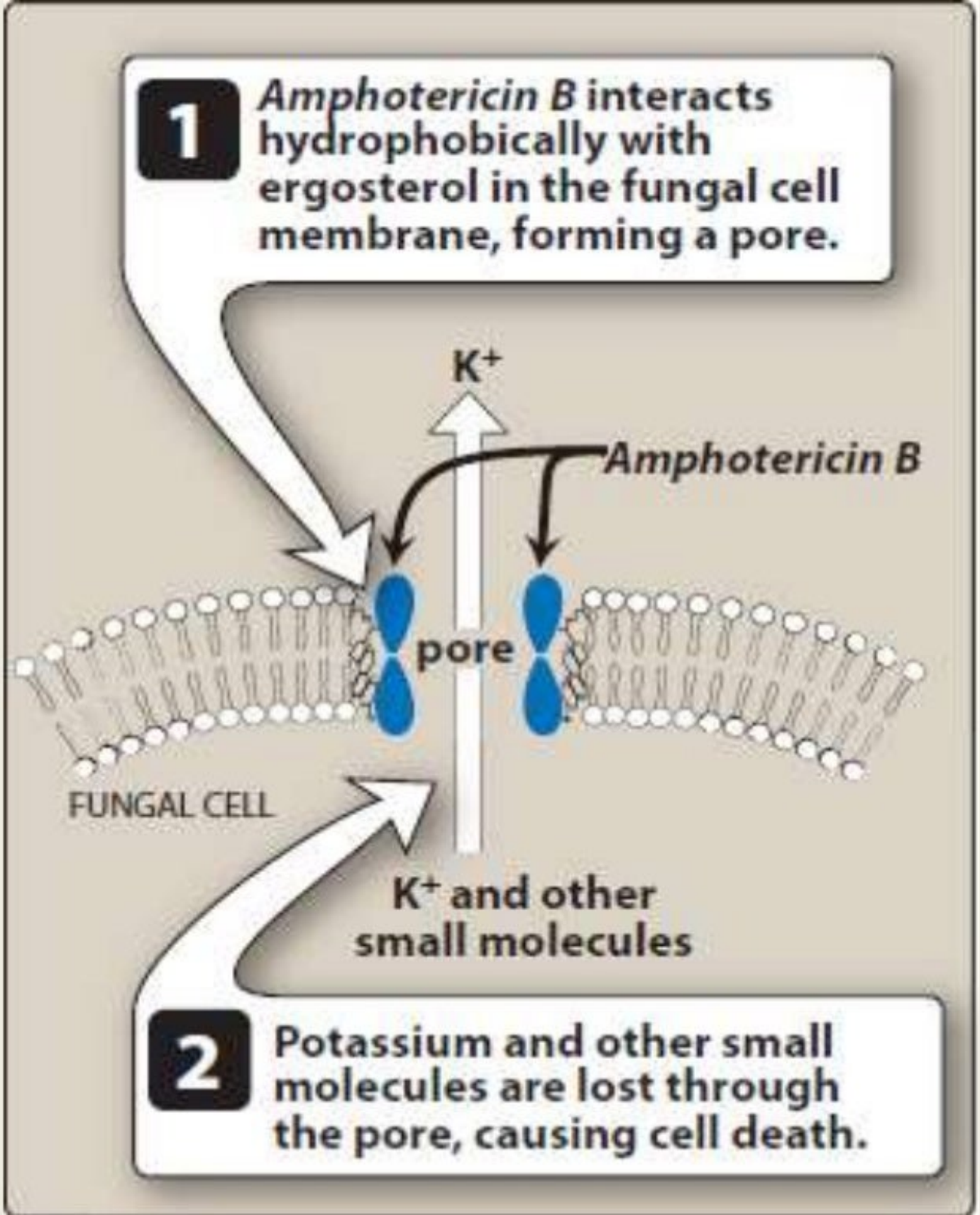
Forms pores in the cell membrane

LIPOPHILIC PART

Binds with ergosterol and bilipid layer

Cell contents such as Na^+ and K^+ leak trough the spores from the cytoplasm

FUNGICIDAL ACTION


1 Amphotericin B interacts hydrophobically with ergosterol in the fungal cell membrane, forming a pore.
K+
Amphotericin B
pore
FUNGAL CELL
K+ and other small molecules
2 Potassium and other small molecules are lost through the pore, causing cell death.

Antifungal spectrum:

It is effective against a wide range of fungi, including

- ✓ Candida albicans
- ✓ Histoplasma capsulatum
- ✓ Cryptococcus neoformans
- ✓ Coccidioides immitis
- ✓ Blastomyces dermatitidis
- ✓ Aspergillus

Amphotericin B is also used in the treatment of the protozoal infection leishmaniasis.

Dose

- ✓ Amphotericin B has a low therapeutic index.
- ✓ The total adult daily dose of the conventional formulation should not exceed 1.5 mg/kg/d, whereas lipid formulations have been given safely in doses up to 10 mg/kg/d.

Adverse effects:

Fever and chills:

These occur most commonly 1 to 3 hours after starting the IV administration but usually subside with repeated administration of the drug. **Premedication** with a **corticosteroid or an antipyretic** helps to prevent this problem.

Renal impairment

- ✓ Patients may exhibit a decrease in glomerular filtration rate and renal tubular function.
- ✓ Serum creatinine may increase, creatinine clearance can decrease, and potassium and magnesium are lost.
- ✓ Renal function usually returns with discontinuation of the drug, but residual damage is likely at high doses.
- ✓ To **minimize nephrotoxicity**, sodium loading with infusions of normal saline and the lipid-based amphotericin B products can be used.

Hypotension:

- ✓ A shock-like fall in blood pressure accompanied by hypokalemia may occur, requiring potassium supplementation.
- ✓ Care must be exercised in patients taking digoxin and other drugs that can cause potassium fluctuations.

Thrombophlebitis:

Adding heparin to the infusion can alleviate this problem.

THERAPEUTIC USES

- Intestinal candidiasis
- Topical candidiasis
- Febrile neutropenia
- Leishmaniasis – kala Azar

- Limited use in systemic infections because of increased toxicity

AMB FORMULATIONS

CONVENTIONAL AMB

- Na^+ salt of AMB i.e., Sodium desoxycholate AMB
- It is water soluble and stable

LIPOHILIC AMB

- AMB formulated in liposomes which releases drug periodically
- 10% AMB is surrounded by unilammellar, lipophilic membrane made up of Lecithin
- Increased specificity as liposomes will be coated with Abs mediating site specific delivery
- Increased BA and decreased nephrotoxicity

NYSTATIN

- Posses very high systemic toxicity
- Not given in IV
- Used to treat topical infections
- Earlier it was used to treat moniliasis

It is administered as an oral agent ("swish and swallow" or "swish and spit") for the treatment of --

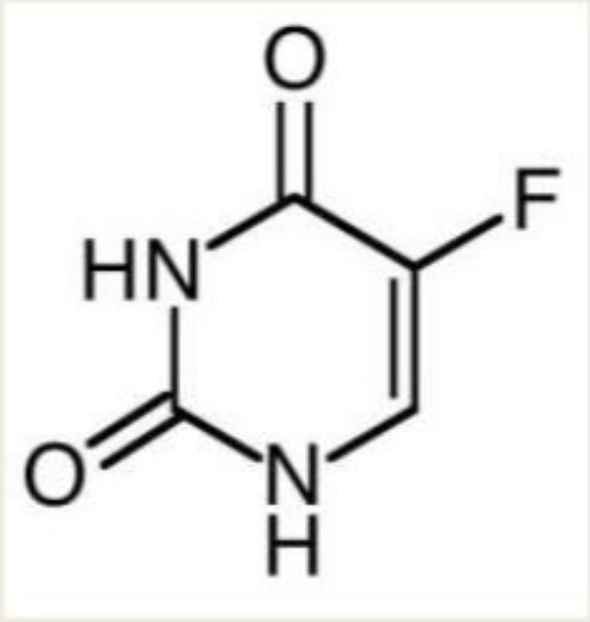
✓ Oropharyngeal candidiasis (thrush)

✓ Intravaginally for vulvovaginal candidiasis

✓ Topically for cutaneous candidiasis.

ANTIMETABOLITES
FLUCYTOSINE

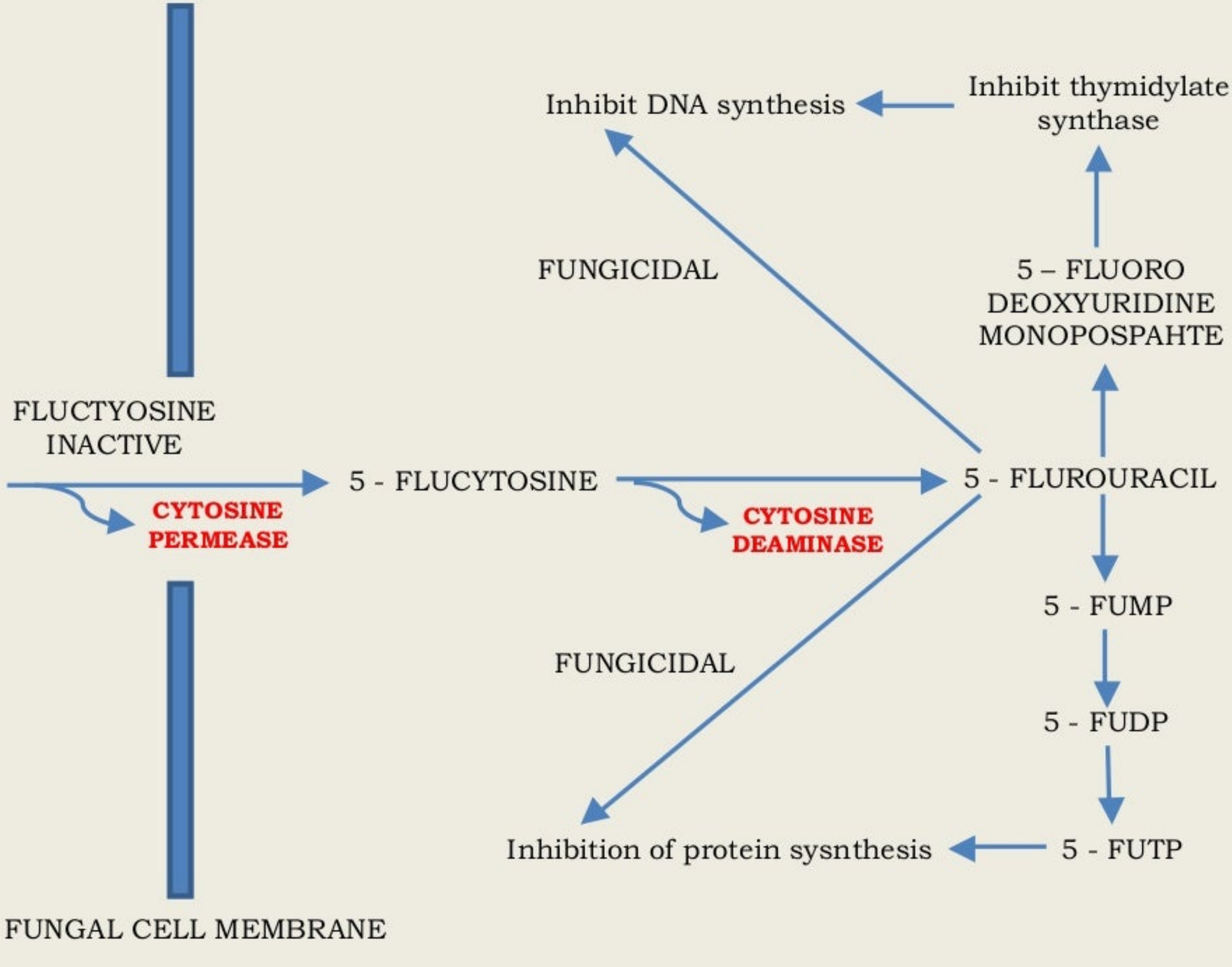
- FLUCYTOSINE is a cytosine moiety
- It is a pyrimidine analogue
- 6 membered ring structure
- Posses 2 ‘N’ atoms
- Earlier used as an Anticancer agent
- But was proved to have potent action against ***Cryptococcus*** sp., and ***Candida*** sp.,



PHARMACOKINETICS

- $t_{1/2}$ - 3 to 6 hours
- Orally well absorbed
- Distributes throughout the body and even into CSF.
- Metabolized by liver
- **5-FU** is detectable in patients and is probably the result of **metabolism of *5-FC* by intestinal bacteria**.
- Excreted unchanged in urine

MECHANISM OF ACTION



MECHANISM OF ACTION

- CYTOSINE PERMEASE and DEAMINASE are present only in fungal cells and absent in mammalian cells
- Hence activation of 5 – FC to 5 – FU occurs only in fungal cells causing inhibition of both DNA and protein synthesis resulting in fungicidal action

Resistance:

- ✓ Resistance due to **decreased levels of any of the enzymes** in the conversion of *5-FC* to *5-fluorouracil* (*5-FU*) and beyond or from increased synthesis of cytosine can develop during therapy. This is the primary reason that ***5-FC* is not used as a single antimycotic drug.**
- ✓ The rate of emergence of resistant fungal cells is lower with a **combination** of *5-FC* plus a second antifungal agent than it is with *5-FC* alone.

ADRS

- Bone marrow suppression
- Hepatotoxicity
- 5 FC administered in excess stimulate intestinal colonic bacteria which produce Cytosine deaminase

THERAPEUTIC USES

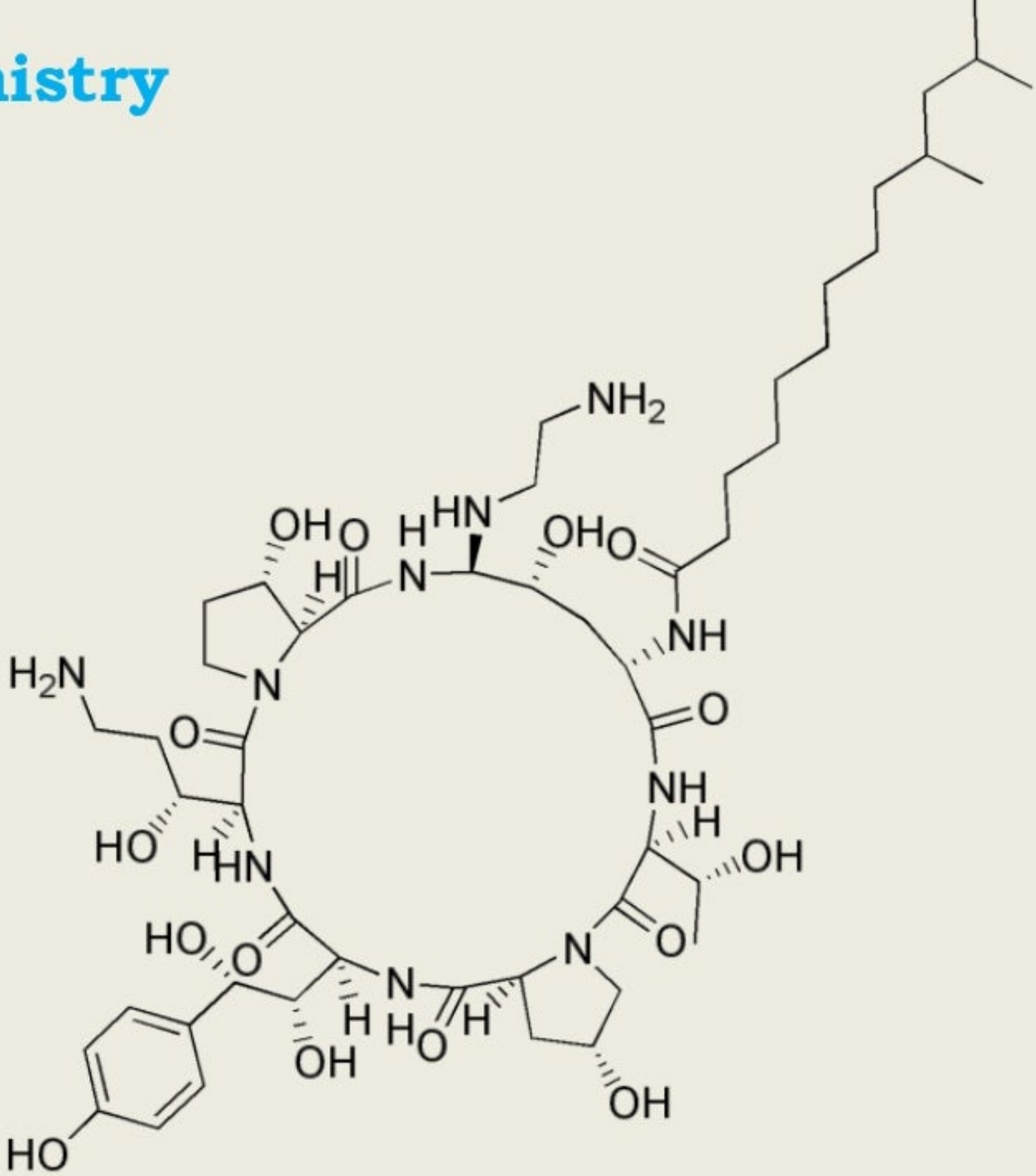
- **Synergistic with AMPHOTERICIN** as it increases permeability in to fungal cells by formation of pores in the cell membrane.
- Cryptococcosis
- Candidiasis

ECHINOCANDINS

- Newer antifungal agents that inhibit the fungal cell wall synthesis
- Discovered serendipitously
- During fermentation process, some metabolites were found to inhibit ***Candida*** sp., and they were named ***Echinocandins***
- 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.

- ✓ One of the first echinocandins, discovered in 1974, echinocandin B, could not be used clinically due to risk of high degree of hemolysis.
- ✓ Caspofungin, micafungin, and anidulafungin are semisynthetic echinocandin derivatives with clinical use due to their solubility, antifungal spectrum, and pharmacokinetic properties.
- ✓ All these preparations so far have low oral bioavailability, so must be given **intravenously only.**

Chemistry



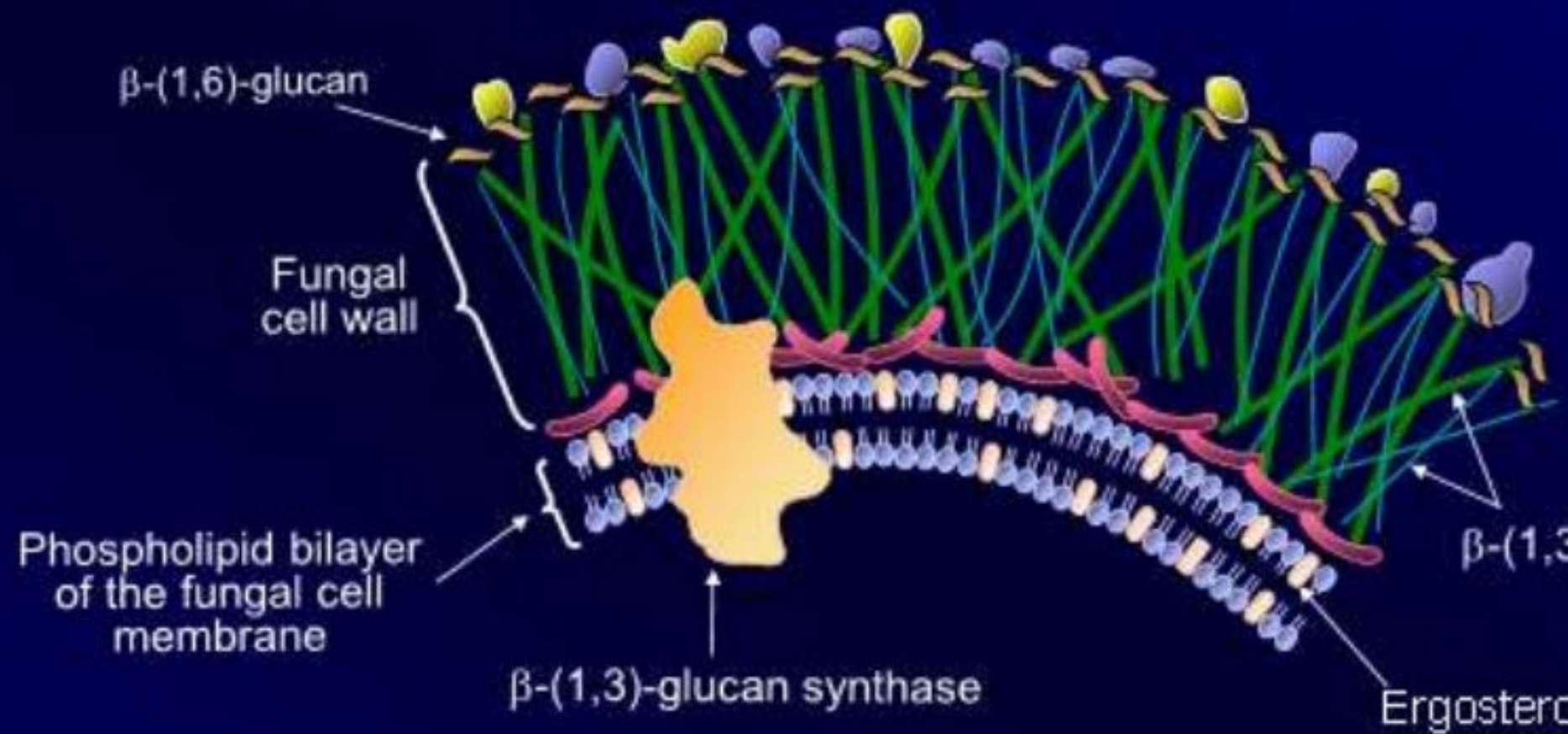
Chemistry

- ✓ The present-day clinically used echinocandins are semisynthetic pneumocandins, which are chemically **lipopeptide** in nature, consisting of large cyclic (hexa)peptoid.
- ✓ Caspofungin, micafungin, and anidulafungin are similar cyclic hexapeptide antibiotics linked to long modified N-linked acyl fatty acid chains.
- ✓ The chains act as anchors on the fungal cell membrane to help facilitate antifungal activity

MECHANISM OF ACTION

Inhibits the synthesis of β 1,3 – D- glucan via noncompetitive inhibition of the enzyme 1,3-β glucan synthase and are thus called "penicillin of antifungals“ resulting in the inhibition of cell wall, leading to lysis and death.

Caspofungin: Mechanism of Action



- Caspofungin specifically inhibits beta (1-3)-D-glucan synthesis, essential to the cell-wall integrity of many fungi, including *Aspergillus* and *Candida* spp, thereby compromising the integrity
- As a result, the fungal cell wall becomes permeable, and cell lysis
- Beta (1-3)-D-glucan synthesis does not occur in human cells

Pharmacokinetics

- ✓ Due to the large molecular weight of echinocandins, they have poor oral bioavailability and are administered by intravenous infusion.
- ✓ In addition, their large structures limit penetration into cerebrospinal fluid, urine, and eyes. In plasma, echinocandins have a high affinity to serum proteins.
- ✓ Echinocandins do not have primary interactions with CYP450 or P-glycoprotein pumps.

- ✓ Caspofungin has **triphasic** nonlinear pharmacokinetics.
- ✓ Micafungin (hepatically metabolized by arylsulfatase, catechol O-methyltransferase, and hydroxylation) and anidulafungin (degraded spontaneously in the system and excreted mostly as a metabolite in the urine) have **linear elimination**.

Resistance

- ✓ Echinocandin resistance is rare.
- ✓ Resistances include alterations in the glucan synthase and overexpression of efflux pumps.

Advantages of echinocandins:

- ✓ **Broad range** (especially against all *Candida*), thus can be given empirically in febrile neutropenia and stem cell transplant.
- ✓ Can be used in case of **azole-resistant *Candida*** or use as a second-line agent for refractory aspergillosis
- ✓ **Long half-life** (polyphasic elimination: alpha phase 1–2 hours + beta phase 9–11 hours + gamma phase 40–50 hours)

- ✓ **Not an inhibitor, inducer, or substrate** of the cytochrome P450 system, or P-glycoprotein, thus minimal drug interactions
- ✓ **No dose adjustment** is necessary based on age, gender, raceBetter (or no less effective) than amphotericin B and fluconazole against yeast infections
- ✓ **Low toxicity:** only histamine release (3%), fever (2.9%), nausea and vomiting (2.9%), and phlebitis at the injection site (2.9%), very rarely allergy and anaphylaxis

Disadvantages of echinocandins:

- ✓ Embryotoxic (category C) thus should be avoided if possible in pregnancy
- ✓ Needs dose adjustment in liver disease
- ✓ Poor ocular penetration in fungal endophthalmitis

Caspofungin

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.

Micafungin and Anidulafungin:

Micafungin 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.

AZOLE ANTIFUNGALS

Azole antifungals are made up of two different classes of drugs

- ✓ **Imidazoles**
- ✓ **Triazoles.**

Although these drugs have similar mechanisms of action and spectra of activity, their pharmacokinetics and therapeutic uses vary significantly.

- ✓ **Imidazoles** are given **topically** for cutaneous infections.
- ✓ **Triazoles** are given **systemically** for the treatment or prophylaxis of cutaneous and systemic fungal infections.

AZOLES

IMIDAZOLES

TOPICAL

CLOTRIMAZOLE

SECONAZOLE

OXICONAZOLE

MOCONAZOLE

ECONAZOLE

BUTOCONAZOLE

SULCONAZOLE

TERCONAZOLE

SYSTEMIC

KETOCONAZOLE

TRIAZOLES

VORICONAZOLE

ITRACONAZOLE

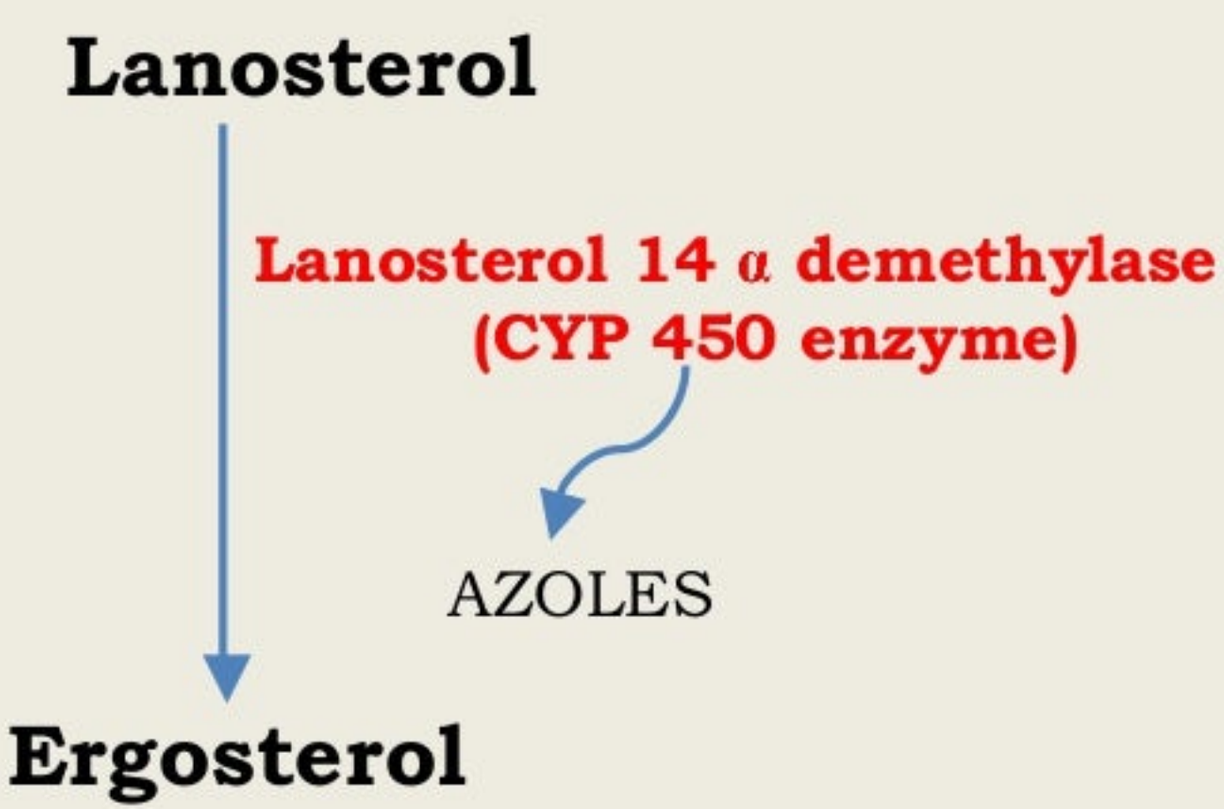
POSACONAZOLE

FLUCONAZOLE

AZOLE ANTIFUNGALS

- **Broad spectrum of cation with minimal ADRs**
- **More efficacious, Fungicidal**

MECHANISM OF ACTION



TOPICAL AZOLES

- **Used to treat oral, vulvovaginal, cutaneous candidiasis**
- **Used to treat T. corporis, cruris and capitis infections**
- **MICONAZOLE is more efficacious than other topical azoles**
- **$t_{1/2}$ - 1 to 6 hours**
- **Treatment ranges from 2 – 6 months based on the area of infection**

SYSTEMIC AZOLES
KETOCONAZOLE

- **Oral ketoconazole** has historically been used for the treatment of **systemic fungal infections** but is **rarely used today** due to the risk for severe **liver injury, adrenal insufficiency, and adverse drug interactions**.

PHARMACOKINETICS

- Orally well absorbed
- Metabolised by liver
- Well absorbed through out the body but does not enter CSF
- It is a potent CYP 450 enzyme inhibitor

PHARMACOKINETICS

- By inhibiting CYP enzymes it increases the concentration of drugs such as

  - DIGOXIN
  - WARFARIN
  - SULFONAMIDES
  - AMLODIPINE
  - STATINS
  - PHENYTOIN
  - NIFEDIPINE
  - CIMETIDINE
  - PHENOBARBITONE
  - CARBAMAZEPINE
  - TERFINADINE – QT interval prolongation and tachyarrhythmias

ADRS

- Inhibits enzymes useful for sterol synthesis
- Decreased production of testosterons leading to impotency, loss of hair, oligozoospermia and Gynaecomastia
- Menstrual irregularities
- Hepatotoxicity

THERAPEUTIC USES

- Systemic candidiasis
- Vaginal moniliasis
- Deep mycotic infections
- Cryptococcal infections
- Coccidioiodo infections

TRIAZOLES
FLUCONAZOLE

Most of its spectrum limited to yeasts and some dimorphic fungi.

Available in oral and IV formuations.

PHARMACOKINETICS

- Orally well absorbed
- Excreted unchanged in urine upto 90%
- Crosses BBB
- Has increased affinity towards fungal lanostreol

Ineffective against

- **Aspergillosis**
- **Histoplasmosis**
- **Blastomycoses**

INDICATIONS

✓ **It is used for prophylaxis against invasive fungal infections in recipients of bone marrow transplants.**

- ✓ **It also 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.**

- ✓ **It is commonly used as a single-dose oral treatment for vulvovaginal candidiasis**

TRIAZOLES
ITRACONAZOLE

- Orally well absorbed
- IV can be given in serious infections
- Not effective against fungal meningitis
- Adverse effects include nausea, vomiting, rash hypokalemia, hypertension, edema, and headache, hepatotoxicity.
- *It* has a **negative inotropic** effect and should be avoided in patients with evidence of ventricular dysfunction, such as heart failure.

INDICATIONS

- FLUCONAZOLE resistant fungal meningitis
- Histoplasmosis
- Blastomycoses
- Sporotrichosis
- Mucormycosis
- Coccidioiodomycosis
- Paracoccidioidomycosis

ITRACONAZOLE is the drug of choice

POSACONAZOLE

- Newer and most costliest of all the azoles
- Limited use due to increased cost
- It is available as an oral suspension, oral tablet, or IV formulation.
- *It* is commonly used for the **treatment and prophylaxis of invasive Candida and Aspergillus infections in severely immunocompromised patients.**
- **CYP inhibitor**

VORICONAZOLE

- It has **replaced amphotericin** B as the drug of choice for **invasive aspergillosis.**
- It is also approved for treatment of invasive candidiasis, as well as serious infections caused by **Scedosporium and Fusarium** species.
- Adverse effects are similar to those of the other azoles; however, high trough concentrations are associated with **visual and auditory hallucinations** and an **increased incidence of hepatotoxicity.**

All azoles are teratogenic hence contraindicated in pregnant and lactating women

	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)

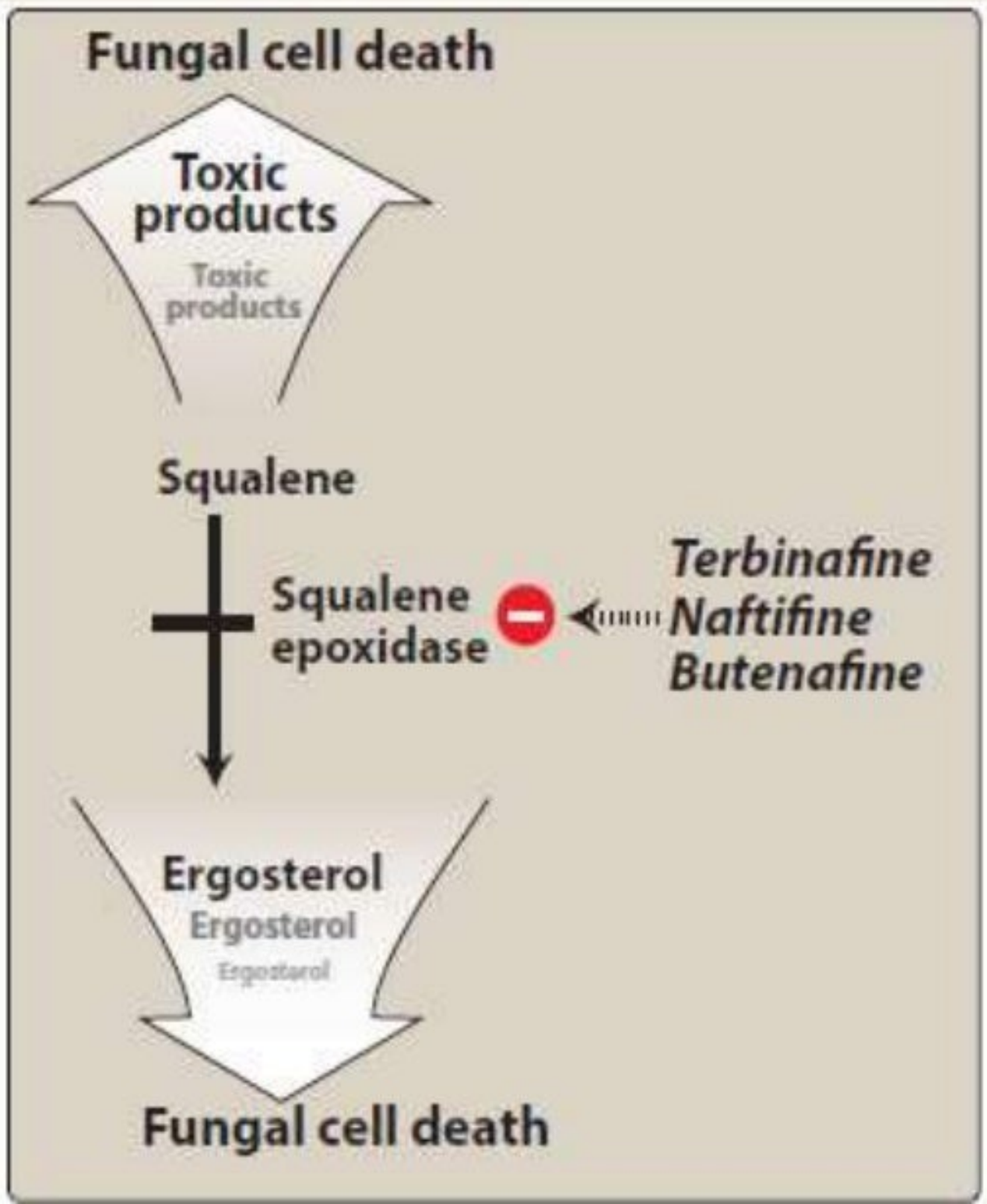
DRUGS FOR CUTANEOUS MYCOTIC INFECTIONS

- ✓ Mold-like fungi that cause cutaneous infections are called dermatophytes or tinea.
- ✓ Common dermatomycoses, such as tinea infections that appear as rings or round red patches with clear centers, are often referred to as **"ringworm."** This is a misnomer because fungi rather than worms cause the disease.
- ✓ **Trichophyton, Microsporum, and Epidermophyton.**

Squalene epoxidase inhibitors

Allylamine derivatives

- ✓ Terbinafine
- ✓ Butenafine
- ✓ Naftifine



Terbinafine

- ✓ **Oral *terbinafine*** is the drug of choice for treating **dermatophyte onychomycoses** (fungal infections of nails, therapy requires **3 months**)

- ✓ **Topical terbinafine** (1% cream, gel or solution) is used to treat **tinea pedis, tinea corporis** (ringworm), and **tinea cruris** (infection of the groin). Duration of treatment is **usually 1 week.**

Pharmacokinetics

- ✓ Terbinafine is available for **oral and topical** administration, although its bioavailability is only **40% due to first-pass metabolism**.
- ✓ It is **highly protein bound** and is deposited in the **skin, nails, and adipose tissue**.
- ✓ *It* accumulates in **breast milk** and should not be given to nursing mothers.
- ✓ A prolonged terminal half-life of **200 to 400 hours** may reflect the slow release from these tissues.

Adverse effects:

- ✓ Common adverse effects of *terbinafine* include **gastrointestinal disturbances** (diarrhea, dyspepsia, and nausea), headache, and rash.
- ✓ **Taste and visual disturbances** have been reported, as well as transient elevations in serum hepatic transaminases.

Terbinafine is an **inhibitor of the CYP450 2D6** isoenzyme.

GRISEOFULVIN

- Obtained from ***Streptomyces griseus***
- Effective against dermatophytes

PHARMACOKINETICS

- Well absorbed orally
- Absorption is enhanced in the presence of lipophilic substances
- Accumulation is enhanced in tissues made up of keratin such as skin, nails, and hair
- Can prevent further spread but cannot treat already infected keratinocytes

MECHANISM OF ACTION

GRISEOFULVIN

↓ Binds to

Tubulins

↓ inhibiting

Mitotic spindle formation

↓ Resulting in

Inhibition of separation of daughter nuclei

↓

FUNGISTATIC EFFECT

INDICATIONS

- It has been largely replaced by oral *terbinafine* for the treatment of onychomycosis, 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 for onychomycosis).

- Duration of therapy is dependent on the rate of replacement of healthy skin and nails.

ADRS

- Rashes
- Nausea
- Vomitings
- Diarrhoea
- Mild Hepatotoxicity

THERAPEUTIC USES

- *T. unguium*
- *T. corporis*
- Dermatophyte infections

GRISEOFULVINs use is limited because of extensive replacement by Azoles and Terbinafine

NYSTATIN

- Polyene antifungal, Posses very high systemic toxicity
- Not given in IV
- Used to treat topical infections
- Earlier it was used to treat moniliasis

It is administered as an oral agent ("swish and swallow" or "swish and spit") for the treatment of --

✓ Oropharyngeal candidiasis (thrush)

✓ Intravaginally for vulvovaginal candidiasis

✓ Topically for cutaneous candidiasis.

Ciclopirox

- ✓ Ciclopirox **inhibits the transport of essential elements** in the fungal cell, disrupting the synthesis of DNA, RNA, and proteins.
- ✓ It is active against Trichophyton, Epidermophyton, Microsporum, Candida, and Malassezia.
- ✓ Ciclopirox 1% shampoo is used for treatment of seborrheic dermatitis. Tinea pedis, tinea corporis, tinea cruris, cutaneous candidiasis, and tinea versicolor may be treated with the 0.77% cream, gel, or suspension.

Tolnaftate

- ✓ *Tolnaftate* **distorts the hyphae and stunts mycelial** growth in susceptible fungi.
- ✓ It is active against **Epidermophyton, Microsporum, and Malassezia furfur.**
- ✓ *Tolnaftate* is used to treat **tinea pedis, tinea cruris, and tinea corporis.**
- ✓ It is available as a 1% solution, cream, and powder.

DRUG OF CHOICE FOR VARIOUS FUNGAL INFECTIONS

FUNGUS	DISEASE	FIRST DOC	SECOND DOC
Cryptococcus neoformans	**Meningitis**	**AMPHOTERICIN B ± 5-FLUCYTOSINE**	**FLUCONAZOLE**
Candida albicans	**Candidiasis (oral, vaginal, or cutaneous)**	**FLUCYTOSINE NYSTATIN CLOTRIMAZOLE**	**ITRACONAZOLE**
	Deep mycosal/ disseminated	**AMPHOTERICIN B VORICONAZOLE**	**FLUCONAZOLE**
Pityrosporom orbiculare	**Pityriasis versicolor/ Tinea versicolor**	**TREBINAFINE**	**FLUCONAZOLE**
Histoplasma capsulatum	**Histoplasmosis**	**ITRACONAZOLE AMPHOTERICIN B**	**FLUCONAZOLE**
Coccidiodes immitis	**Coccidiomycosis**	**AMPHOTERICIN B FLUCONAZOLE**	**ITRACONAZOLE KETOCONAZOLE**
Blastomyces dermatides	**Blaatomycosis**	**ITRACONAZOLE AMPHOTERICIN B**	**KETOCONAZOLE FLUCONAZOLE**
Sporothrix sp.,	**Sporotrichosis**	**AMPHOTERICIN B**	**ITRACONAZOLE**

DRUG OF CHOICE FOR VARIOUS FUNGAL INFECTIONS

FUNGUS	DISEASE	FIRST DOC	SECOND DOC
Aspergillus fumigatus	**Pulmonary aspergillosis** **Asperglioma** **Asthma associated with aspergillosis** **Sinusitis** **Respiratory infections**	**AMPHOTERICIN B** **VORICONAZOLE**	**ITRACONAZOLE**
Paracoccidioides braziliensis	**Paracoccidioidomycosis**	**ITRACONAZOLE**	**AMPHOTERICIN B**

Questions

1. Which of the following antifungal agents is MOST likely to cause renal insufficiency?

A. Fluconazole.

B. Amphotericin B.

C. Itraconazole.

D. Posaconazole.

Correct answer = B. Amphotericin B is the best choice since nephrotoxicity is commonly associated with this medication.

- ✓ Although the dose of fluconazole must be adjusted for renal insufficiency, it is not associated with causing nephrotoxicity.
- ✓ Itraconazole and posaconazole are metabolized by the liver and are not associated with nephrotoxicity.

2. A 55-year-old female presents to the hospital with shortness of breath, fever, and malaise. She has a history of breast cancer, which was diagnosed 3 months ago, and has been treated with chemotherapy. Her chest x-ray shows possible pneumonia, and respiratory cultures are positive for Aspergillus fumigatus.

Which of the following is the MOST appropriate choice for treatment?

A. Voriconazole.

B. Fluconazole.

C. Flucytosine.

D. Ketoconazole.

Correct answer = A. Voriconazole is the drug of choice for aspergillosis.

Studies have found it to be superior to other regimens including amphotericin B.

Fluconazole, flucytosine, and ketoconazole do not have reliable in vitro activity and are therefore not recommended.

3. Which of the following antifungal agents should be avoided in patients with evidence of ventricular dysfunction?

A. Micafungin.

B. Itraconazole.

C. Terbinafine.

D. Posaconazole.

Answer B. Itraconazole has a **negative inotropic** effect and should be avoided in patients with evidence of ventricular dysfunction, such as heart failure.

4. A 56-year-old female with diabetes presents for routine foot evaluation with her podiatrist. The patient complains of thickening of the nail of the right big toe and a change in color (yellow). The podiatrist diagnoses the patient with **onychomycosis** of the toenails.

Which of the following is the most appropriate choice for treating this infection?

A. Terbinafine.

B. Micafungin.

C. Itraconazole.

D. Griseofulvin.

Correct answer = A. Terbinafine is better tolerated, requires a shorter duration of therapy, and is more effective than either itraconazole or griseofulvin. **Micafungin is not active for this type of infection.**


Thank
YOU