Antifungal drugs

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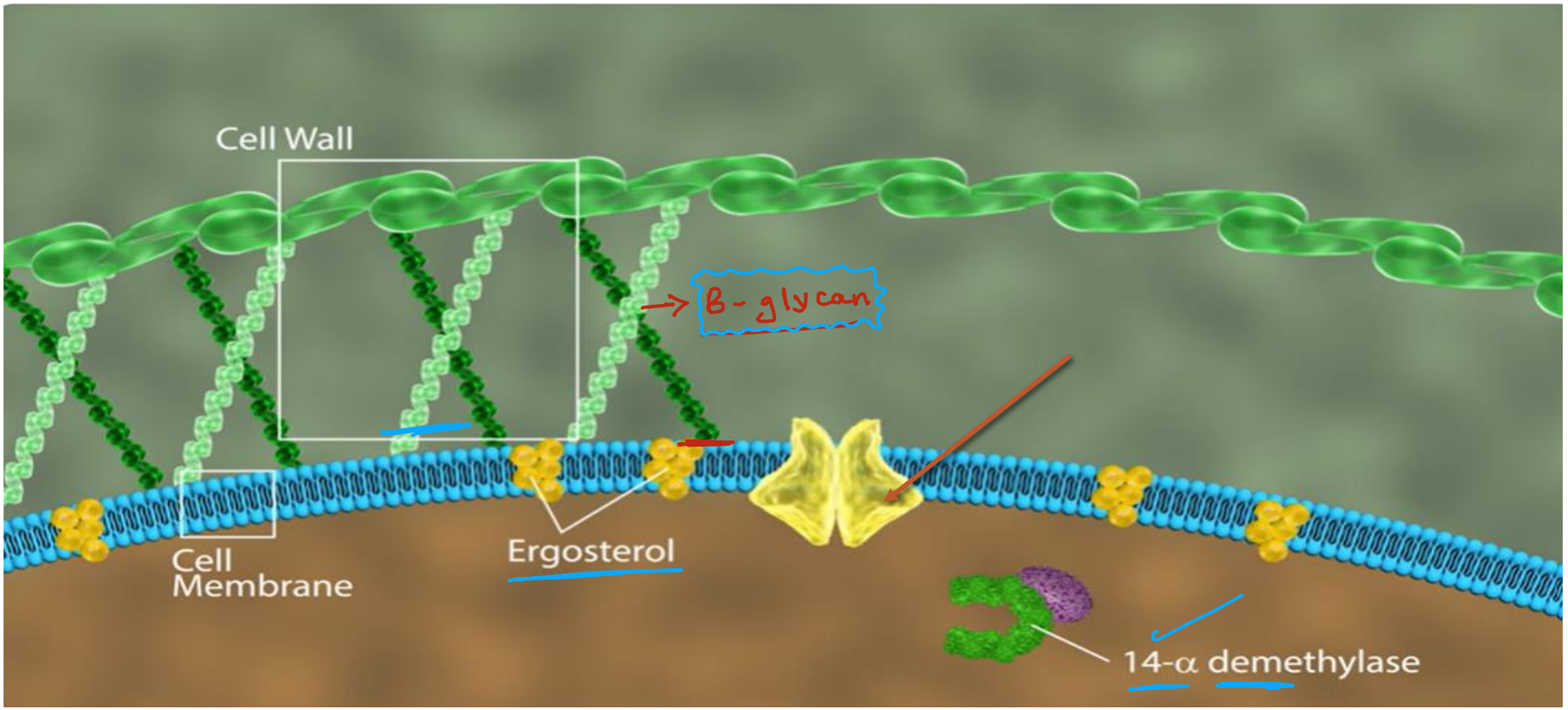
FUNGAL CELL WALL STRUCTURE

→ it appear when the immunity distrupted !!

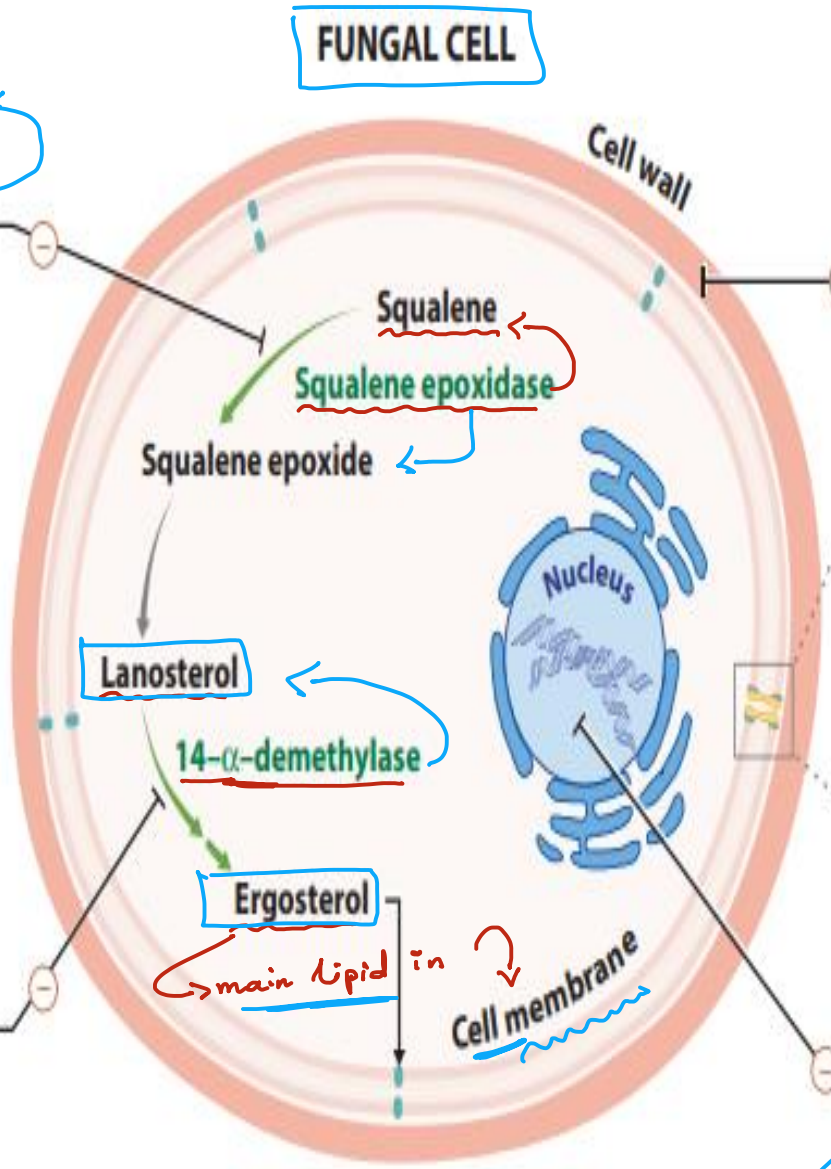


1- How does the lipid of cell membrain formed ?

2- whatfire the drug does it involved in distruption of fungi cell membrain ?

3- whatfire the division of antifungal drug ?

Antifungal therapy



LANOSTEROL SYNTHESIS

Terbinafine Fungicidal

جلين سنافين ؟!

ERGOSTEROL SYNTHESIS

Azoles Fungicidal :-

- Clotrimazole
- Fluconazole
- Itraconazole
- Ketoconazole
- Miconazole
- Voriconazole

↳ prevent the formation of Ergosterol

Fungicidal

CELL WALL SYNTHESIS :-

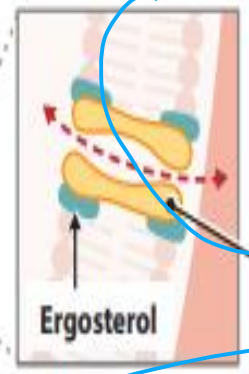
Echinocandins

- Anidulafungin
- Caspofungin
- Micafungin

أم فوتيسين

Fungicidal

CELL MEMBRANE INTEGRITY



Polyenes

- Amphotericin B parenteral
- Nystatin not absorbed just local

↳ Nice tatain

NUCLEIC ACID SYNTHESIS

Poliy DNA

↳ static

Flucytosine cancer drug

↳ Fungal infection.

↳ ص خلية بكتيريا

→ classification according to Target

Antifungals

Cell well inhibitors ①

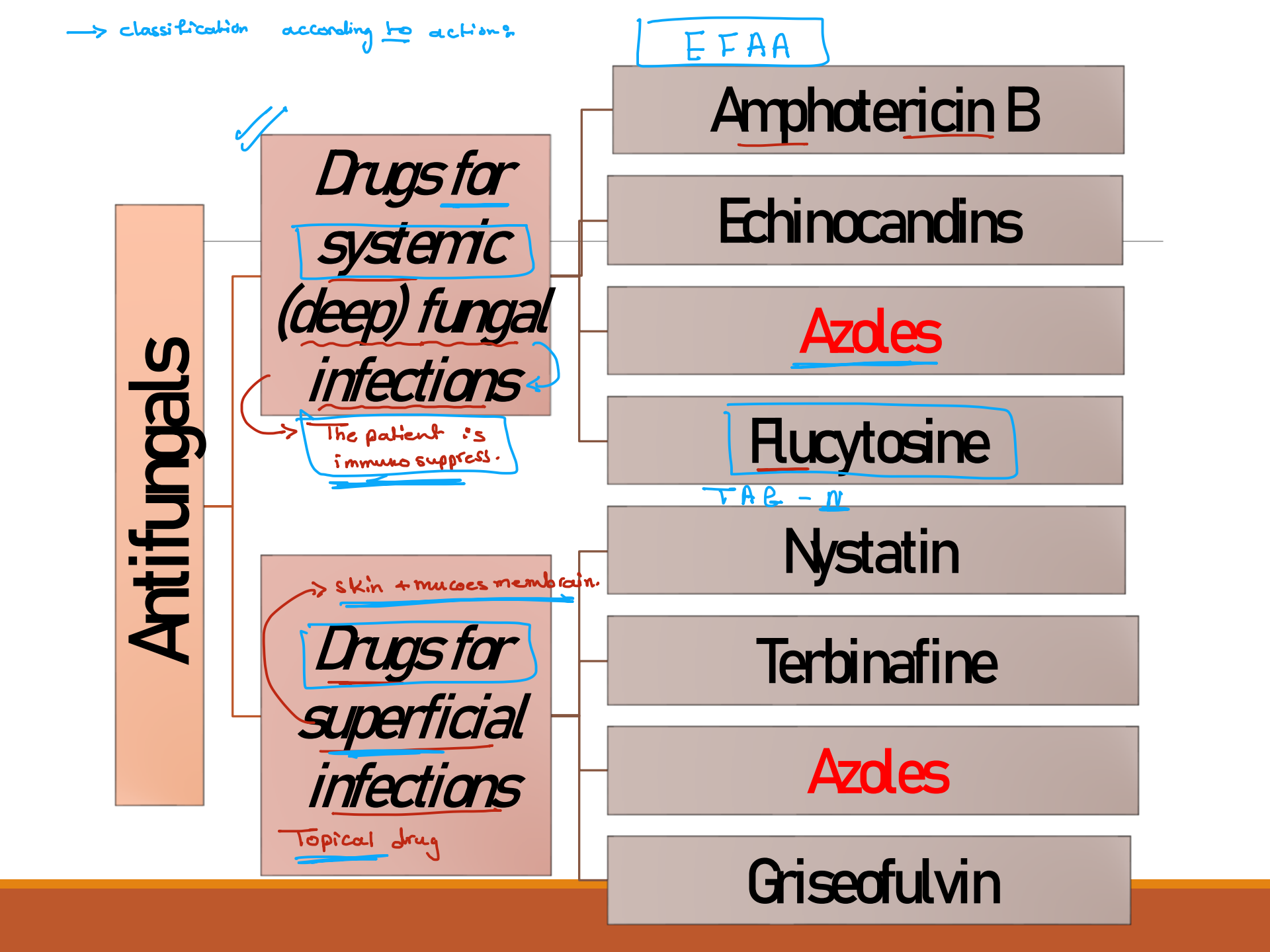
cidal

- Terbinafine
- Amphotericin B
- Nystatin
- Echinocandins
- **Azoles**

Antimetabolites ②

static

- Griseofulvin
- ① Flucytosine


→ classification according to action:
EFAA
Antifungals
Drugs for systemic (deep) fungal infections
The patient is immunosuppress.
Amphotericin B
Echinocandins
Azoles
Flucytosine
TAB - IV
Drugs for superficial infections
skin + mucoes membrain.
Topical drug
Nystatin
Terbinafine
Azoles
Griseofulvin

1- what's the pk: ?
2- what's the machanism of it?
3- what're the indiction and side effect?

Terbinefine

→ Cell membrain inhabitor / superficial infections.

→ inhabition of squeen epioxdease.

pk:

- *Oral active, Bioavailability 40% due to 1st pass metabolism* ✓
- *99% bound to plasma protein* / ↓ Vol distribution.
- *Deposited in nails, skins, and fats, milk* [Any cell have keriten].
  - not for pregent.
- *T1/2=200-400h*
- *Extensive metabolism in liver*
- *Excreted in urine*

Mechanism: ***fungicidal*** → inhabit the synthise of lanosterol !

Inhibition of squalene epoxidase enzyme which is essential for ergosterol synthesis of cell membrane. [Lanosterol].

Indications:

① Systemic (oral) → active orally. & ② topical for dermatophytcs → Superfacial infections. (more effective than griseofulvin). Duration of treatment up to 3 months.

Side effects:

① GIT and taste disturbances, ④ hepatotoxicity, ② headache, ③ visual disturbance.

→ because the duration of treatment ③ m .so they affect the liver enzyme.

Advantages over Azoles:

1. Squalene epoxidase enzyme is not present in human (more selective toxicity).

2. No inhibition of cytochrome P_{450} (no serious adverse effect of azoles).

But affected by enzymes inducers and inhibitors

1- what's the feature of it ?
2- what's the machanizm of action ?
3- what're the membrain of them ?
4- what's the bad feature of it ?
5- what're the membrain 2.

Azoles

First anti fungal is discovered. to treat fungal infection.

Mechanism of action: fungicidal :-

inhibit ergosterol synthesis of cell membrane by inhibiting fungal cytochrome p450 (14 α demethylase) leading to membrane dysfunction.

Members :

1- Ketoconazole

2- Itraconazole

3- Fluconazole

4- Posaconazole

→ inhabition of cytochrome for fungel
→ more selective.

→ it work in both cytochrome p 450 of human and fungel.

1- what's the most important feature of it ?

2- what's the pk ?

3- what're the indication of it?

4- what's the red flag combination ?

5- what're the side effect ?

Ketoconazole:

1st oral broad spectrum antifungal.

Pk:

→ Oral and required acidic ph to be absorbed ✓

Extensive bound to plasma protein

Extensive metabolism in liver

It is used for:

- Deep fungal infections (mild - non meningeal). 2nd line to amphotericin
- Candida infection.
- Dermatophyles resistant to grisofulvin & terbinafine (oral and topical).

Avoid combination with:

- Antacids or H_2 blockers → decrease gastric acidity → decrease ketoconazole absorption.
- Amphotericin B: ketoconazole → decrease amphotericin effect by decreasing ergosterol

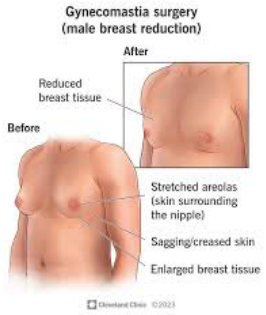
→ because it absorbed in acidic media just.

Adverse effects:

1. Nausea - vomiting - rash (common).
2. Hepatotoxic (serious). + Terbenaphin.
3. **Inhibition of human cytochromeP450**
4. **Enzyme inhibitor**

→ if the patient take astmeazole with Ketokonazol [enzyme inhabitor] → prevent the metabolite of it lead to arrthymia.

Gynecomastia is the non-cancerous enlargement of one or both breasts in men due to the growth of breast tissue as a result of a hormone



1- what're the effect of inhabition of cytochrom p450 ?

2- what're the result?

Inhibition of human cytochrome P450 leading to inhibition of :-

Steroid synthesis which depends on cytochrome P450:

- Corticosteroids → adrenal suppression (used in Cushing's disease). ⇒ Acute adrenal failer → Adeson syndroma.
- Testesterone → gynecomastia & impotence (used in cancer prostate).
- Female sex hormones → menstrual irregularities & infertility

Metabolism of drugs → drug interactions:

- Increased level of astemizole & terfenadine → arrhythmia.
- Increased level of oral anticoagulants & antiepileptics.

enzyme inhabitor.

As an enzyme inhabitors. by inhabition of metabolizm.

1- what's special about these drug?

2- what's the difference from ketoconazol?

Itraconazole and fluconazole

→ more selectivity → just work on ? Fungi cytochrome p450.

- These drugs are azoles (*) that are more specific to fungal cylochrome P_{450} than to human cytochme P_{450} compared to ketoconazole.
- Less toxic (1) (less effect on human cytochrome P_{450}): less (2) hepatotoxic, less adrenal suppression (3) & less drug interactions (4).
- More effective.

1-what're the important indications of it?

2-what's the combination of it?

Fluconazole:

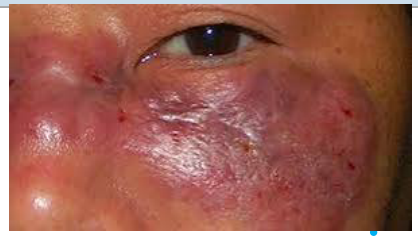
Drug of choice in esophageal and oropharyngeal candidiasis.

- Drug of choice in treatment and secondary prophylaxis against cryptococcal meningitis.
- Equivalent to amphotericin B in systemic candidiasis

→ due to immune suppression in children, a white spots start to appear in the oral and they painful.

1- what's the feature of PLP?
2- what're the indications ?

Posaconazole



- The broadest-spectrum azole.
- The only azole with activity against mucormycosis.
- It is used for prophylaxis of fungal infections during cancer chemotherapy.
- Inhibitor of CYP3A4 → increasing the levels of cyclosporine and tacrolimus

1- what're the machanism of amphotericin B ?
2- what're the indications ?
3- what're the side effect and treatment of it?

→ cell membrain integrety / deep infections.

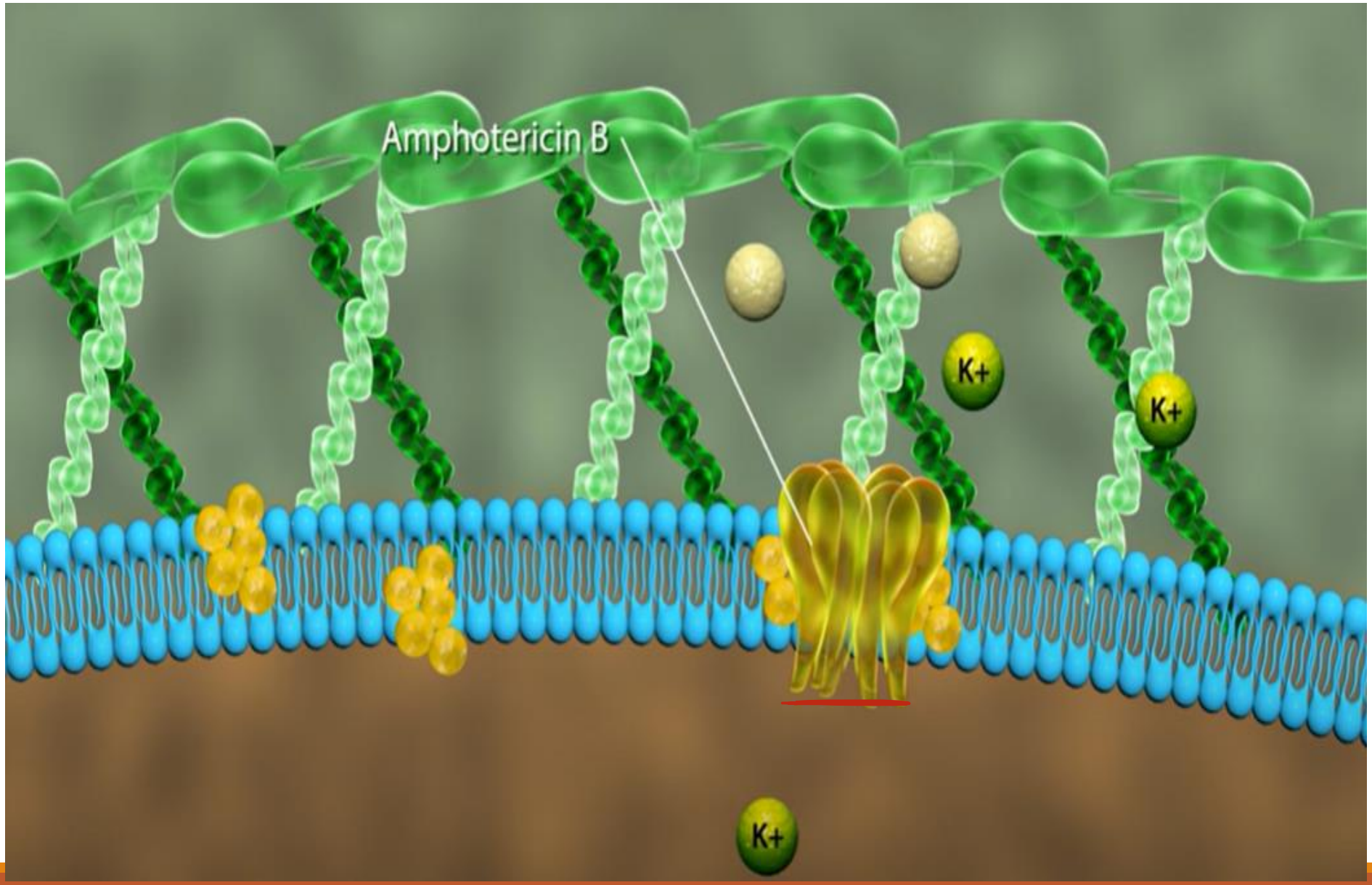
Amphotericin B

Mechanism of action: fungicidal

- Binds to ergosterol of cell membrane → formation of artificial pores → leakage of important cell constituents' → cell death.

Indications: deep infections especially:

- Severe life threatening (I.V - not absorbed orally).
- Meningitis (intrathecal- does not reach CSF after I.V.I).


Amphotericin B
K+
K+
K+

Side effects & toxicity:

- **Infusion related:** Fever, rigors, vomiting, hypotension & shock after I.V infusion.

Can be avoided by: Slow infusion rate and pretreatment with antihistamines, antipyretics.

- **Dose-related:** nephrotoxicity. **Can be decreased by:** dose reduction.

- **Convulsion.**

1- what's the pk ?
2- what's the mechanism of it ?
3- what're the indications ?

Nystatin

Mechanism:

→ used locally, NoT absorbed → it treat the infection.
→ if it absorbed → Toxic.

Binds to ergosterol of fungal cell membrane → formation of artificial pores—» damage of membrane → leakage of important cell constituents → cell death.

Indications: (too toxic for systemic use).

Locally use

Used locally in:

1. Oropharyngeal and GI Candida: oral (not absorbed).
2. Cutaneous Candida: topical (non irritant- rarely causes allergy).
3. Vaginal Candida: It is given both topically and orally because quite often vaginal Candida is associated with gastrointestinal Candida which acts as a source of reinfection of vagina.

1- what's the machanism?
2 - what're the indications ?
3- what're Ad effect 2

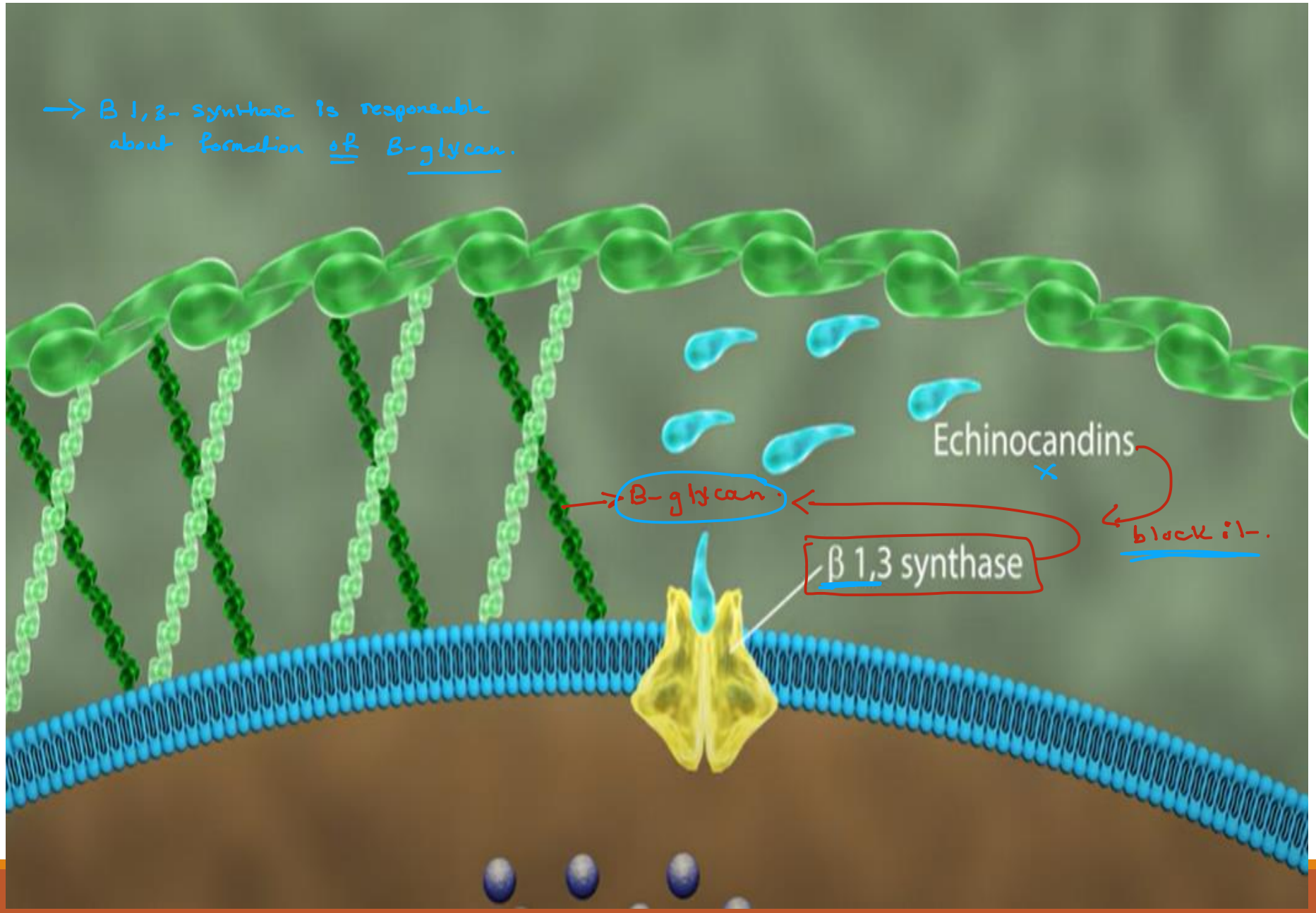
→ cell membrain / deep infections.

Echinocandins

Caspofungin – Micafungin

Mechanism:

Inhibits synthesis of a glucose polymer (glycane synthase) that is necessary for maintaining structure of fungal cell wall → loss of cell wall integrity → lysis & death.


→ B 1,3- synthase is responsible about formation of B-glycan.
Echinocandins
B-glycan
block it.
β 1,3 synthase

Uses: (IV)

Caspofungin: candidiasis & invasive aspergillosis refractory to amphotrericin.

Micafungin: mucocutaneous candidiasis and for prophylaxis of *Candida* infections in bone marrow transplant patients

Adverse Effects:

Infusion-related: GIT upset, headache, fever & flushing (histamine release).

1- what's the machanizm of it ?
2- why it Selective toxic ?
3- what're the indications?
4- what're the advers effect ?

X Transformed →

Antimetabolite

Flucytosine

دوا سرطان

like nucleotide of DNA.

Mechanism of action:

- Cytotoxic ①, transformed ② to 5-flurouracil (5-FU) → inhibits nucleic acid synthesis.
- Selective toxicity: occurs because mammalian cells cannot transform flucytosine into 5-FU.
- ***Indications:***

Given orally with amphotericin or azoles in Cryptococcal infections.

Adverse effects:

1. Bone marrow depression (reversible).
2. Hair loss.
3. Hepatotoxic.

Advantages of combination of flucytosine with amphotericin B:

1. Decrease resistance to amphotericin B.
2. Decrease amphotericin nephrotoxicity (lower doses of amphotericin are used).

Griseofulvin

Mechanism: *Fungistatic*

Concentrated in newly formed keratin (e.g nails) preventing its infection by:

Interfering with microtubular function → interfere with mitosis.

Inhibiting nucleic acid synthesis.

Indications: not active topically, duration of treatment 6-12 months

- Dermatophyte infections (given orally: decreased absorption by high fat diet).
- Largely replaced by terbinafine & azoles

Adverse effects :

1. Nausea-vomiting.
2. Headache - mental confusion.
3. Hepatotoxic.
4. Enzyme inducer → decrease warfarin level.
5. Teratogenic , Carcinogenic

Systemic therapy is used in:

1- Resistance to topical therapy.

2- Wide or inaccessible areas.

3- Severe infections.

4- Low immunity of patient.

N.B: Superficial fungal infections are treated first with topical agents