Anti-Fungal Drugs

Classification of Antifungal drugs:

I- ***Drugs for systemic (deep) fungal infections*** **:**

1- Amphotercin B.

2- Flucytosine.

3- Caspofungin.

4- Azoles: ketoconazole – fluconazole – itraconazole.

II- ***Drugs for superficial infections :***

A. Drugs given systemically : azoles – griseofulvin – terbinafine.

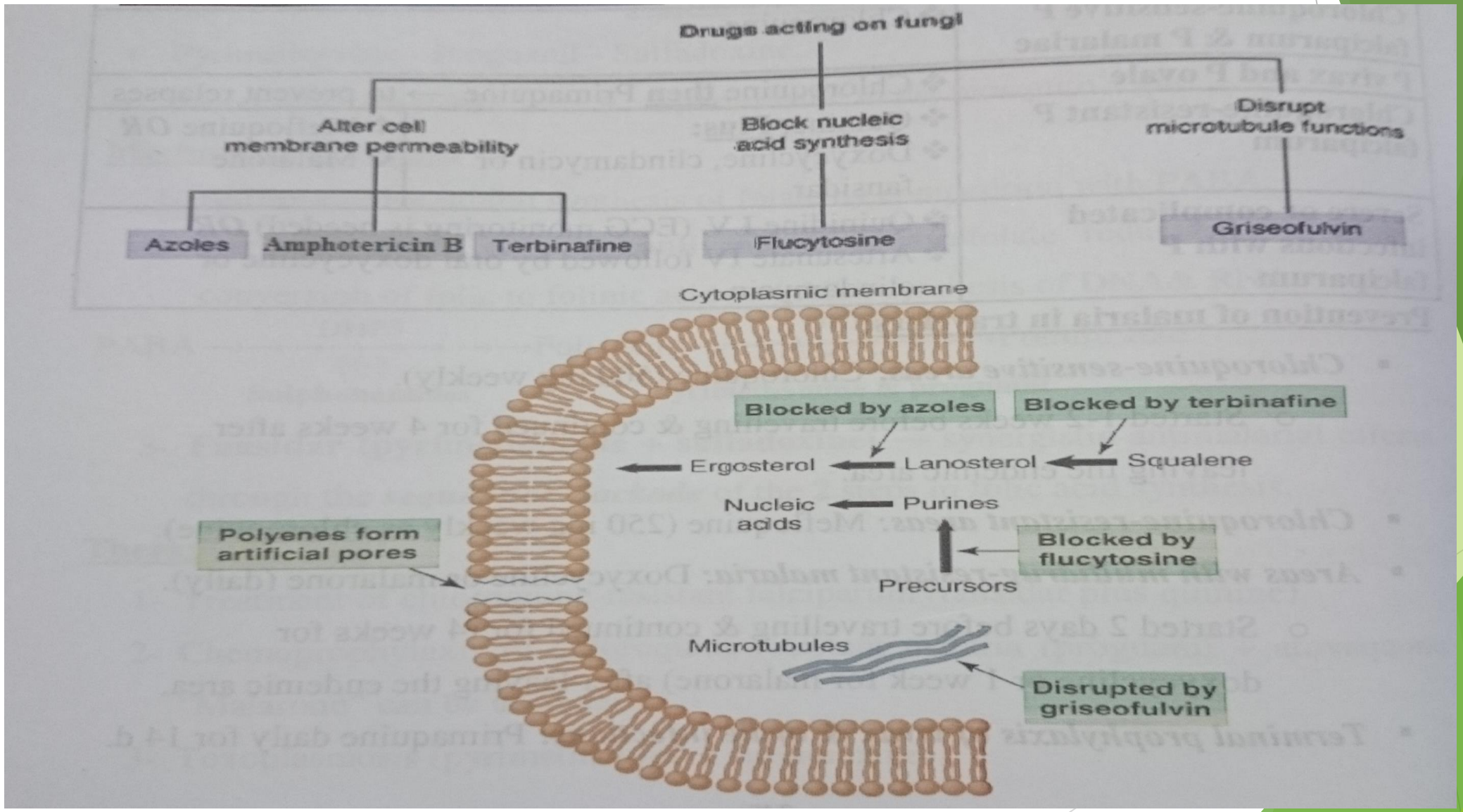
B. Drugs given topically : azoles – nystatin – terbinafine.

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

Systemic therapy is used in:

1) Resistance to topical therapy.
2) Wide or inaccessible areas.
3) Severe infections.
4) Low immunity of patient.

According to mechanism of action, antifungal drugs are classified as following:



Flucytosine

Mechanism of action:

- It is transformed to 5-flurouracil (5-FU) ⟶ inhibition of nucleic acid synthesis.
- Human cells cannot transform flucytosine into 5-FU ⟶ selective toxicity.

Indications: given orally **with amphotericin or azoles** in **Cryptococcal infections.**

Adverse effects:

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

Amphotericin B

Mechanism of action: ***fungicidal***

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

- It is selectively toxic to fungi **because** they interact with ergosterol, a sterol unique to fungal cell membranes.

Indications: the most important antifungal in ***deep fungal infections*** especially:

- Severe life-threatening (IV – not absorbed orally).
- Meningitis (intrathecal- does not reach CSF after IV injection)

Side effects :

A. **Infusion Related:** Fever, rigors, hypotension& shock. They can be avoided by:
   1- Slow infusion rate.
   2- Pretreatment with antihistamines, antipyretics, meperidine or glucocorticoids.

B. **Dose-related nephrotoxicity.** This can be decreased by:
   1- Dose reduction (& combine with flucytosine).
   2- Use of **liposomal formulations**(less binding of the drug to renal cells)

C. **Convulsion (** with intrathecal injection).

Advantages of combination of flucytosine with amphotericin B:

1. Decrease resistance to amphotericin B.
2. Lower doses of amphotericin are used ⟶ less nephrotoxicity.

Azoles

- Ketoconazole – Fluconazole – Itraconazole.
- Given orally.

Mechanism of action: *fungicidal*

- Inhibition of ergosterol synthesis by inhibiting fungal cytochrome P_{450} leading to membrane dysfunction.

Ketoconazole : 1st oral broad spectrum antifungal. **It is used for:**

1. Deep fungal infections (mild &non-meningeal) as alternative to amphotericin.
2. Candida infection.
3. Dermatophytes resistant to grisofulvin & terbinafine (oral and topical).

Avoid combination with :

1. Antacids or H_2 blockers → decrease gastric acidity → decrease absorption.
2. Amphotericin B: ketoconazole → decrease amphotericin effect by decreasing ergosterol (target for amphotericin).

Adverse effects:

1. Nausea – vomiting – rash (common).
2. Hepatotoxic (serious).
3. Inhibition steroid synthesis which is dependent on cytochrome P_{450} .

- Corticosteroids → adrenal suppression (used in Cushing`s disease).
- Testosterone → gynecomastia & impotence (used in cancer prostate).
- Female sex hormones → menstrual irregularities & infertility.

4. Inhibition of metabolism of drugs → **drug interactions**

- Astermizole &terfenadine (antihistamines) → arrhythmia.
- Warfarin & antiepileptics.

Itraconazole and fluconazole:

- They are more specific to fungal than human cytochme P_{450} .
- ✓ Less hepatotoxic.
- ✓ Less adrenal suppression.
- ✓ Less drug interactions.
- More effective.

- **Fluconazole :**

1. Drug of choice in esophageal and oropharyngeal candidiasis and cryptococcal meningitis .
2. Equivalent to amphotericin B in systemic candidiasis.

Griseofulvin

Mechanism: ***Fungistatic***

1) Interfering with microtubular function ⟶ inhibition of mitosis.
2) Inhibiting nucleic acid synthesis.

Uses: not active topically so given orally in ***dermatophyte infections.***

N.B. It is largely replaced by terbinafine & azoles.

Adverse effects:

1) Nausea & vomiting.
2) Headache & mental confusion.
3) Hepatotoxic.
4) Enzyme induce ⟶ decrease warfarin level.

Advantages of fluconazole over ketoconazole & itraconazole:

1. Better absorption (not dependent on gastric acidity) → Not affected by the use of antacids or H_2 blockers.
2. Reaches CSF → could be given in fungal meningitis.
3. Single dose → higher patient`s compliance.

Posaconazole:

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

Echinocandins

Caspofungin – Micafungin

Mechanism: inhibit synthesis of a glucose polymer that is necessary for maintaining structure of fungal cell wall → loss of cell wall integrity → lysis & death.

Uses: (by IV route)

1) **Caspofungin:** candidiasis & invasive aspergillosis refractory to amphotericin.
2) **Micafungin:** mucocutaneous candidiasis and prophylaxis of *Candida* infections in bone marrow transplant patients.

Adverse effects:

- ***Infusion-related :*** Headache, fever & flushing (histamine release).

Terbinefine

Mechanism: ***Fungicidal***

- Inhibition of squalence epoxidase enzyme which is essential for ergosterol synthesis of cell membrane.

Advantages over azoles:

1. Squalene epoxidase enzyme is not present in human (more selective toxicity).
2. No inhibition of cytochrome P_{450}.

Uses :

- Oral & topical for dermatophytes (more effective than griseofulvin).

Side effects (safe) : GIT and taste disturbances.

Nystatin

Mechanism:

- Binds to ergosterol of fungal cell membrane → formation of artificial pores → leakage of important cell components → cell death .

Uses : (too toxic for systemic use). ***Used in:***

1. Oropharyngeal and GIT candidiasis: given orally (not absorbed)
2. Cutaneous candidiasis: topical (not irritant & rarely causes allergy).
3. Vaginal candidiasis : given both topically and orally as GIT candidiasis forms a source of reinfection of vagina.