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YU-Medicine

PHARMACOLOGY



- Sheet (**21**)
- Lecture title : **Antifungal Drugs**
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Antifungal Drugs

General Pharmacology

M212

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Ph.D. Pharmacology



Note that the Underlined sentences
in the doctor's slide indicates what
she said in the lecture

Antifungal Drugs

- **Fungal cell Wall is rigid, composed of chitin** and its cell membrane contains **ergosterol**.
- Human cell membrane contains Cholesterol. Bacterial cell wall contains peptidoglycan.
- Fungi are resistant to antibacterials and bacteria to antifungals.
- Fungal infections are common in:
- Immunosuppressed patients Chemotherapy therapy, steroid therapy & AIDS. (note the last point in slide 6)

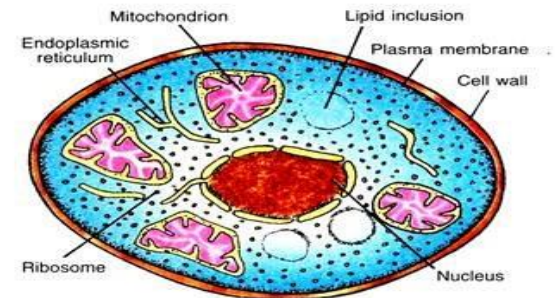


Fig. 1.8. Fungi. Fine structure of *Torula* Yeast cell based on an electron micrograph.

Notes about the previous slide :

- Antifungals are safe to the human cells. In general they are safe and very selective in its toxicity.
- Fungi can cause any of bacterial infection for example:
 1. Urinary tract infection
 2. Meningitis
 3. Pneumonia
 4. Hepatitis .
- But the problem with fungous infection is that it's very difficult to be treated.(difficult to eradicate it)
- The main reason is that fungi differ from bacteria in replication (they are very slow in replication) and as we now these types of drugs act on the next generations so in fungous infection we always need a longer duration of treatment

Cont. Notes about the previous slide :

- So I need to wait the next generation to be produced which needs longer time.
- Duration of treatment by antifungal drugs needs mostly 6 weeks to 8 weeks . Sometimes infection by mycosis needs 3 months to be treated.
- Where we can find fungus infection? It's not easy to infect people with normal immune system , rather than this it mostly occur by to ways :
 1. In immune compromised people for example those who have AIDS or who used corticosteroids for a long time (or other drugs which effect the normality of immune system) .
 2. Regions which contains epidemiological fungous (you can get infection here).

Fungal infections

- Fungal infections is called **Mycosis** , it is often chronic.
 1. **Superficial fungal infections involve:** cutaneous surfaces (skin, nails, and hair) (note slide 8)
 2. **subcutaneous mycosis** (note slide 9)
 3. **Systemic mycosis** (note slide 9)

Common Fungi are: **candida spp** and **Aspergillus spp**

- Aspergillus can cause asphergilosis
- candida causes candidiasis

Notes about the previous slide :

- Fungus infection is three types:
 1. Superficial : means it's outside (nails , hair and skin)
- Example about hair is dandruff . It's not always caused by humidity, fungi can cause it
- We can use ketoconazole to treat it.
- About nails : it's very rare but if it happens it's very difficult to treat it.
Why?
- Because in this case the drug is given orally (not locally by cream or gel) which means it's not easy to reach the nails because the blood supply is very low and narrow.

Cont.

2. subcutaneous mycosis : for example oropharynx .

- It causes oral thrush or ulceration in the mouth
- One type of fungi which cause this infection is candida albican.
- this infection most commonly occurs in neonates during breast feeding when the mother has nipple infection so in these case you have to treat the nipples and neonate mouth (by gel).

3. Systemic mycosis : now fungal infection is deeper.

- it entered the GIT, meningitis and liver hepatocytes ,urinary tract , etc.
- In this case you need deeper and stronger antifungals.

Antifungal Drugs

- I. **Antifungals damaging permeability of the cell membrane** (see slide 12)
 1. **Polyene** : bind with ergosterol (see slide 13)
 - Amphotericin B and Nystatin
 2. **Azoles: inhibit ergosterol synthesis** (see slide 14)
 - **Imidazole:**
 - Ketaconazole, Clotrimazole , Econazole and Miconazole.
 - **Triazole**
 - Fluconazole, Voriconazole and Itraconazole.
 3. **Allylamines: inhibit ergosterol synthesis** (see slide 14)
 - Naftifine and **Terbinafine**
- In general, imidazoles are given topically for cutaneous infections, whereas triazoles are given systemically for the treatment or prophylaxis of cutaneous and systemic fungal infections.

Antifungal Drugs

II. Antifungals inhibiting mitosis

Caspofungin, Griseofulvin

III. Antifungals inhibiting synthesis of nucleic acids

➤ **Flucytosine**

Notes about the previous slides :

- We want to study antifungal drugs one by one depending on the target for each group:
 1. Acting on the cell membrane :
 - This type of drug acts by two mechanisms :
 - a) Binding to the ergosterol in the cell membrane (effect both the mother cell and the neo generations) .
 - b) Inhibit synthesis of ergosterol , so they have to enter the cell in the ER(which effect the neo generations).
- Both of them causes pores in the cell membrane and lead to loose of permeability of it.

Cont.

- Depending on antifungals that damaging permeability of the cell membrane we have 3 groups (one binds to ergosterol and two inhibit synthesis of it) .
 - A. Polyene : bind with ergosterol
 - ✓ Amphotericin :
 - it's similar to antibacterial called aminoglycoside by:
 1. Given by IV
 2. causing nephrotoxicity
 3. not the first line
 4. has narrow therapeutic index .
 - So it's not easy drug
 - ✓ Nystatin : it's not given by IV , very nephrotoxic (so they excluded it), given to treat oral thrush caused by candida. موضعي فقط

Cont.

B. Azoles: inhibit ergosterol synthesis:

- This is the most common group , they are available in oral dosage form , oral gel, vaginal cream , vaginal pessaries , some of them are in IV form and it can be used for outpatients .

C. Allylamines: inhibit ergosterol synthesis

- Naftifine and Terbinafine are used to treat regions in the body which have keratin for example hair nails and skin
- For example scalp fungus.

2. Antifungals inhibiting mitosis : it can also inhibit chitin synthesis , means it's a double active fungicidal.

3. Antifungals inhibiting synthesis of nucleic acids

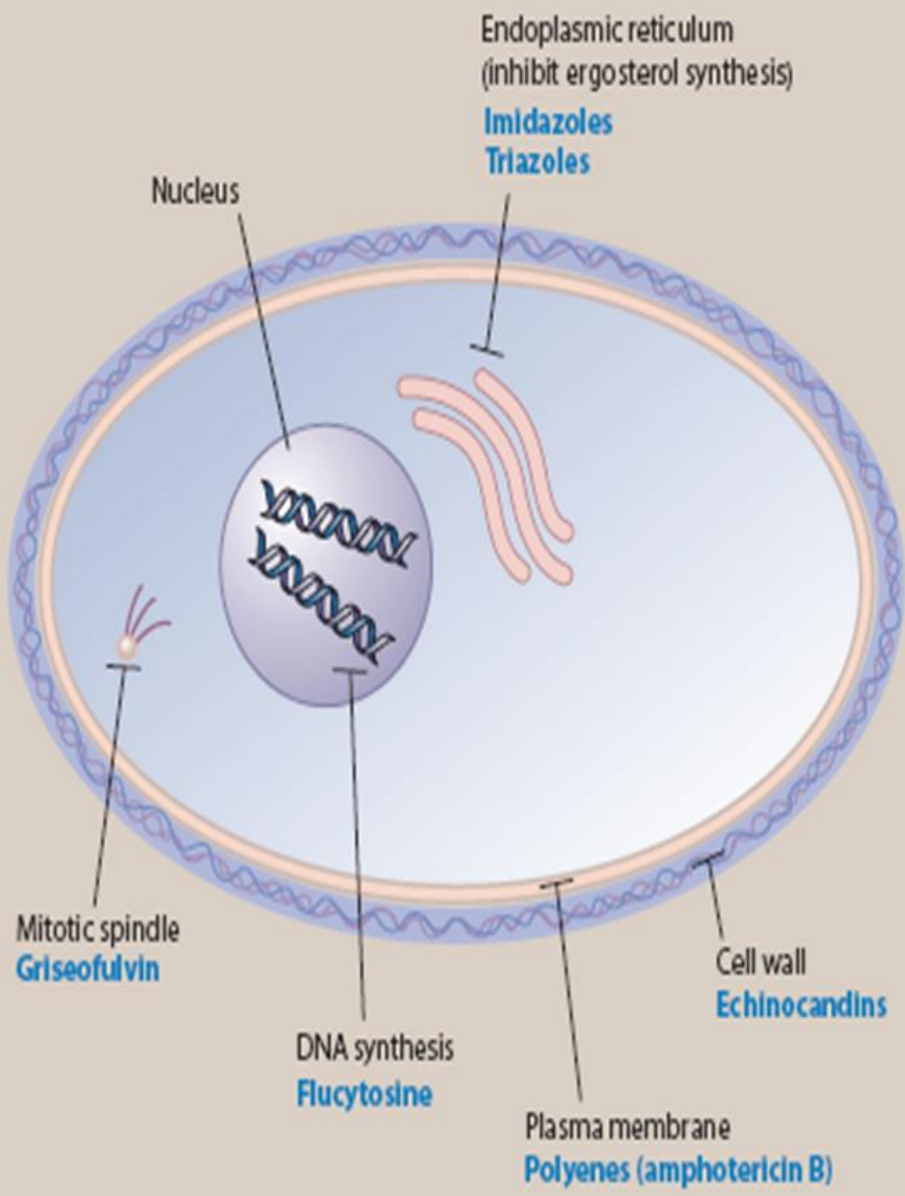
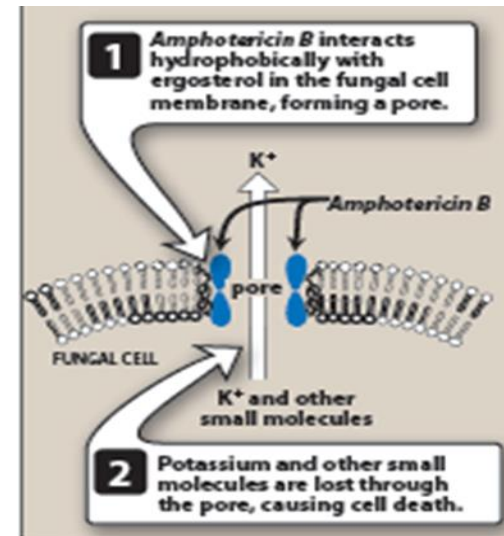


Figure 42.3

Cellular targets of antifungal drugs.

1. Polyene: Amphotericin and Nystatin

- MOA: Binds to fungal cell membrane ergosterol lead to **form pores** in fungal cell membrane → *increased fungal cell membrane permeability* and the loss of intracellular constituents loss of macromolecules and ions (K^+) → irreversible cell damage



Amphotericin B

- ❑ Fungicidal
- ❑ **Broad Spectrum:** Candida albicans, Histoplasma, Cryptococcus neoformans, Blastomyces dermatitidis, aspergillus
- ❑ Administered by **slow I.V. infusion.** (note the second point in the next slide)
- ❑ For systemic and subcutaneous Mycosis
- ❑ Slow elimination in urine and bile → long t_{1/2} (2weeks) (note the third point in the next slide)
- ❑ Treatment needs 6-12 wks. (from record : some times we give it daily)
- ❑ *Amphotericin B* has a low therapeutic index. (note the fourth point in the next slide)
- ❑ Given parentally:
 - IV infusion- systemic fungal infection .
 - Intrathecal (IT) – fungal meningitis.
 - Intraarticular – fungal joint infections (note the fifth point in the next slide)



Notes about the previous slides:

- Amphotericin B is one of the life saving antifungal and very important in hospitals to treat lethal or fatal fungus infection.
- It's given parentally by IV slow infusion so you can monitor the patient and the side effect during infusion (monitor the blood pressure because it may cause hypotension).
- Mainly eliminated in renal so if patient has a renal problem don't give the drug or be cautious by giving a small dose.
- It's very therapeutic index so you have to do TDM between dose and dose and monitor the plasma concentration so you don't reach the toxic dose.
- Why we give the drug Intraarticular for fungal joint infections ?
Because it's deliver the drug directly to the joints if we don't do that we need a long duration of treatment (2-6 months).

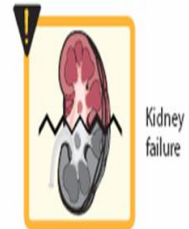
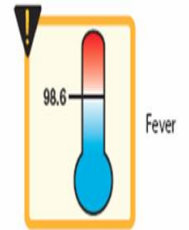
Amphotericin B

- The total adult daily dose should not exceed **1.5 mg/kg/d**.

(note the first two point in the next slide)

Side effects:

- **Nephrotoxicity**, **Adequate hydration is necessary** (note the third point in the next slide)
- **Chills and fever**: **premedication with a corticosteroid or an antipyretic helps to prevent it**
- **Thrombophlebitis** at site of injection, **adding heparin to the infusion** to avoid the clotting
- **Anemia** (by long duration)
- **Hypotension and hypokalemia**: **requiring**
- **K⁺ supplementation** (the normal concentration of K⁺ is (3.5 - 5.5)
- **IV ,cautiously, initial small dose with careful monitoring, then slow infusion.**
- **amphotericin B does cross the placenta**(can cause teratogenicity to the baby)



Notes about the previous slide:

- As we said Amphotericin B has a very narrow therapeutic index so you have to calculate the dose per KG (the dose is not the same for all patients rather than it depends in the body weight).
- The daily dose shouldn't exceed 1.5 mg/kg/d , so you have to multiply the dose with the weight , if you want to give it twice a day divide it by 2.
- Nephrotoxicity : the most dangerous side effect so to avoid it you have to give a patient one or two units of normal saline hydration (by IV) before you give the drug.

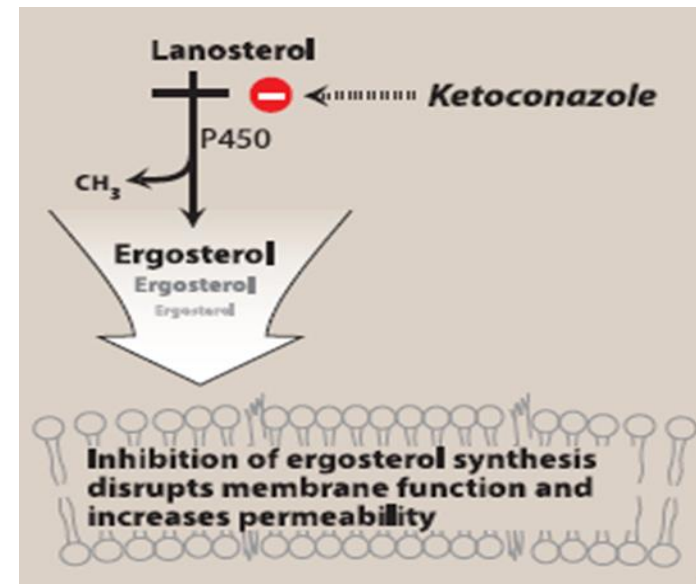
Nystatin

- Same mechanism as amphotericin
- Too toxic for systemic use.
- it is not used parenterally due to systemic toxicity (nephrotoxicity).
- Not absorbed from GIT.
- It is administered as an oral agent (“swish and swallow” or “swish and spit”) for the treatment of oropharyngeal candidiasis (thrush), intravaginally for vaginal candidiasis, or topically for cutaneous candidiasis.
- **Adverse effects** are rare after oral administration, but nausea and vomiting occasionally occur. Topical and vaginal forms may cause skin irritation.
- **Used topically:** cream, vaginal pessaries and oral for buccal and intestinal Fungal Infection.
- Nystatin is limited to the **topical treatment of superficial** cutaneous **infections caused by C. albicans**
- Infections commonly treated by this drug include:
 - oral candidiasis (thrush),
 - mild esophageal candidiasis,
 - vaginitis.



2. Azoles

- 1. For systemic mycosis:** Ketoconazole, itraconazole, fluconazole, voriconazole
 - 2. For superficial cutaneous (Topical infection):** Miconazole, clotrimazole
- MOA:** All azoles inhibit **ergosterol synthesis** in cell membrane. Reduced fungal membrane ergosterol concentrations result in **damaged, leaky cell membranes**



Notes about the previous slide:

- The best way to differentiate between these drugs is to know how you can give it , so we have systemic and topical ones . What is the different between them ?
- The topical ones has absorption problems so you can only use it in a topical way.
- But the others are well absorbed in acidic environment such as ketoconazole , but the problem with it is that ketoconazole has 95% no absorption in basic environment , the new systemic drugs , for example , voriconazole are less effected by basic environment.

Ketoconazole



- Orally for systemic fungal infections
- Available as oral tablet and cream
- It remains useful in the treatment of *cutaneous and mucous membrane and yeast infections*,
- Ketoconazole is usually effective in the treatment of *oral thrush* (note the first three points in slide 27)
- can be absorbed orally, but it **requires an acidic gastric environment** (note the fourth point in slide 27)
- **Teratogenic** - not administer in pregnancy

Ketaconazole

- Inhibition of CYP450 increase level of **phenytoin**, **warfarin** (it can cause bleeding), **oral hypoglycemics** and **cyclosporin**.
- Rifampin (inducer of CYP450) can shorten the duration of action of azoles.
- **Drugs that decrease gastric acidity – decrease the absorption of ketoconazole (it need acidic)**
- **Ketoconazole and amphotericin B** should not be used together (decrease in ergosterol reduces action of amphotericin B). (Antagonism) (note the fifth point in slide 27)

Notes about the previous slides:

- We use ketoconazole for oral thrush!!
- it's commonly used with patient who has AIDS or immune radiation therapy for example oropharynx cancer patient , after radiation he will have an oral thrush
- You can't give him a Nystatin cream because it's very weak with those patients.
- Remember this drug needs a gastric environment so you can't give it with anti acidic drugs , that will cause a treatment failure.
- There is no synergism between ketoconazole and Amphotericin B because one bind with ergosterol and the other inhibit ergosterol synthesis means different MOA but the same result, so one will inhibit the synthesis and the other will not find ergosterol to bind with , so this will be antagonism drug drug interaction.

Ketaconazole:

Side effects

- **hepatotoxicity** : increase transaminases enzymes in liver (note the first point in the next slide)
- **Endocrine effects** *reduction in testosterone synthesis* and blocks the adrenal response to corticotrophin:
 - gynecomastia and decreased libido in male (note the third point in the next slide)
 - menstrual irregularity in female
 - Uses: for hirsutism in female
- **photophobia**
- **skin rash,**

Notes about the previous slide:

- All azole drugs causes hepatotoxicity.
- Ketoconazole is acting on the testosterone receptors so it's decrease sex hormone levels , particularly on testosterone .
- We main by gynecomastia is a presence of a female characteristics in the male : for example breast enlargement and less hair in his chin
- It doesn't effect on estrogen levels in female but it maybe causes a menstrual irregularity .
- We can use one type of drugs called nizoral (ketoconazole) which is a scalp lotion used to treat dandruff by fungus.

Fluconazole



- Orally and IV
- does not require an acidic environment for GI absorption.
- About 80 to 90% of an orally administered dose is absorbed. (because it doesn't affected very much by acidity)
- distributed to tissues even CSF (cerebrospinal fluid) more than ketoconazole.
- **Uses:**
 - The drug penetrates widely into Cerebrospinal fluid permitting effective treatment for *fungal meningitis*.
 - About 80% of the drug is excreted unchanged in the urine. So, a **3-day course of oral fluconazole** is an effective treatment for **Candida urinary tract infection**
 - It is commonly used as a single-dose oral treatment for vaginal candidiasis
- Side effects: **hepatotoxicity** (by long duration)

Itraconazole

- **Itraconazole** is lipophilic and water insoluble and requires a low gastric pH for absorption
- for systemic and topical use.
- Oral bioavailability is variable (20 to 60%).
- a broad antifungal spectrum compared to *fluconazole*. *Itraconazole* is the
- A drug of choice for the treatment of blastomycosis, sporotrichosis and histoplasmosis
- Itraconazole is most useful in the long-term suppressive treatment of disseminated **histoplasmosis in AIDS** and in the oral treatment of **nonmeningeal blastomycosis**.
- It is the drug of choice for **sporotrichosis**



Notes about the previous slide:

- It's a very selective drug and usually we don't use it if the patient doesn't have one of these diseases : of blastomycosis, sporotrichosis and histoplasmosis.
- It's the first and the only line in these cases.
- It's a broad spectrum but as we said we use it in specific cases.
- It's absorption is less than the previous drugs (50%).
- Voriconazole can be used in place of fluconazole

Topical azole

- **Clotrimazole** is a broad-spectrum fungistatic
 - as oral solution (just for topical use for example treatment for candidiasis), cream and vaginal pessaries for candidiasis
 - used in the topical treatment of oral, skin, and vaginal infections with *C. albicans*.
 - It is also employed in the treatment of infections with cutaneous dermatophytes.
 - Side effects - associated with contact dermatitis (but not significant), and edema.
- **Miconazole**: ointment, cream, vagina supp and gel for skin and vaginal infection locally

Notes about the previous slide:

- Miconazole can be used in place of Clotrimazole.
- You can use two drugs to treat the same disease for example Miconazole as a cream and econazole orally or cream with vagina supp and this the right way for treatment

3. Allylamines



. Terbinafine

- MOA: **Fungicidal**: Inhibits ergosterol synthesis
- Drugs for cutaneous mycotic infections
- Drug of choice: in fungal infection of the nails **“onychomycosis”**
- **Orally for up to 3 months.**
- Orally active, well absorbed, concentrated in the skin and diffuse to nails.
- More than 99 % bound to plasma proteins.
- Accumulates in breast milk-- should not be given to nursing mothers.
- Side effects: **Change in taste, visual disturbances**, and increase in liver enzymes. (check point 4 in slid number 36)

3. Allylamines

2. Naftifine

- is available for topical use only
- *Naftifine* 1% cream and gel are used for topical treatment of tinea spp infection. Duration of treatment is usually 2 weeks. (check the last 2 point in the next slide)



Notes about the previous slide:

- This type of drugs attach with keratin which is located in nails , skin and hair.
- Terbinafine is very important for treatment of oncomycosis .
- We can use Griseofulvin to treat it but that will need a very long time (6 -12 months) so Terbinafine which needs a single tablet every day for 3 months to treat this case is the first line.
- the side effect of Terbinafine occur after a long duration so you have to tell the patient only if he will take it for long time , also these side effects are reversible.
- Naftifine is also used to treat oncomycosis .
- Naftifine is the first line to treat tinea spp infection, which is an infection causes athletic foot

Antifungals inhibiting mitosis

Griseofulvin

- ✓ MOA: it **inhibits fungal growth** by binding to the microtubules responsible for mitotic spindle formation: Inhibits fungal “mitosis” and fungal nucleic acid synthesis.
- it is still used for dermatophytosis of the scalp and hair.
- Has affinity to skin, nails and hair – **bound to keratin**.
- *Griseofulvin* is fungistatic and requires a long duration of treatment (for example, 6 to 12 months for onychomycosis so it is replaced by Terbenafine).
- ✓ Orally, absorption increased by fatty meal.
- ✓ It induces CYP450 (WARFARIN) and may potentiate alcohol toxicity by **Blockade of alcohol dehydrogenase**
- ✓ Side effects : Hepatotoxicity and photosensitivity.

Notes about the previous slide:

- It's the first line to treat scalp dermatopytosis.
- It goes to the liver causing hepatotoxicity , also this is the reason that why this drug effect on CYP450 activity
- Scalp dermatophytosis



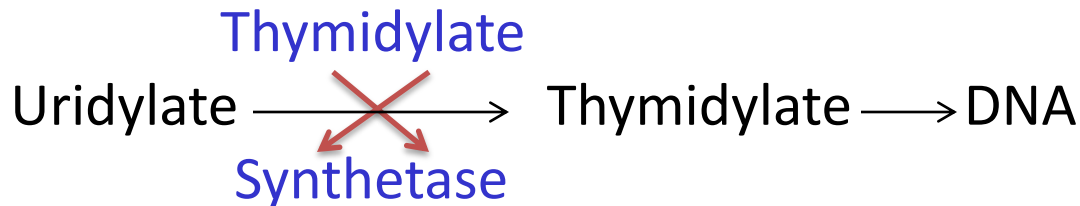
Antifungals inhibiting synthesis of nucleic acids

Flucytosine “5 flurocytosine”

- ❑ Oral and IV antifungal.
- ❑ It is a prodrug: Susceptible fungi

MOA: 1. **Flucytosine** enters the fungal cell via a specific permease, an enzyme not found in mammalian cells – **converted to 5-flurouracil**

2. Flurouracil inhibits thymidylate synthetase.



- ❑ Well absorbed. orally, well distributed, even to CSF,
- ❑ excreted by kidney, renal failure leads to accumulation.
- ❑ Use of high dose leads to **BM depression, hair loss and impaired liver functions.**
- ❑ **Give Uracil reverse BM toxicity but not antifungal effect.**
- ❑ **synergistic action: with Amphotericin B** --- increases cell permeability , so more 5-FC to the cell - for Cryptococcus neoformans and Candida albicans

Notes about the previous slide:

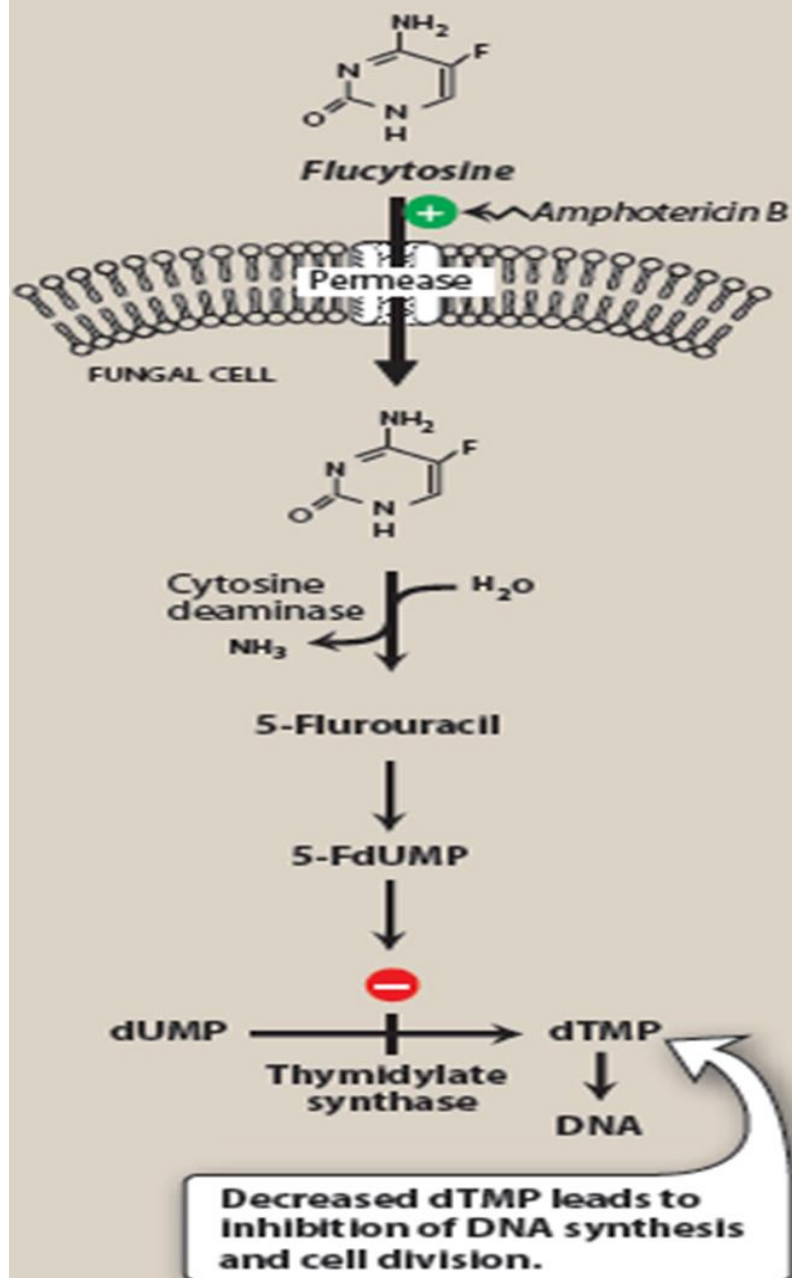
- The function of Flucytosine is similar to chemotherapy drugs.
- MOA:
- The first thing you have to know that is Flucytosine is prodrug , means it's not active until it enter a specific place (not just the liver it depends on the drug).
- Now when you give this drug it's enter the fungus cell by enzyme known as permease enzyme , once the drug enters it will be converted into 5-flurouracil which is the active form of the drug (note that this drug doesn't effect human cells because it is just activated when it entered the fungus).
- 5-flurouracil will inhibit enzyme known as Thymidylate Synthetase, which synthesis Thymidylate, which is an important precursor for DNA . So it will inhibit synthesis of nucleic acids.

Cont. Notes about the previous slide:

- At high doses this will effect the bone marrow and other places where there is a high demand for DNA because of high replications like hair pulp and GIT.
- To avoid bone marrow toxicity we give Uracil to bind with Adenine , which can't be used by fungus cell.
- Some notes about cancer drugs:
- The cancer patients lose their hair not because of the concourse cell but because of chemotherapeutic drugs which acts as similar as Flucytosine.
- So we always note that cancer patient are given erythropoietin to induce the bone marrow to produce RBC'S and avoid the side effects of cancer drugs.

Cont. Notes about the previous slide:

- So this drug (Flucytosine) is very toxic and no easy to use , we can said it's the last line drug in antifungal drugs.
- Can I give Flucytosine with Amphotericin ?
- In a case of difficult meningitis , Amphotericin will make pores in the membrane which facilitates the entry of Flucytosine
- We can use this combination after we ensure that :
 1. The patient don't have resistance to Amphotericin .
 2. No problems with renal blood flow.
 3. No problems with bone marrow.



ANTIFUNGAL DRUGS

Drugs for subcutaneous and systemic mycoses

Amphotericin B

Ketoconazole

Itraconazole

Flucytosine

Fluconazole

Drugs for cutaneous mycoses (dermal)

Terbinafine

Nystatin

Miconazole

Griseofulvin

Clotrimazole