Drugs For Subcutaneous And Systemic Mycotic Infection

- **A. Amphotericin B**
- **B. Antimetabolite antifungals**
  - **Flucytosine (5-FC)**
    - Synthetic pyrimidine antimetabolite
    - Combination with amphotericin B for the treatment of systemic mycoses and for meningitis caused by *C. neoformans* and *C. albicans*.
    - Amphotericin B increases cell permeability, allowing more 5-FC to penetrate the cell and leading to synergistic effects.
Figure 42.7
Mode of action of flucytosine.
5-FdUMP = 5-fluorodeoxyuridine 5′-monophosphate; dTMP = deoxythymidine 5′-monophosphate.
Antifugal Spectrum

- 5-FC is fungistatic.
- Combination:
  - Itraconazole
  - Fluconazole
  - Amphotericin B
- Resistance:
  - Resistance due to decreased levels of any of the enzymes in the conversion of 5-FC to 5-fluorouracil (5-FU).
  - 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
Pharmacokinetics

✓ Excretion of both the parent drug and its minimal metabolites (5FU) is by glomerular filtration, and the dose must be adjusted in patients with compromised renal function.

✓ 5-FC is well absorbed by the oral route.

✓ Penetrates well into the CSF.

• Adverse effect:

✓ dose-related bone marrow depression.

✓ Gastrointestinal disturbances
C. **Azole antifungals**

- **Imidazoles**
- **Triazoles**.

- have similar mechanisms of action and spectra of activity
- 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.

- The triazole antifungals include **fluconazole**, **itraconazole**, **posaconazole**, and **voriconazole**.
• Azoles are predominantly fungistatic.
• Inhibit C-14 α-demethylase [CYP450] enzyme)
• Thereby blocking the demethylation of lanosterol to ergosterol, the principal sterol of fungal membranes.
• The inhibition of ergosterol biosynthesis disrupts membrane structure and function, which, in turn, inhibits fungal cell growth.

Figure 42.8
Mode of action of azole antifungals.
• Fluconazole
  • first member of the triazole
  • It is the least active of all triazoles. Resistance is a concern
  • Fluconazole 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
  • Fluconazole is effective against most forms of mucocutaneous candidiasis.
  • It is commonly used as a **single-dose oral** treatment for vulvovaginal candidiasis.
  • Fluconazole is available in oral or IV dosage formulations.
  • It is well absorbed after oral administration and distributes widely to body fluids and tissues.
  • Drug is excreted unchanged via the urine, and doses must be reduced in patients with renal dysfunction.
  • The most common adverse effects with fluconazole are nausea, vomiting, headache, and skin rash
• **Itraconazole**
  • synthetic triazole that has a broad antifungal spectrum compared to fluconazole.
  • Itraconazole is available in two oral dosage forms, a capsule and an oral solution.
  • The oral capsule should be taken with food, and ideally an acidic beverage, to increase absorption.
  • In contrast, the 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 feces and urine.
  • **Adverse effects** include nausea, vomiting, rash (especially in immunocompromised patients), hypokalemia, hypertension, edema, and headache.
  • Hepatotoxicity can also occur, especially when given with other drugs that affect the liver.
  • Itraconazole has a negative inotropic effect and should be avoided in patients with evidence of ventricular dysfunction, such as heart failure.
• **Posaconazole**
  
  a synthetic triazole, is a broadspectrum antifungal structurally similar to itraconazole.
  
  It is available, as an oral suspension, oral tablet, or IV formulation.
  
  Posaconazole is commonly used for the treatment and prophylaxis of invasive Candida and Aspergillus infections in severely immunocompromised patients.
  
  Posaconazole has a low oral bioavailability and should be given with food.
  
  Unlike other azoles, posaconazole is not metabolized in the liver by CYP450 but is eliminated via glucuronidation.
  
  The most common adverse effects include gastrointestinal disturbances (nausea, vomiting, and diarrhea) and headaches.
  
  Like other azoles, posaconazole can cause an elevation in serum hepatic transaminases.
  
  Drugs that affect the gastric pH (for example, proton pump inhibitors) may decrease the absorption of oral posaconazole and should be avoided if possible.
• **Voriconazole:**
  o a synthetic triazole related to fluconazole
  o has the advantage of being a broad-spectrum antifungal agent that is available in both IV and oral dosage forms.
  o Voriconazole has replaced amphotericin B as the drug of choice for invasive aspergillosis.
  o Voriconazole has high oral bioavailability and penetrates into tissues well.
• Elimination is primarily by metabolism through the CYP450 enzymes.

• **Echinocandins:**
  o interfere with the synthesis of the fungal cell wall.
Figure 42.9
By inhibiting cytochrome P450, *voriconazole* can potentiate the toxicities of other drugs.
Drugs for cutaneous mycotic infections

- Mold-like fungi that cause cutaneous infections are called dermatophytes or tinea.
- Tinea infections are classified by the affected site.
- The three different fungi that cause the majority of cutaneous infections are:
- Trichophyton, Microsporum, and Epidermophyton.
Drugs for cutaneous mycotic infections

A. Squalene epoxidase inhibitors

- These agents act by inhibiting squalene epoxidase
- Blocking the biosynthesis of ergosterol, an essential component of the fungal cell membrane
- Accumulation of toxic amounts of squalene results in increased membrane permeability and death of the fungal cell.
- **Terbinafine:**
  - Oral terbinafine is the drug of choice for treating dermatophyte onychomycoses (fungal infections of nails).
  - It is better tolerated, requires a shorter duration of therapy, and is more effective than either itraconazole or griseofulvin.
  - Therapy is prolonged (usually about 3 months) but considerably shorter than that with griseofulvin.

- Terbinafine is available for oral and topical administration
- Common adverse effects of terbinafine include gastrointestinal disturbances (diarrhea, dyspepsia, and nausea), headache, and rash.

- **Naftifine**
- **Butenafine**
• **Griseofulvin**
  - Causes disruption of the mitotic spindle and inhibition of fungal mitosis
  - 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.
  - Ultrafine crystalline preparations are absorbed adequately from the 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, which increases the rate of metabolism of a number of drugs, including anticoagulants.
  - The use of griseofulvin is contraindicated in pregnancy.

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**Figure 42.14**
Inhibition of mitosis by *griseofulvin*.
• **Nystatin**
  
  Nystatin is a polyene antifungal, and its structure, chemistry, mechanism of action, and resistance profile resemble those of amphotericin B.

• 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 (acute infusion-related adverse effects and nephrotoxicity).

• It is administered as an oral agent for the treatment of oropharyngeal candidiasis (thrush), intravaginally for vulvovaginal 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.
• **Imidazoles:**
  • Imidazoles areazole derivatives which currently include
    • Butoconazole
    • Clotrimazole
    • Econazole
    • Ketoconazole
    • Miconazole
    • Oxiconazole
    • Sertaconazole
    • Sulconazole
    • Terconazole
    • Tioconazole
  • Imidazoles as a class of topical agents, they have a wide range of activity
  • Topical use is associated with contact dermatitis.

• **Ciclopirox**
• **Tolnaftate**