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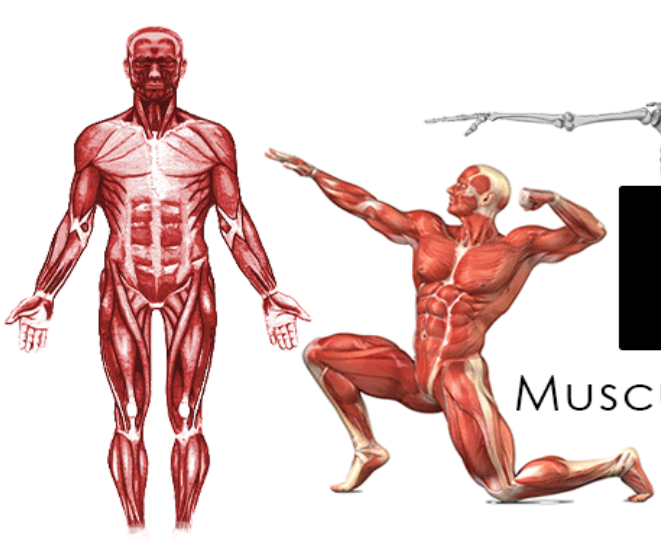

MSS

Musculoskeletal System

Pharmacology

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❖ Antifungal chemotherapy

Fungal infections are termed *mycoses* and can be divided into:
(1) Superficial infections: affecting skin, nails, scalp, or mucous membranes.
(2) Systemic infections: affecting deeper tissues and organs.

We're going to focus mainly on the topical uses of antifungal agents and mention some systemic antifungals briefly.

- ✓ Superficial fungal infections can be classified into the dermatomycoses and candidiasis.
- ✓ Dermatomycoses are infections of the skin, hair and nails, caused by dermatophytes. The commonest are due to *Tinea* organisms which cause various forms of "ringworm".

- ➢ **Azole Derivatives:**
  Family of antifungals that are mainly used topically, although they have some systemic indications to treat skin and mucous membrane infections.
  They have activity against dermatophytes and yeasts, including *Candida albicans.*
  They include:
  – **Clotrimazole**
  – **Econazole.**
  – **Ketoconazole.**
  – **Miconazole.**
  – **Oxiconazole.**
  – **Sulconazole.**

  Note: although metronidazole that we talked about in the last lecture ends in the prefix (zole), it's an antiparasitic and an antibacterial agent that mainly targets anaerobic bacteria.

Side note

Why is metronidazole toxic only to parasites and bacteria and not toxic to human cells?

It has a nitro group that must be reduced to do its action, and the enzyme that is responsible for this process is present in the electron transport chain that exists only in parasites and anaerobic bacteria. Although, high concentration may show toxicity on human cells.

An example on superficial infections: **superficial candidiasis**, the yeast-like organism infects the mucous membranes of the **mouth (thrush**), the **vagina (vaginal thrush**), or the **skin (penis).**
Remember that candida albicans are part of normal flora, but an imbalance in the normal flora, that is mainly caused by the abuse of antibiotics, may cause these fungal infections to occur. That's why when someone takes antibiotics to treat tonsillitis for example, he might develop fungal infection in the oral cavity or other mucous membranes.

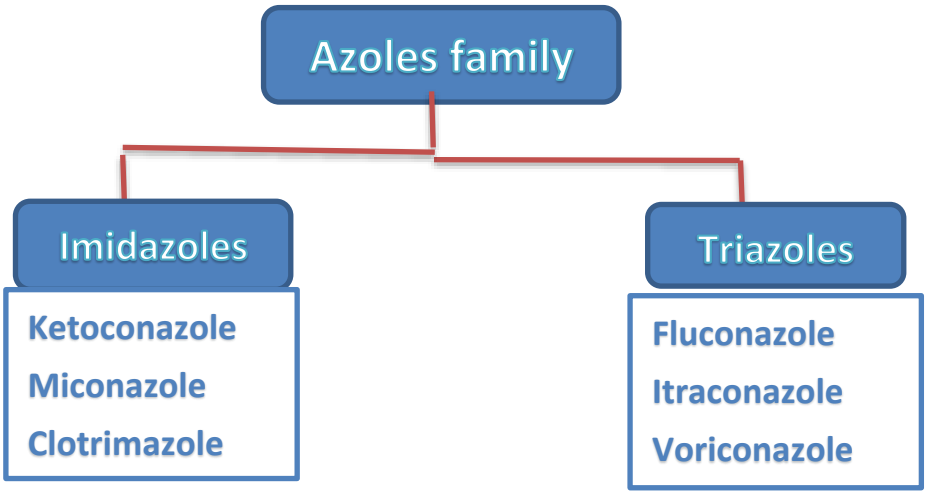
Systemic infections include: **systemic candidiasis**, **cryptoccocal meningitis** or **endocarditis**, and **pulmonary aspergillosis**.

Mechanism of action of antifungals

1) **Azoles and allylamines:** Inhibition of ergosterol synthesis.
   Ergosterol is an integral part of plasma membrane of fungi. And as we know, there is similarity in structure between ergosterol and cholesterol in our bodies. So these drugs might have some toxicity especially to the liver where the cholesterol metabolism takes place.
2) **Polyenes:** Disruption of plasma membrane integrity by binding to ergosterol, increasing the membrane permeability, which leads to leakage of intracellular contents such as potassium ions, and cell lysis.
3) **Polyoxins:** Inhibition of chitin synthesis, which is part of fungal cell wall.
4) **5-flourocytosine:** Inhibition of nucleic acid synthesis by acting as nucleoside analogs, so they bind to DNA chain of replicating fungi causing termination of the chain.
5) **Griseofulvin:** Disruption of the replication by affecting the microtubule formation that is important in mitosis.

Azole Antifungal Agents

- The azole antifungal agents can be divided into two broad classes: the **Imidazoles** and the **Triazoles**.
- They share the same antifungal spectrum and the same mechanism of action.
- They are used topically and systemically.
- Triazoles have less liver toxicity than Imidazoles, thus they can be used systematically to treat systemic infections.
- **Mechanism of action**: they inhibit the synthesis of **sterol 14-a-demythelase**, this enzyme is involved in the synthesis of ergosterol.



- **Topical indications**

  Clotrimazole and **Miconazole**

  To treat ringworm, tinea versicolor and mucocutaneous candidiasis.

  Although these drugs are used topically, we still have systemic absorption. For example, miconazole that is absorbed after its topical administration especially if it's applied on large surface area of skin. Miconazole can act as a potent inhibitor of Warfarin metabolism, by inhibition of CytP450 enzyme.

  This applies on all azoles antifungal agents (they are all inhibitors of CytP450). We have to be careful when prescribing these agents to individuals who are taking drugs that are substrates for this enzyme, especially those drugs which have a narrow therapeutic index such as warfarin.

Other topical antifungal agents

- **Ciclopirox olamine**: to treat Tinea versicolor.
- **Naftifine, Terbinafine and Tolnaftate:** part of allylamines, to treat tinea pedis, tinea cruris, and tinea corporis.
- **Nystatin and Amphotericin B:**

  Polyene macrolide antibiotics that function by binding to fungal cytoplasmic membranes. Thus, they interfere with membrane permeability and transport functions. One significant outcome is the loss of cellular K+.

Nystatin

- Only used to treat Candida albicans.

- Infections commonly treated by this drug include oral candidiasis (thrush), mild esophageal candidiasis and vaginitis.
- Available as topical preparations, oral suspension, or vaginal tablets. All of these are topical uses even the oral suspension, because it's used to treat infections of the oral cavity (thrush) and esophagus. Fortunately, this drug is poorly absorbed from the GI tract when it's swallowed.
- It is highly toxic and is not used systemically at all.

Amphotericin B

- Produced by the actinomycete Streptomyces.
- It is most commonly used to treat serious disseminated yeast and dimorphic fungal infections in immuno-compromised hospitalized patients.
- Poorly absorbed, so it's given IV if we want to use them systemically.
- Amphotericin has a lesser affinity for the mammalian cell membrane component cholesterol, but this interaction does account for most adverse toxic effects associated with this drug.
- It is very toxic so we should be careful about its use.
- **Side effects:** **Fever**, **chills**, and **tachypnea (rapid breathing)** commonly occur shortly after the initial intravenous doses of amphotericin. These effects disappear after the infusion but, there are other serious side effects that include **anemia**, **hypokalemia**, **liver damage**, **thrombocytopenia** and **anaphylactic reactions**.
- The most important associated toxicity is **nephrotoxicity**. 80% of patients get reduction in kidney function which generally recovers after treatment.

Oral antifungal agents

➢ **Azoles derivatives** can also be used systemically including:

– Fluconazole.

– Itraconazole.

– Ketoconazole.

- As we said they have **systemic side effects**: hepatitis and liver enzyme elevations, and interactions.
- Effective in systemic mycosis, mucocutaneous candidiasis, and other cutaneous infections.

➢ **Griseofulvin**

- It is used to skin infections that are not responding to topical drugs like miconazole.
- Effective against ringworm (tinea) infections.
- Requires prolonged treatment: 4-6 weeks for the scalp, 6 months for fingernails, 8-18 months for toenails.
- Has many side effects.

➢ **Terbinafine**

- Recommended for onchomycosis (ringworm of the nail).
- 6 weeks for fingernails, 12 weeks for toenails.

❖ Topical Antiviral Agents

Examples on their use:

1) Treatment of herpes simplex infections:

remember that at the first encounter of the virus it causes mucous membrane and skin infection with vesicular rupture, and it's self-limiting (resolves after two weeks). The virus may recurrent in the case of immunosuppression or stress since it remains dormant at the dorsal root ganglia. Ointments and creams are useful for recurrent **orolabial** herpes simplex infection.

2) Treatment of varicella zoster infection:

It causes chickenpox in the first encounter, and also remains dormant with the possibility of reactivation to cause **shingles**. Topical creams can be used for the treatment of this condition. Sometimes, the condition is severe, so the patient requires systemic treatment with oral antivirals.

They include:

- **Acyclovir.**
- **Valacyclovir.**
- **Penciclovir.**
- **Famciclovir.**

Mechanism of action:

1) nucleoside analogs. **2)** Inhibition of DNA polymerase.

Mechanism of selectivity (why are the drugs selective to the virus and not to the host):

They are prodrugs that are activated by three steps of phosphorylation. The first step of the three step process is catalyzed by thiamine kinase, which is present in the virus and not in host cells.

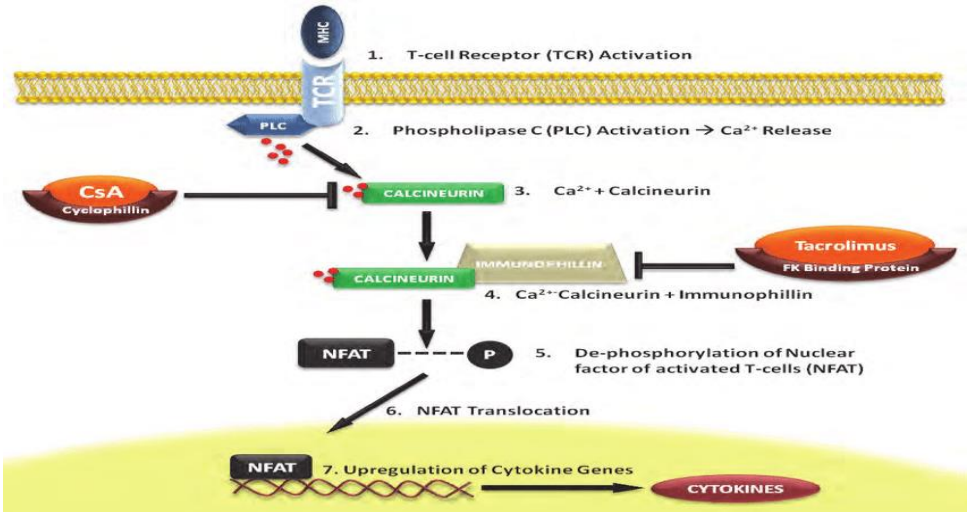
❖ Immunomodulators

➢ Imiquimod

- It is used topically for external genital and perianal warts (condyloma acuminatum) which is caused by HPV.
- Actinic keratosis on the face and scalp (precancerous patchy keratinized layers that develop on the skin) which happens due to exposure to UV light.
- Primary basal cell carcinoma (considered one of the most benign malignant cancers since it's completely incapsulated).
- **Mechanism of action:** it works by modulating the immune system to increase the production of interferon- α by peripheral mononuclear cells. It also stimulates macrophages to produce IL-1, IL-6, IL-8, TNF- α.

➢ Tacrolimus, Pimecrolimus

- **Mechanism of action:** It binds to FK binding protein inside the T-lymphocyte creating a complex that inhibits calcineurin thus preventing the dephosphorylation and translocation of transcription factor NFAT to the nucleus, resulting in a decrease in the production of IL-2 and related cytokines, and **inhibition of T-lymphocyte proliferation**.



Extra image to illustrate the mechanism of action of tacrolimus

- It is substrate for CytP450, thus it has a variable bioavailability among individuals, that is why we need to have close monitoring for this drug concentrations.
- **Side effects:** nephrotoxicity, neurotoxicity, seizures, increase LDL levels which increases the risk for developing atherosclerosis.

  Note: patients with high LDL levels are given many drugs, one of these is **atorvastatin (lipitor)**, which inhibits CytP450 enzyme, thus it affects the tacrolimus levels and increases its toxicity.

  So tacrolimus and lipitor would have competitive effects. Therefore, it's very imperative to monitor both drugs levels, for example decreasing the dose of tacrolimus during the treatment with Lipitor.
- **Indications:**

  It's used systematically after organ transplant.

  It's used topically for the treatment of atopic dermatitis, and psoriasis.

❖ Ectoparasiticides

Drugs that are used to treat lyse and scabies infections.

- **Permethrin**
  - Toxic to Pediculus humanus, Pthirus pubis, and Sarcoptes scabiei.
  - To treat pediculosis: cream applied for 10 minutes and then rinsed off with warm water.
  - To treat scabies: cream applied for the whole body for 8-14 hours.

- **Lindane (Hexachlorocyclohexane)**
  - Also used to treat pediculosis
  - 10% absorbed and concentrated in fatty tissues.
  - Very toxic if absorbed, can cause neurotoxicity and hematotoxicity.

- **Crotamiton**

  drug that is used both as a scabicidal (for treating scabies) and as a general antipruritic (decreases itching).

- **Sulfur**
- **Malathion**

❖ Agents affecting Pigmentation

They reduce the pigmentation that may be caused by exposure to certain environmental factors, such as sun exposure, or by certain diseases in spleen and liver, or tumors, or by certain drugs such as continuous use of corticosteroids. They can also be used for cosmetic purposes like skin whitening.

- **Hydroquinone:** topical application skin whitening to reduce the color of skin.
- **Monobenzone**
  may be toxic to melanocytes resulting in permanent depigmentation.
- **Mequinol**
  Topical hydroquinone, usually results in temporary lightening.

  Mechanism of action: Reduce hyperpigmentation of skin by inhibiting the enzyme tyrosinase, which will interfere with biosynthesis of melanin.

In some cases, we need to re-stimulate the melanocytes to produce melanin and induce pigmentation, such as in albinism or vitiligo, such drugs involve:

- **Trioxsalen**
- **Methoxsalen**
  both drugs are psoralens, meaning that they require activation by light to perform their action, so after these drugs are administered they must be photoactivated by long wavelength UV light to produce beneficial effect, which is stimulation of melanocytes to produce pigments on the skin.
  Side effects: they can cause cataract or skin cancer, because they intercalate with DNA.
  So they must be used with cautioun, and the patients are advised not to be exposed to sun light for long periods.

❖ Sunscreens and sunshades

Sunscreens: absorb UV light, causing quenching of the light preventing its harmful effects on the skin.
Examples are **para amino benzoic acid (PABA)** and its esters.
Sunshades: opaque materials that reflect light, like **titanium dioxide**.

- ✓ It's better to have both sunscreens and sunshades in the active ingredients of the product for better protection especially, in the prolonged exposure to sunlight.

They are also used to treat some conditions such as:

- **polymorphous light eruption** (autoimmune disease that involves vesicular eruption after exposure to sun light).
- **Lupus erythematosus**
- **Drug –induced photosensitivity**

💜 **BEST OF LUCK** 💛