Sheet 5

FUNGAL INFECTIONS

Done by:

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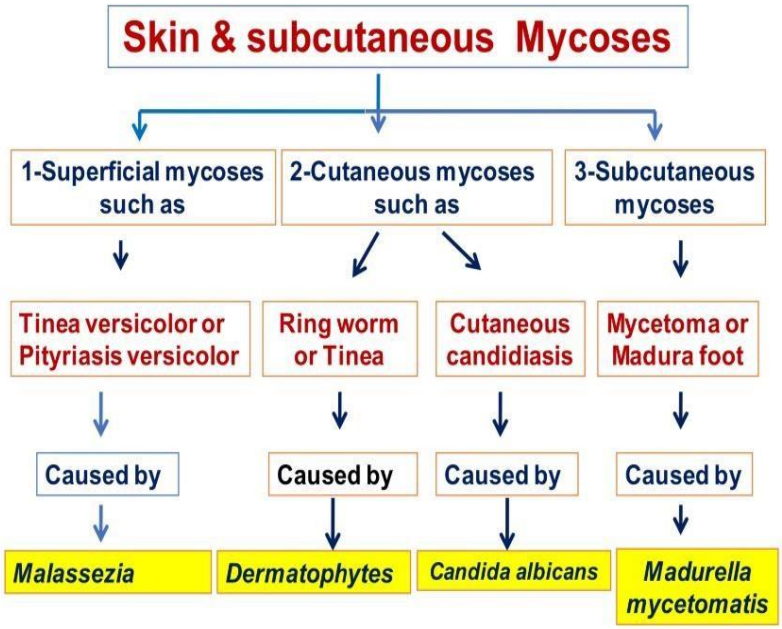
Fungal Infections

As mentioned in the last lecture, besides fungal allergies and fungal toxins, fungal infections (mycoses) are the most medically important types of fungal diseases in humans.



These 2 pages are an introduction that was mentioned also in the last lecture.

Skin & Subcutaneous Mycoses

Fungal infections are categorized according to the type of tissue involved and the site of infection. Superficial and cutaneous mycoses affect the skin and dermis, whereas subcutaneous mycoses may affect fascia and muscles.

1- **Superficial mycoses affect the outermost layer of the skin, also known as the <u>stratum corneum</u>, <u>without pathogenesis or inducing an immune response</u>. Treatment is mainly sought for cosmetic purposes.**

   An example on superficial fungal infections is Tinea versicolor also known as Pityriasis versicolor. The causative agents in this type of infection belong to the Malassezia genus. This genus includes several species of Malassezia, most notably *Malassezia furfur*, *Malassezia globosa*, and *Malassezia sympodialis*.

   Other examples of superficial mycotic infections are Tinea nigra and black and white Piedra.

2- Cutaneous fungal infections (keratinized layer of the skin as hair and nails) actually result in pathogenesis and trigger an immune response, which results in obvious symptoms including itching (pruritus) and even pain in some conditions.

Examples of cutaneous mycotic infections that are very highly communicable diseases and among the most common in the society are Ringworm (Tenea + suffix according to the organ involved) infections caused by Dermatophytes (consist of three genera: Epidermophyton, Microsporum, and Trichophyton) and another example is Cutaneous candidiasis caused by *Candida albicans, The most common species.*

3- Subcutaneous mycoses also result in tissue damage, which in turn triggers the body's immune system, resulting in inflammation and the symptoms that accompany it. As mentioned previously, in order for these infections to reach subcutaneous tissue layers, traumatic inoculation is required, which may be due to skin cuts, abrasions, and even burns, as intact skin acts as a physical barrier against subcutaneous mycoses).

Subcutaneous mycoses include Chromoblastomycosis as well as Sporotrichosis (also known as rose gardener's disease) which is caused by Sporothrix as mentioned in the previous lecture. In this lecture we will focus on another type of subcutaneous mycoses known as Eumycetoma or Madura foot, caused by Madurella mycetomatis.

Superficial Malassezia Infections

-They are lipophilic yeast, round in shape, and are normal commensals of the skin (part of the normal skin microflora) in both humans and animals. This means that they are noncontagious infectious agents that originate from one's normal microbiota (as opposed to dermatophytes, which are communicable).

-They can cause skin infections (Tinea versicolor) and catheter associated infections, such as adults that are in the ICU that take total parenteral nutrition (they consume lipids and it's a lipophilic yeast so this is a favorable condition for it).

Malassezia can also cause fungemia especially in premature infant hosts.

Pityriasis versicolor:

-Pityriasis versicolor is an infection that only affects the stratum corneum (the outermost layer of the epidermis) especially in the trunk region -including the chest, abdomen, back, and even parts of the neck and face, as well as proximal limb surfaces.

-The causative agents responsible for Pityriasis versicolor are species of the Malassezia genus, such as:

M. furfur, M. globosa.

Regarding its precipitating factors, genetic predisposition may play a role. Although Malassezia is a commensal organism, a compromised immune state can enable it to gain new virulence factors. Additionally, excessive sun exposure and high humidity promote its growth.

-This condition is more common in tropical regions. Malassezia is also precipitated by more sun exposure.

-It is believed that the production of carboxylic acid by the Malassezia species is responsible for the depigmentation of the lesions that result from this condition.

These lesions are characterized by discoloration, appearing as hyperpigmentation in individuals with lighter skin tones and hypopigmentation in those with darker skin tones.

Affected individuals often exhibit blotchy pigmentation relative to their baseline skin tone.

Clinical observations:

- Clinically, patients with Tinea versicolor are asymptomatic with non-itchy hypo or hyper pigmented macules (discolored patches of the skin).
Due to the absence of symptoms, people with Pityriasis versicolor often remain unaware of their condition until they notice the macules themselves or other people inform them.

The clinical description of the observed skin lesions is that they are well demarcated, yellow/white/pink lesions.

-These lesions often tend to coalesce to form scaly plaques / furfuraceous scales.

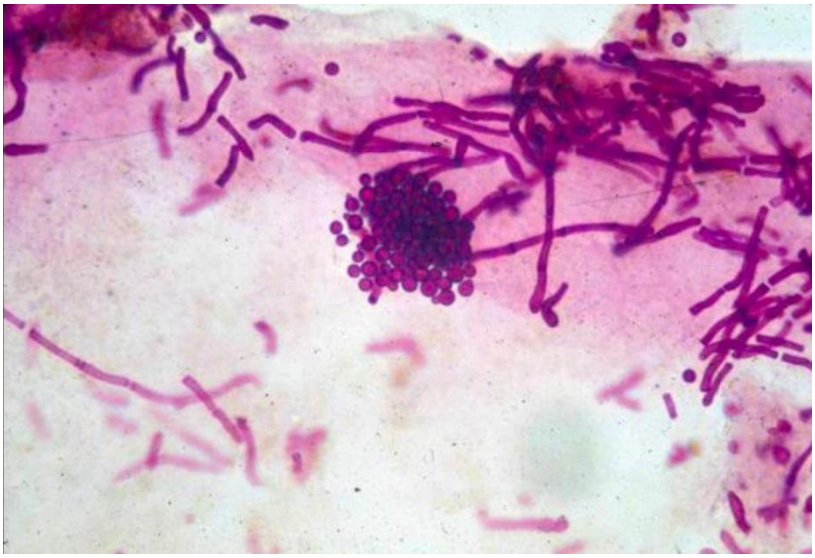
Discoloration usually occurs according to the background pigment of patient. Caucasians are more commonly affected by hyperpigmentation, where individuals with darker skin tones usually experience hypopigmentation. This discoloration is where the name versicolor (changeable in color) comes from.

Diagnosis:

Diagnosis of Pityriasis versicolor is usually very simple as clinical inspection of the skin lesions may only be required.

-UV light may also be used, revealing a pale greenish color under Wood's ultra-violet light or even showing a coppery orange tone.

-For more specific diagnosis, shallow scale samples are taken via skin scraping and are treated with ink staining and potassium hydroxide to be viewed under the microscope. Under the microscope, clusters of budding yeast cells are seen along with short angular hyphae that tend not to be septate (this indicates that some have turned pathogenic). This is referred to as the spaghetti and meatballs appearance.



Treatment:

-Some of these infections tend to resolve spontaneously without any extra treatment.

-If needed, treatment is done for cosmetic reasons and is usually done by topical administration of azole containing creams/shampoos for 2 weeks, and in severe cases, oral azoles are prescribed.

-Although their treatment is usually simple with no complications, these skin lesions have a high reoccurrence rate (more than 50%), because their causative agent is part of the skin microflora.

Seborrheic dermatitis:

-Skin hyperproliferation with dandruff is the mildest manifestation of this infection.
-Lesions are red and covered with greasy scales and itching is common in the scalp.

It is theorized that Malassezia furfur is a correlation factor to the pathogenesis of this condition (it is associated with Seborrheic dermatitis and dandruff but isn't its causative agent).

Seborrheic dermatitis has varying levels of severity. It may present as simple dandruff on the hair, folliculitis, or even as eczema affecting the scalp of the head.

Some factors suggest that the relationship between Malassezia and seborrheic dermatitis is correlational rather than causative. For example, many individuals carry Malassezia on their skin, but only some develop dandruff. Patients with dandruff, which is the mildest form of seborrheic dermatitis, often respond well to treatment with azole compounds. When treated with ketoconazole shampoo, their dandruff typically resolves after washing and consistent use.

We previously discussed superficial mycotic diseases, including white and black piedra. These conditions are characterized by nodules that form on hair shafts, with the nodule color corresponding to their name—white or black. Additionally, we mentioned Tinea nigra, a condition that causes black pigmentation on the palms of the hands. These conditions have a specific geographical distribution and, in comparison to Pityriasis versicolor, are relatively uncommon.

Cutaneous Mycoses

Cutaneous mycoses affect the deeper layers of the skin and involve pathogenesis through either direct fungal proliferation or the production of metabolites. These infections trigger a host immune response, leading to symptoms in affected patients. Additionally, cutaneous mycoses are contagious.

Ringworm or Tinea:

-Caused by Dermatophytes (filamentous fungi/molds, not yeasts) which include 3 genera: Epidermophyton, Microsporum, & Trichophyton.

Dermatophytes is one of the most common communicable diseases that affect humans.

-These fungi affect keratinized tissues such as skin, hair, & nails.

Infections by these fungi are characterized by ring shaped inflamed lesions and hence the name: Ringworm infections (although they aren't caused by parasites or worms).

The ring-shaped lesions have red and inflamed margins that become clearer towards the center of the ring (central diminishing).

They are usually itchy (cause pruritus).

-Infection does not spread to deeper tissues

Source of infection:

1- Man to man by direct contact (Anthrophilic).

Usually causes chronic dermatophytosis, with very high recurrence, and no cure for this recurrence.

2- From animals e.g. dogs and cats (Zoophilic).

They cause acute dermatophytosis, with lower recurrence, and respond better for treatment.

3- From the soil (Geophilic).

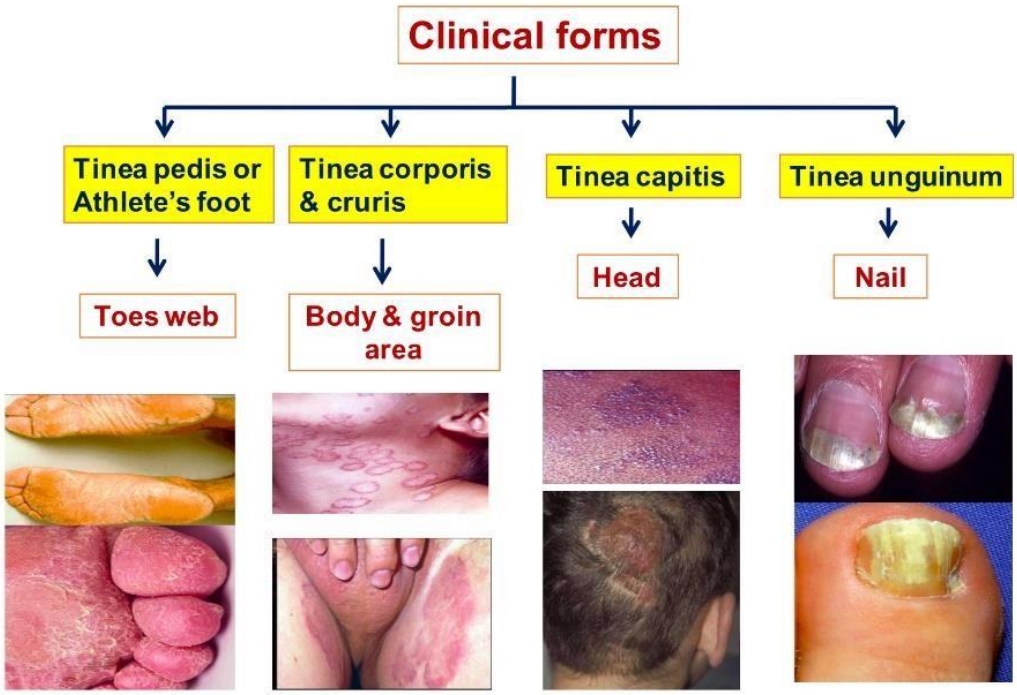
Geophilic fungi, originating from the soil, can also spread through shared environments such as swimming pools, carpets, and wardrobes. If fungal scales are present, they can remain viable for up to one year. These molds contribute to infections, as the scales from infected individuals or animals (human or diseased animals) can spread to others, leading to fungal lesions.

Geophilic transmission of Dermatophytes usually results in acute and severe infections.

***Important Notes:**

-Intact skin is an important barrier against infection.

-Heat and humidity enhance the infection (increase the precipitation of Dermatophyte lesions).

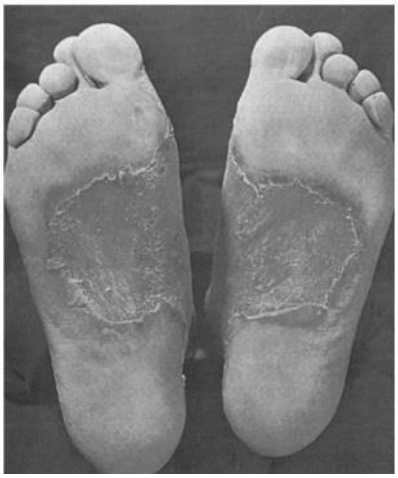


Ringworm infections can also be referred to as: Tinea + a suffix that matches the site of the fungal infection (which is also the contact site where transmission occurred):

❖ Clinical Pictures

- **Red, itchy scaly rash, ring like with raised more inflamed border on the body or groin.**
- **Scaling and hair loss leaving black dots.**
- **White and opaque / yellow , thickened &broken nails.**
- **DDX: Eczema, psoriasis, impetigo, alopecia, drug reactions.**

1. **Tinea pedis or Athlete's foot: Its most common type is Toe web.**
   Tinea pedis infection has different levels of severity which may vary from mild interdigital scalping to severe maceration and loss of volume of the foot.



2. **Tinea corporis: occurs in hairless areas of the skin (may occur in any area of the body that lacks hair other than the feet, groin area, and nails).**

- **Notice the RING-LIKE legions; recall that dermatophytes are also called ring worms.**
- **The border of the legion is more intensely red.**
- **The inflammation fades as we go to the center.**

- **Tinea barbae: If it occurs on hairy regions for males.**

3. **Tinea cruris: occurs near the perineum, or the scrotum in males.**
4. **Tinea capitis: occurs in the scalp and affects hair follicles. Its most severe form, known as Tinea favosa, results in permanent hair loss along with black dots in the area of infection.**
5. **Tinea unguinum: affects nails, resulting in extremely white, opaque, or yellow nails that are very brittle and easily broken. Dermatophyte infection of nails is painless, even with all the other effects it has on the nails (unlike candida infection of nails, which results in painful inflammation and will be discussed later on in the lecture).**

   Onychomycosis can be caused by either Tinea unguium or Candida. When differentiating between the two, Candida infections are typically painful, whereas Tinea unguium infections are generally painless.

   Tinea unguinum typically develops slowly over several months, which often leads patients to be less concerned about it initially. In contrast, paronychia caused by Staphylococcus aureus leads to acute changes and rapid onset of symptoms.

Diagnosis

Microscopic examination

❖Skin scales, nail & hair are examined microscopically after digestion using 10% KOH.

➢Branching hyphyae are detected among epithelial cells of skin & nails.

➢Hyphae or spores are detected in the hair. Spores either detected inside the hair (endothrix) or outside the hair (ectothrix).

Culture

❖Culture on Sabouraud's dextrose agar (SDA):

❖The agar incubated at room temperature for 4 ws.
The arising colonies examined microscopically after staining with lactophenol cotton blue stain.

Treatment

Local antifungal cream as miconazole or oral terbinafine weeks to months

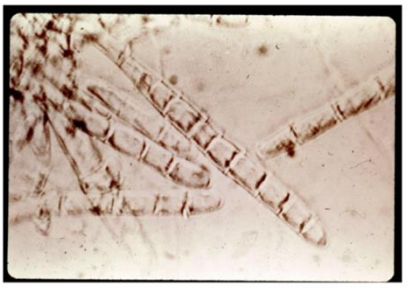
Common Dermatophytes

Epidermophyton floccosum:

Bifurcated hyphae with multiple, smooth, club shaped macroconidia (2-4 cells)

Microsporum:

Thick wall spindle shape multicellular

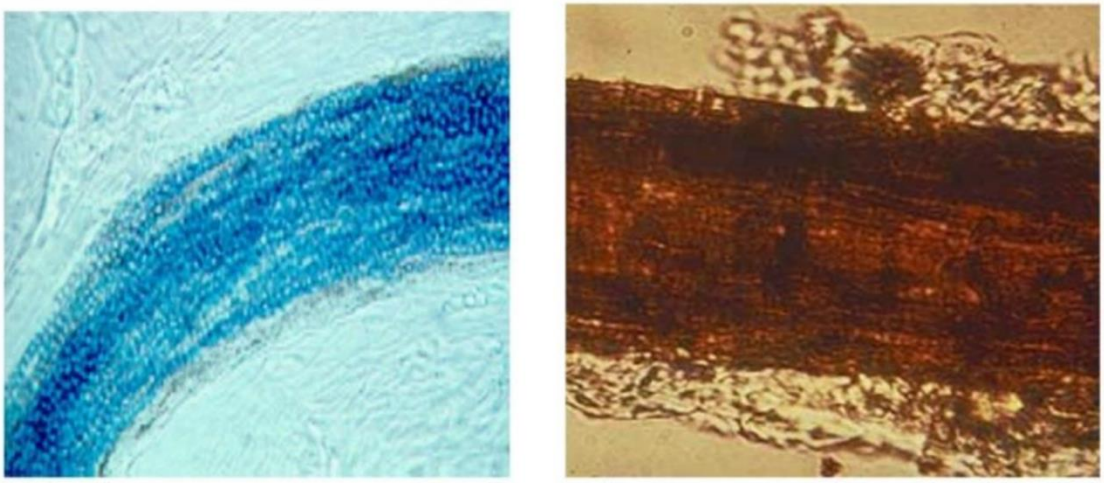


Trichophyton:

Large, smooth, thin wall, septate, pencil-shaped

Or cigarette-shaped

Hair Examination



In the picture on the left, we see endothrix, where the dermatophytes are located inside the hair shafts. In contrast, the picture on the right shows ectothrix, where the dermatophytes are present on the surface of the hair shafts rather than inside, as seen in the left image.

Subcutaneous mycoses

Here the infection must reach the subcutis (as muscles and fascia) and to reach this the skin must not be intact (skin cut, abrasions), and this is known as traumatic inoculation.

An example is Rose Gardener's Disease (Sporotrichosis), which often affects individuals who work with plants and flowers, particularly those with thorns. The hyphae of the causative fungus live on these thorns, and when the skin is punctured, it can lead to subcutaneous nodules and a chronic granulomatous infection.

Mycetoma (Madura foot):

-Mycetoma is a chronic granulomatous infection that usually affects the lower limbs and hands.

This disease is characterized by the formation of hard nodules at the infection sites, which can develop into abscesses filled with purulent fluid. These nodules may also progress into sinuses (openings that discharge fluid) or fistulas (connections between two nodules without discharge). The discharge from these nodules often contains granules of varying colors, such as black granules.

-These infections can be caused by fungi that grow in soil & on decaying vegetation.

-The causative organism is introduced into subcutaneous tissues through trauma.

-It occurs after trauma and usually affects farmers (especially ones that work barefooted in soil fields).

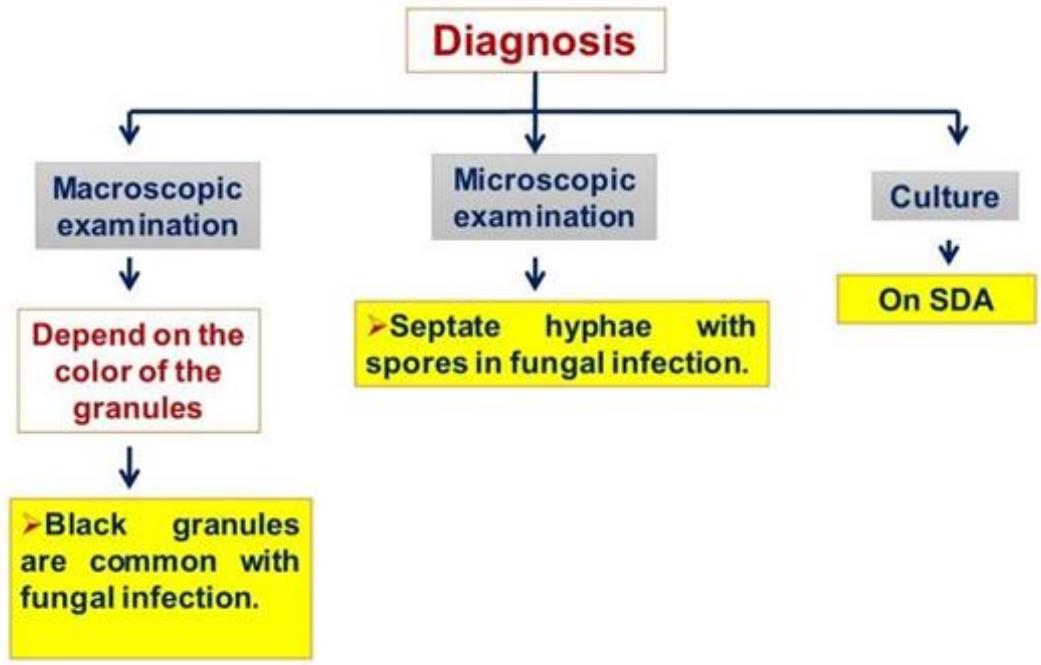
Causative organisms of Mycetoma:

Mycetoma may result from fungal infections (known as Eumycetoma) or from bacterial infections (known as Actinomycetoma). In both cases, they share the same presentation and pathogenesis (chronic granulomatous infections at the affected sites).

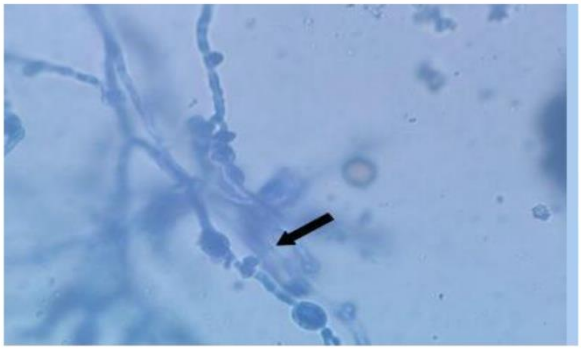
1- **Eumycetoma: caused by the fungi *Madurella mycetomatis* which has true septate hyphae.**
   The granules released from the nodules of Eumycetoma are black in color, while the nodules themselves don't cause pain, and the patients are farmers so there pain threshold is high. (therefore the patients don't show symptoms in the form of pain).
2- **Actinomycetoma: caused by species of actinomycetes such as Nocardia (filamentous aerobic bacteria that is viewed using acid fast stain).**
   The granules released from the nodules of Actinomycetoma are not black (they are usually silver, but can also be other colors such as yellow, white, or red), while the nodules themselves are painful.

Clinical pictures

Swelling following trauma, purplish discolouration & multiple sinuses that drain pus containing yellow, white, red or black granules.



Madura foot



Madurella mycetomatis with intercalary chlamydospores

They will release discharge that contains black granules.

Antifungals alone are not sufficient for those people; they must be accompanied by surgical debridement.

Intercalary chlamydospores: In the middle of the hyphae, not like the terminal chlamydospores of candida.

Treatment:

1. **Medical** (Antifungal drugs)
   a) **Ketoconazole** b) **Itraconazole** c) **Amphotericin B** (IV)
2. **Surgical debridement**

Opportunistic Mycosis

Opportunistic fungal infections primarily affect immunocompromised individuals, as immunocompetent people are generally resistant to them unless the fungi acquire new virulence factors. In contrast, endemic systemic fungal infections can affect even immunocompetent individuals, though they are typically confined to specific geographical regions. The number of immunocompromised patients has significantly increased due to factors such as the rise in AIDS cases, congenital immunodeficiencies, cancer, organ transplantation, and the use of broad-spectrum antibiotics or corticosteroids.

- **Opportunistic mycoses are caused by globally distributed fungi that are either members of the human microbiota, such a Candida species, or environmental yeasts and molds.**
- **They can produce diseases ranging from superficial skin or mucous membrane infections to systemic involvement of multiple organs.**

- **Patients at risk include those with hematologic dyscrasias (e.g., leukemia, neutropenia), patients with HIV/AIDS with CD4 counts less than 100 cells/µ L, as well as those treated with immunosuppressive (e.g., corticosteroid) or cytotoxic drugs.**

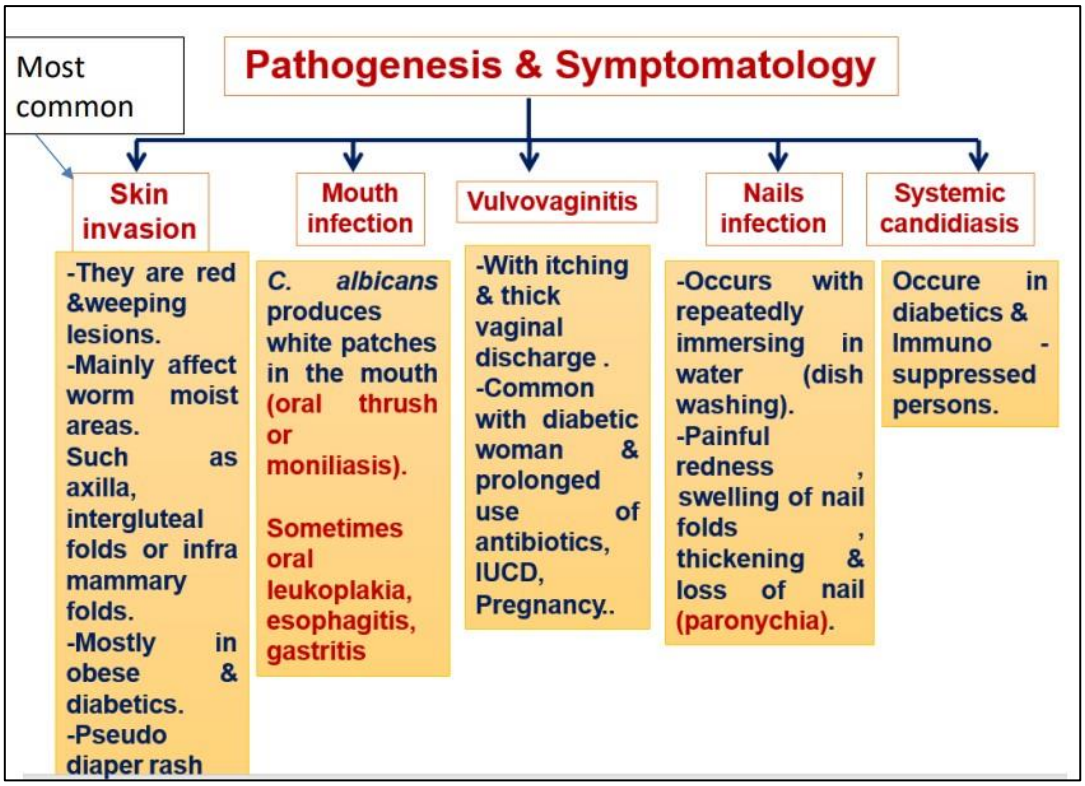
Candidiasis:

Might be cutaneous, mucocutaneous, or systemic candidiasis in the form of fungemia (candidemia).

- **Candida albicans is the most important species of candida (other species…).**
- **Candida albicans is an oval gram-positive budding yeast which produces pseudohyphae.**
- **It colonizes (meaning that it's part of the normal flora) the mucous membranes of the upper respiratory, upper GIT (on the mucous membranes) & female genital tracts.**
- **It causes superficial infections but can predominate with lowering in immunity causing infection, so it is one of the opportunistic fungi.**

Predisposing factors to Candida infections:

1. **Diseases as AIDS & diabetes melllitus.**
2. **Drugs: prolonged treatment with broad spectrum antibiotics & corticosteroids.**
3. **General debility (general weakness, e.g.: patients in the ICU).**
4. **Indwelling urinary catheter**



Skin invasion: Cutaneous candidiasis (in warm, moisture areas), it usually involve inframammary, axilla, intragluteal and the groin region.

-Pseudo diaper rash is named so because other skin invasions are in body folds, but the diaper rash is because of contact dermatitis (the diaper is not in direct contact with infra gluteal folds, but it compresses it).

- **Every AIDS patient suffers or has suffered from oral thrush in his/her life.**
- **IUCD: Intrauterine contraceptive device.**
- **Vulvovaginitis is characterized by intense itching and a creamy, curd-like discharge.**

Nails can be affected by various pathogens, including Candida, dermatophytes, and bacteria such as Staphylococcus aureus, which causes paronychia. In the case of Tinea unguium, the condition is chronic onychomycosis, whereas bacterial infections like those caused by Staphylococcus aureus are typically acute. Candida infections, however, are chronic and painful. While Candida-induced paronychia may resemble bacterial paronychia, the latter is acute and develops rapidly, whereas Candida infections are more chronic, often persisting for over six weeks.

The picture on the left shows a newborn with a whitish color on his lower lip which is a cutaneous candidiasis, the picture on the right shows an adult with oral thrush

Candida infections of the fingernails involve the nail plates, nail folds, and nail bed. These infections are characterized by redness, swelling, and significant pain, making them more painful compared to onychomycosis caused by dermatophytes.

The picture on the left shows a pseudo diaper rash (there are lesions inside the infra gluteal fold).

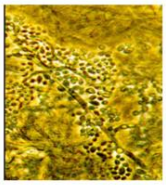
The second picture shows what happens if there is not enough hygiene, for example after the mother changes the diaper, she would touch the baby's mouth which will infect the mouth too.

Another case in cutaneous candidiasis is called fingerweb erosion in people who always wash dishes, chefs, and cooks who deal with vegetables.

Candida fingerweb erosion, related to fatness, occupation, etc.

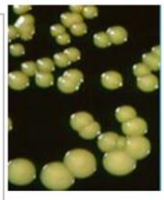
Laboratory diagnosis

Direct microscopic examination



- Specimens from skin, vaginal discharge or exudates from mucous surfaces are examined.
- *C. albicans* is oval gram positive budding yeast cell with pseudohyphyae.

Culture



On nutrient agar, corn meal agar & SDA. Colonies are creamy in color & identified by:

1- Morphology: oval budding gram +ve yeast cells.

2- Differentiation tests:

a. Germ tube test : germ tube is formed when colonies incubated with human serum at 37 C for 30 min.

b. Chlamydospore formation on corn meal agar.

c. Biochemical reactions: *C.albicans* ferments glucose & maltose with acid & gas production.

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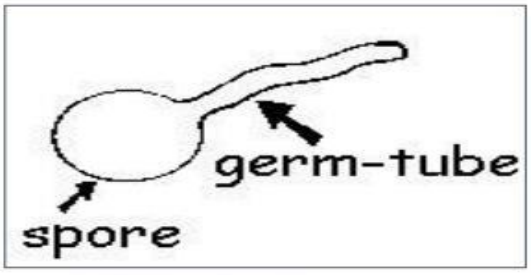
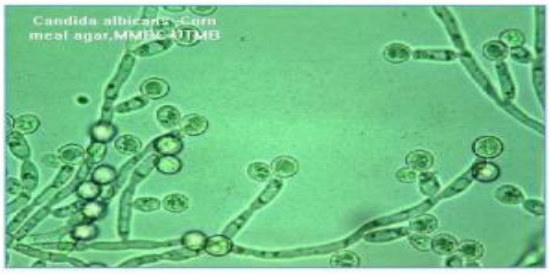
Candida, as previously mentioned, is a gram-positive organism and serves as an example of a simple yeast cell, pseudohyphae, and true hyphae. Regardless of the sample source—whether it is vaginal secretions, skin scrapings, or a swab from the mucous membrane—single budding yeast cells are often observed. These samples can then be cultured on Sabouraud dextrose agar, where Candida forms white, creamy, and waxy colonies. Further identification can be performed using cornmeal agar, and to determine the specific species, additional biochemical tests may be required. One such differentiation test is the germ tube formation test.



Germ tube



Terminal Chlamydospore & pseudohyphyae

Typical for Candida albicans.

Tratment

- Oropharyngeal or oesophageal thrush
  - Nystatin
  - Fluconazole ont
- Skin lesions
  - Nystatin ointment
- Systemic candidiasis
  - Caspofungin IV,
  - Ketoconazole (orally)
  - Amphotericin B (IV)

Cryptococcus neoformans

Always exogenic and pathogenic.

- **Cryptococcus neoformans causes cryptococcosis.**
- **A widespread encapsulated yeast that inhabits soil around pigeon roosts.**

Phagocytosis is the main defense against it, but it has a capsule so it will be impaired phagocytosis.

- **Common infection of AIDS, cancer or diabetes patients.**

When inhaling the spores of Cryptococcus neoformans, especially the neurotropic spores, they tend to travel to the central nervous system causing meningitis, that's why in diagnosis we take CSF (cerebrospinal fluid) samples.

- **Infection of lungs leads to cough, fever, and lung nodules.**
- **Dissemination to meninges and brain can cause severe neurological disturbance and death.**

Diagnosis

1-Microscopic diagnosis

- **India Ink for capsule stain (50-80% + CSF).**

Note that *Cryptococcus neoformans* is the only capsulated fungi (even *Histoplasma capsulatum* fungi is not capsulated). This test's sensitivity is only 50-80% so if you didn't find *Cryptococcus neoformans* in it this doesn't mean that the patient does not have it.

2-Culture

- **Bird seed agar**
- **Routine blood culture**

3-PCR

Aspergillosis:

Another opportunistic fungal infection is Aspergillosis: Diseases of the Genus Aspergillus

- **Very common airborne soil fungus**
- **600 species, 8 involved in human disease: A. fumigatus most commonly.**
- **Serious opportunistic threat to AIDS, leukemia, and transplant patients**
- **Infection usually occurs in lungs – spores germinate in lungs and form fungal balls; can colonize sinuses, ear canals, eyelids, and conjunctiva.**
- **Bronchopulmonary allergy or Invasive aspergillosis in preformed cavities can produce necrotic pneumonia, and infection of brain, heart, and other organs.**
- **Surgery, Amphotericin B and nystatin**

There are three species for medical importance: *Flavus* and *parasiticus* in aflatoxins, *fumigatus* in allergies.

Aspergillus fumigatus is associated with a range of conditions, including bronchopulmonary allergic alveolitis, extensive allergic alveolitis (wood worker disease), rhinitis, and bronchopulmonary spasms. In addition, it can cause invasive aspergillosis. Patients may develop lung cavities where the hyphae of Aspergillus multiply, leading to aspergillosis. These cavities can form fungal balls, known as aspergillomas. Aspergillus species are characterized by dichotomously branching hyphae with acute-angle branching. However, unlike the description, Aspergillus hyphae are septated. This is a defining feature that differentiates it from other fungi.

Zygomycoses:

- **Zygomycota –also called zygomycetes or Mucoromycetes- are extremely abundant saprophytic fungi found in soil, water, organic debris, and food.**
- **The genera most often involved are Rhizopus, Absidia, and Mucor.**
- **In zygomycosis (mucormycosis), the hyphae are characterized by broad, ribbon-like, non-septated (aseptate) structures that exhibit dichotomous branching at angles greater than 90 degrees. This feature is a key distinguishing characteristic of zygomycotic infections compared to other fungal infections.**
- **Usually, harmless air contaminants invade the membranes of the nose, eyes, heart, and brain (cerebrum) of people (Rhinocerebral mucormycosis) with diabetes (diabetic ketoacidosis) and malnutrition, with severe consequences (usually causes death after a few days or a week).**

- **If a patient develops one of the severe complications, such as diabetic ketoacidosis (DKA), it can be life-threatening due to its severity.**
- **The main host defense is phagocytosis.**

Diagnosis:

Is made by direct smear and by isolation of molds from respiratory secretions or biopsy specimens.

Treatment:

- **Control Diabetes (or underlying risk/predisposing factor)**
- **Surgery**
- **Amphotericin B**

Prognosis: very poor.

Pneumocystis:

- **Pneumocystis jirovecii -also called pneumocystis carinii- (in the old days it was considered a parasite but now it's considered a fungi) is the cause of lethal pneumonia, interstitial lung fibrosis or even the typical pneumonia (not the pneumonia caused by streptococcus pneumonia) in immunocompromised persons, particularly those with AIDS.**
- **Pneumocystis cannot be cultured ex vivo or isolated in a laboratory setting. It is typically identified in histopathology sections using eosin methylene blue staining, where it exhibits a honeycomb appearance. Alternatively, silver staining can also be used for detection.**
- **Definite diagnosis of pneumocystosis depends on finding organisms of typical morphology in appropriate specimens (Sputum, BAL)**
- **The organism has not been grown in culture.**
- **TMP-SMX (trimethoprim-sulfamethoxazole and in health centers they call it cotrimoxazole) is a treatment of choice.**

Endemic Mycosis

- Endemic mycosis is caused by a thermally dimorphic fungus (if we are talking about dimorphic fungus, we have the four that are mentioned below and an extra one which causes rose-gardener's disease), and the infections are initiated in the lungs following inhalation of the respective conidia.
- Each of the four primary systemic mycoses—Coccidioidomycosis, Histoplasmosis, Blastomycosis, and Paracoccidioidomycosis—is geographically restricted to specific areas of endemicity in north and south America (so they can infect immunocompetent people).
- Most infections are asymptomatic or mild and resolve without treatment. However, a small but significant number of patients develop pulmonary disease.
- They also affect immunocompromised patients with more severe disease, and all these diseases begin with the inhalation of spores in the respiratory tract.

V0 → V1

Added slide 14 to the sheet

Changed page 9 and 10 accordingly

GOOD LUCK