TEACHING UNIT 12

Mycology

General characteristics of fungi

Opportunistic fungal infections

Fungal infections of the skin, subcutaneous tissue and skin derivatives

Endemic mycoses

Antifungal drugs

General characteristics of fungi

- The kingdom Fungi includes at least 100.000 species distributed throughout the world
- Fungi are **eukaryotes**
- In nature, most fungi provide nutrients by decomposing organic matter from the immediate environment
- They do not have chlorophyll and do not perform photosynthesis
- Almost all fungi are aerobic, the optimum temperature for fungi that cause human diseases is from 35°C to 37°C

Fungi are divided into:

1. Nonpathogenic (saprophytes)

2. Opportunistic pathogens

3. Strict pathogens

Less than 1% causes diseases in humans

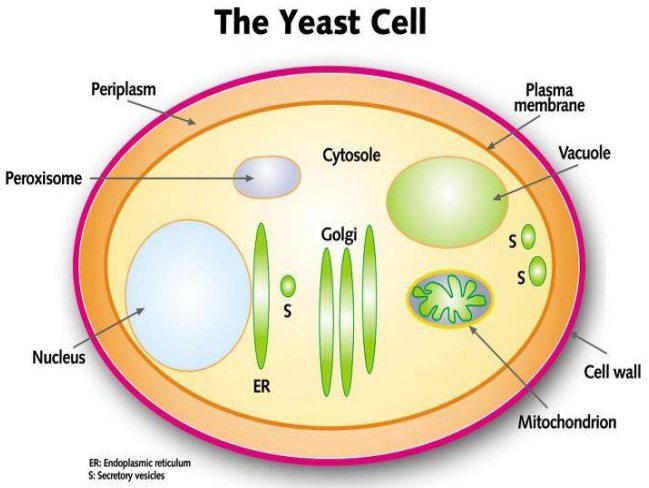
Some fungi are part of normal human microflora

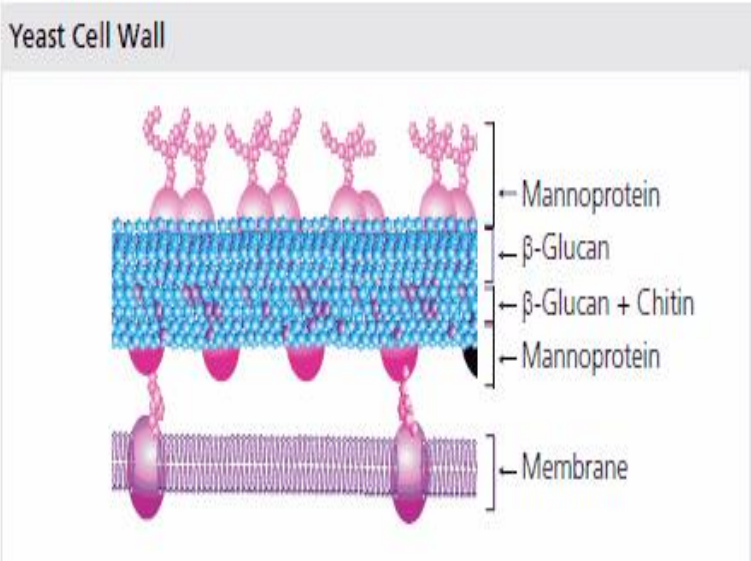
General characteristics of fungi

- Fungi are eukaryotes with a defined nucleus surrounded by a nuclear membrane, cell membrane, mitochondria, Golgi apparatus, ribosomes attached to the endoplasmic reticulum, and cytoskeleton with microtubules and microfilaments

- **Fungi have a cell wall that is made of chitin, mannan and glucan**; mammalian cells do not have a cell wall, and the cell wall of bacteria and plants is significantly different from the cell wall of fungi

- The sterols that make up the cell membrane of fungi are mainly composed of **ergosterol**, while the cell membrane of mammals is predominantly composed of cholesterol

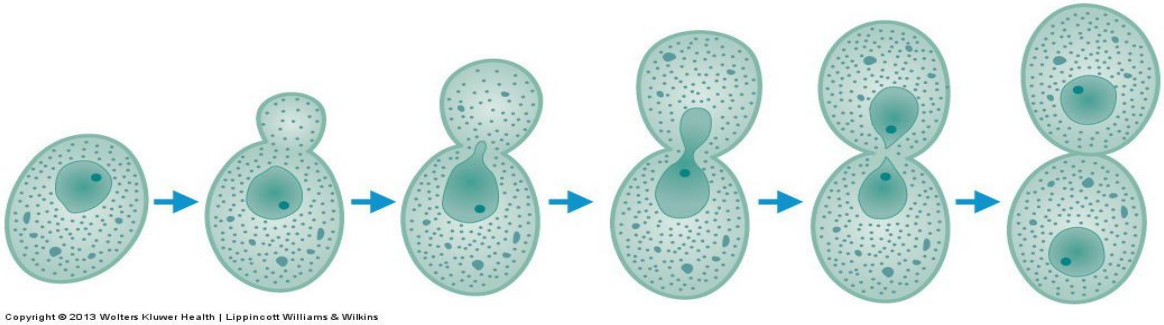




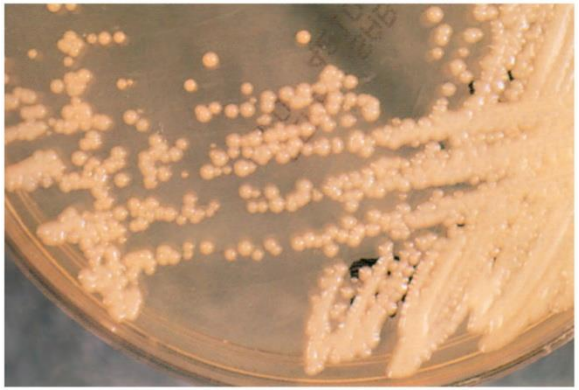
Morphology of fungi - yeasts

- Fungi that cause human diseases have two main forms: **unicellular forms** named **yeasts** and **multicellular filamentous forms** named **molds**

- **Yeasts are unicellular fungi** with oval or spherical shape
- Most yeasts divide by budding (asexually), and the **bud** is called **blastoconidia**



- On agar, yeasts form moist colonies that are similar to, but larger than bacterial colonies



Morphology of fungi - molds

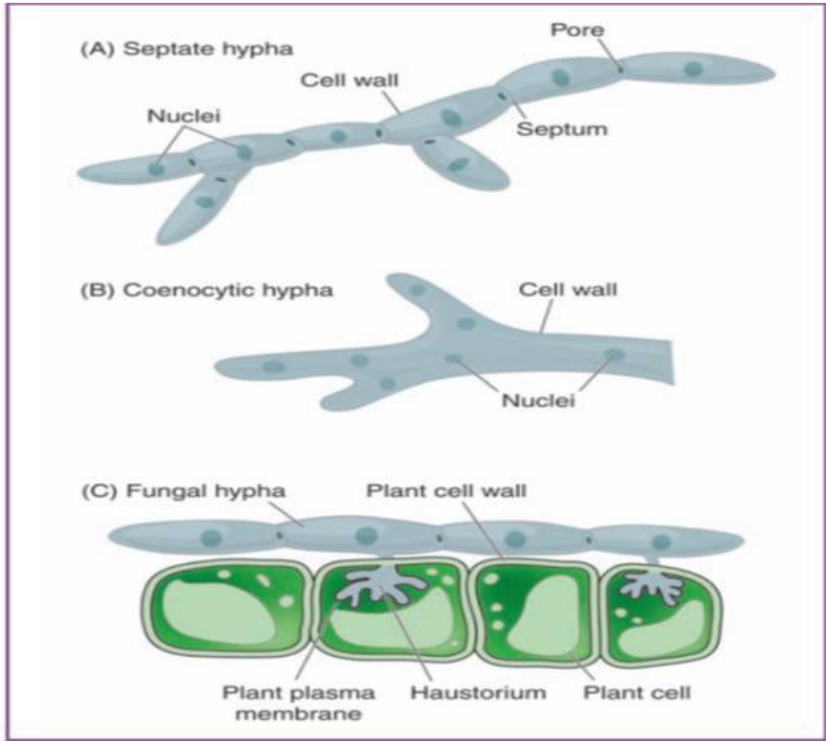
- Molds grow as microscopic, branching, reticulate filaments

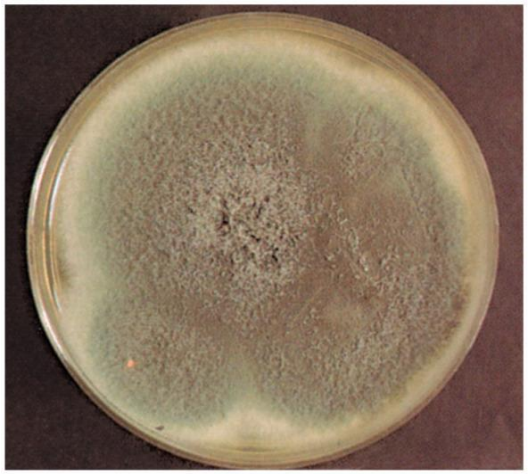
- The filaments, usually 2 to 10 micrometers in diameter, are called **hyphae, and the mass of hyphae** is denoted as **mycelium**

- Hyphae are either **divided (septate)** or **undivided (non-septate) -** multinucleated fungi without transverse walls

- On agar, part of the mycelium grows into the agar to provide nutrients for the aerial hyphae that form the **mold above the agar surface**

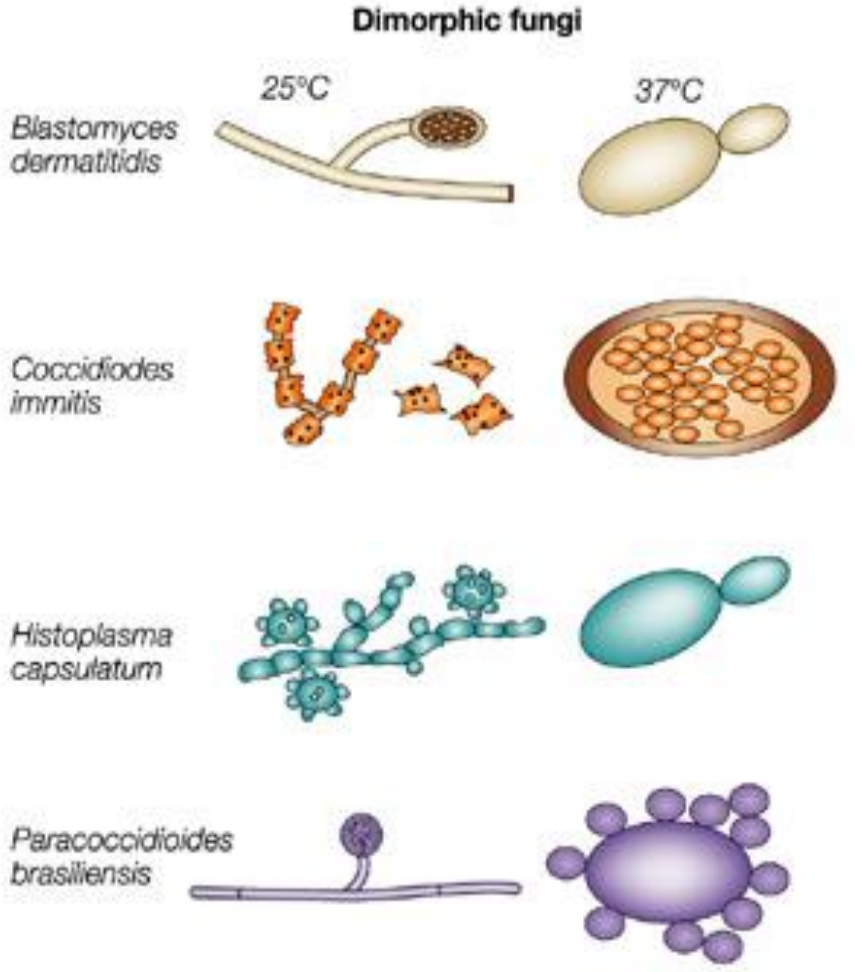
- Aerial hyphae provide support for mycelial reproductive structures





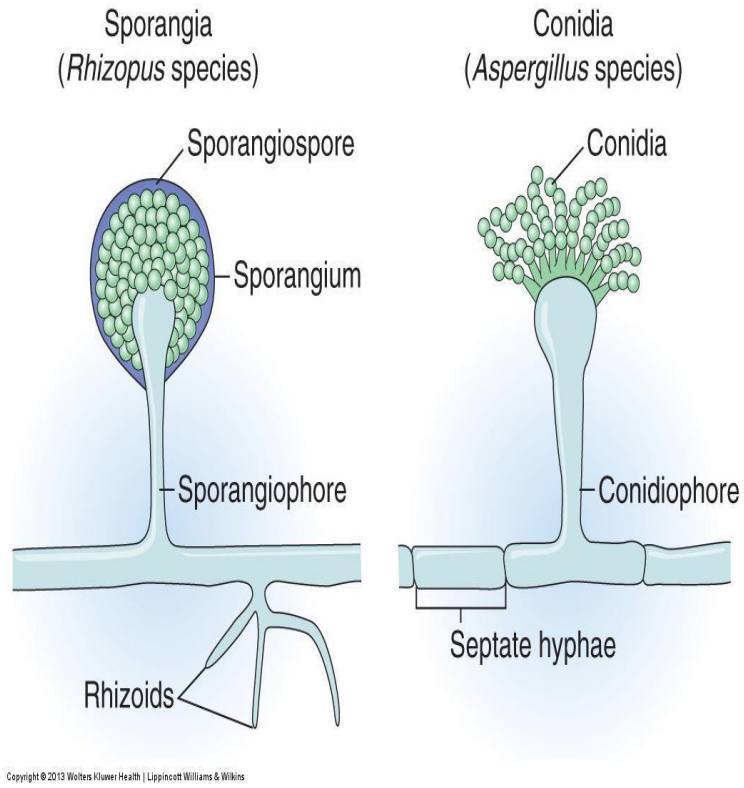
Morphology of fungi - dimorphic fungi

- Many pathogenic fungi have both growth forms - exist both as yeasts or molds
- This phenomenon is called **dimorphism**, and a change in form often occurs when a free-living organism infects a living host
- In most fungi that cause systemic infections in humans, **the mold form is found in the external environment, and the yeast is found in the tissue**



Reproduction of fungi

- Fungi reproduce asexually or sexually
- **Asexual** reproductive structures are called **conidia**. The appearance of conidia varies enormously and is used to identify fungi
- Conidia may form at the tips of growing hyphae, on a specialized structure called a **conidiophore**, directly on the hypha, or within the hypha itself
- **Sexual** reproduction usually takes place through the formation of spores, which are often formed as complex structures



Fungi - natural habitat

The most fungi live free in the environment and people encounter them accidentally during everyday life

- Several fungi that are important human pathogens grow only in certain geographic areas
- Many fungi species are ubiquitous and rarely cause disease in humans
- However, significantly immunocompromised patients can develop progressive and fatal infection after exposition to apparently harmless fungi widespread in nature

Another source of pathogenic fungi is normal human microflora. These fungi can cause serious disseminated infection in immunocompromised individuals

Fungal infections - mycoses

Fungi cause human diseases either by initiating inflammation or directly by destroying or invading tissues

According to their localization, fungal infections can be **superficial, cutaneous, subcutaneous and systemic**

- **Opportunistic mycoses** are caused by fungi that cause life-threatening systemic disease almost always only in immunocompromised patients
- **Subcutaneous mycoses** are a group of fungal diseases in which the skin, subcutaneous tissue and lymphatics are affected
- **Superficial and cutaneous mycoses** are common fungal infections limited to the skin and skin structures
- **Endemic mycoses** are infections caused by pathogens that are present in a certain geographical area. They are caused by "real" pathogens, capable of causing serious systemic infections in healthy individuals

Entering the body and spreading the infection

- Infection with fungi from the external environment
- Infection of immunosuppressed patients
- The significance of the injury
- Disturbance of normal microflora (use of antibiotics)

The importance of the immune system in the pathogenesis of fungal infections:

- phagocytes (chronic granulomatous disease)
- **cellular immune response** (patients suffering from AIDS)
- the role of antibodies

The outcome of the infection is determined by virulence of microorganisms, inoculum size and the state of the host's immune system

Tissue damage occurs either as a result direct fungal invasions or the effects of the triggered inflammatory response

Diagnosis of fungal infections

1. Direct microscopy

10% potassium hydroxide is used to break down tissue debris so that fungi with intact cell walls can be observed, or fluorescent dyes such as calcofluor white are used, which binds to chitin and serves to highlight the fungal cell wall

2. Histopathology

Special colors are used to recognize the specific morphological characteristics of certain fungi

3. Cultivation

Some medicinally important fungi need weeks to grow. Thus, in a seriously ill patient, culture is used in order to confirm the diagnosis, but the culture results are not awaited either to establish a diagnosis or to start therapy

4. Serology

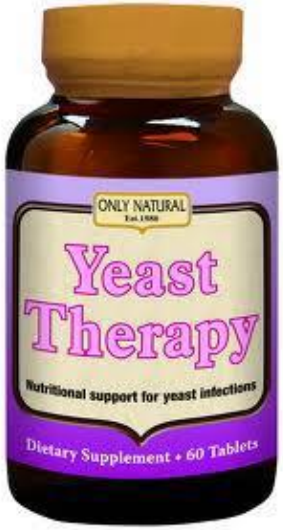
The identification of serum antibodies to fungal antigens is useful in the diagnosis of several endemic mycoses

5. Antigen detection by PCR technique

The detection of fungal antigens in body fluids, urine and serum has been shown to be a sensitive and specific method for the diagnosis of some opportunistic fungi, as well as several endemic mycoses

Treatment of fungal infections

- Not all yeast infections require treatment
- For those infections that require treatment with systemic antifungal drugs, **toxicity is a problem because fungi share many metabolic pathways and structures with mammalian cells that are targeted by antifungal drugs**
- Compared to antibiotics, the number of effective antifungal drugs is quite small



Opportunistic fungal infections

Opportunistic fungal infections

Opportunistic fungi are not considered true pathogens because **they cause the disease only in conditions of weakened immune response**

Immunosuppressed patients have a higher risk for opportunistic fungal infections

Other risk factors are large burn wounds, trauma, inserted central venous catheters, broad-spectrum antibiotic therapy, parenteral nutrition, diabetes, renal failure requiring dialysis, etc.

1. Candidiasis (*Candida albicans* and other *Candida* species)

2. Cryptococcosis (*Cryptococcus neoformans*)

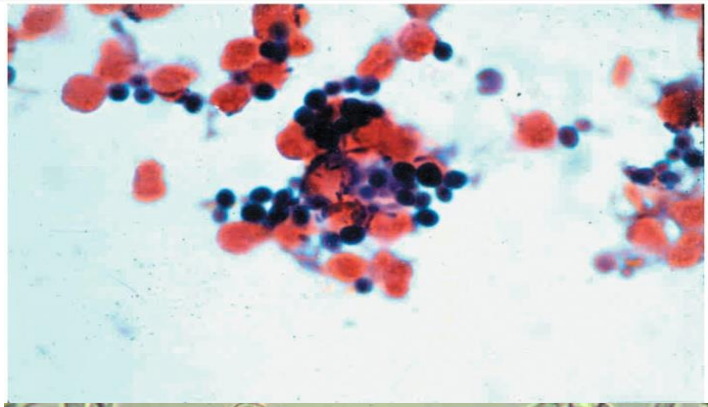
3. Aspergillosis (*Aspergillus fumigatus* and other *Aspergillus* species)

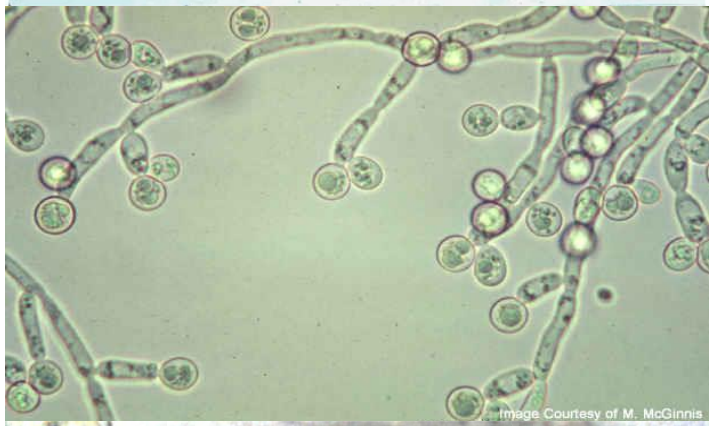
4. Mucormycosis (*Rhizopus*, *Mucor* and other *Mucorales* molds)

5. Pneumocystosis (*Pneumocystis jiroveci*)

Candidiasis
-basic characteristics of the pathogen-

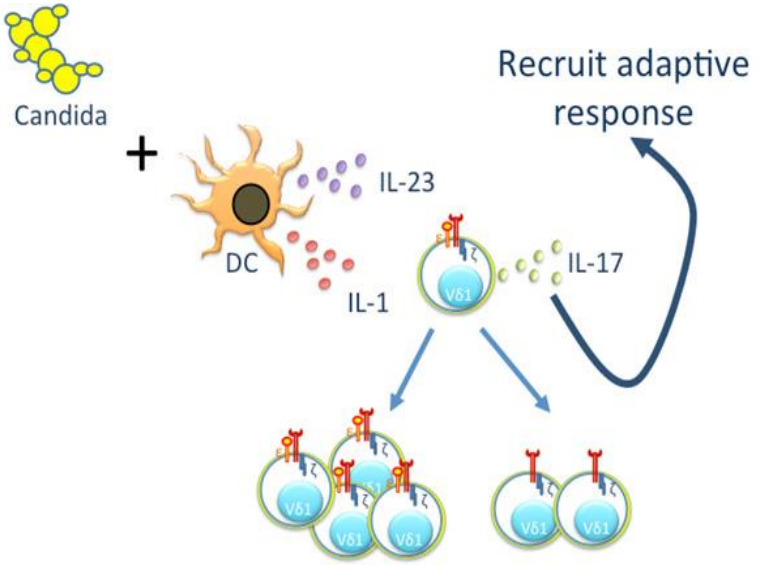
- **Round or oval-shaped yeasts** that reproduce by forming buds or blastoconidia
- They have the potential to **form hyphae *in vivo***, which is seen in invasive infections caused by some, but not all *Candida* species
- The most important member of the genus is ***Candida albicans***, which colonizes humans and is responsible for the majority of diagnosed infections
- Other species important in clinical practice are ***Candida glabrata***, resistant to some antifungal drugs, and ***Candida parapsilosis***, a common cause of infections associated with the use of central venous catheters
- Candida colonizes the gastrointestinal tract, from the mouth to the rectum, the vagina and the skin. **Most infections are endogenous** - meaning they originate from the host's normal microflora
- Risk: immunosuppressed patients

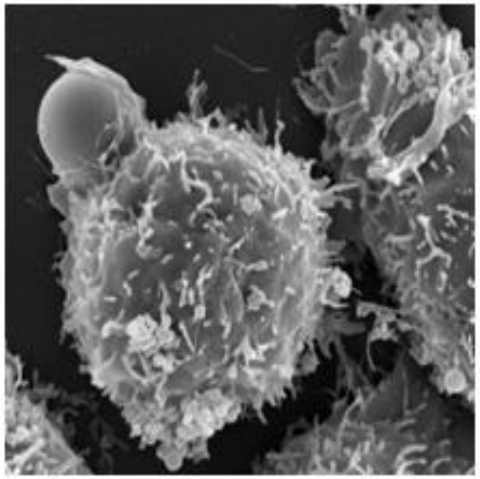




Candidiasis
-pathogenesis-

- *Candida* does not cause infection if the microflora is preserved. The most common reasons for the disruption of the normal flora are the use of broad-spectrum antibiotics and skin maceration
- **Disruption of cellular immunity** allows the proliferation of *Candida* on the surface of mucous membranes (patients with advanced HIV infection and a low number of CD4+ lymphocytes often develop oropharyngeal and vaginal candidiasis)
- **Neutrophils** prevent invasion through mucous membranes and the subsequent spread of infection
- In neutropenic patients, *Candida* disseminates hematogenously to many organs, particularly the eyes, kidneys, heart brain, liver, and spleen



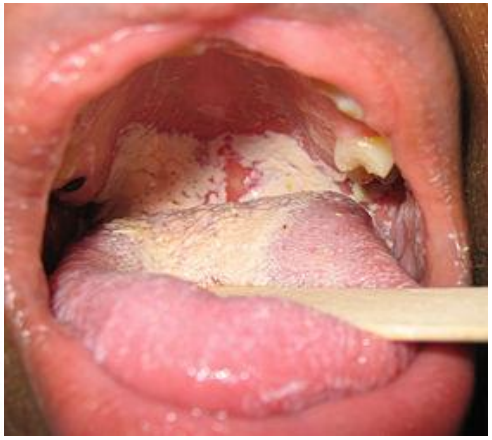


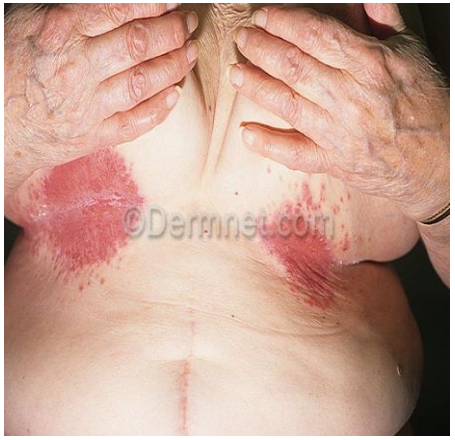
Neutrophil Phagocytosis of Candida albicans

Candidiasis
-clinical picture-

- **Mucosal candidiasis** is characterized by the presence of adherent whitish plaques on the oropharyngeal and vaginal mucosa. The lesions, often called **sores**, are not painful
- Candida overgrowth in warm, moist areas of the skin, especially in the groin and under the breasts is called **intertriginous candidiasis**, and in babies, **diaper rash**
- Deeper tissues are not damaged, and patients have no long-term consequences

Figure – White, curd-like, discrete plaques are evident on the tongue and palate of this otherwise healthy 3-month-old girl. No diaper rash was noted.



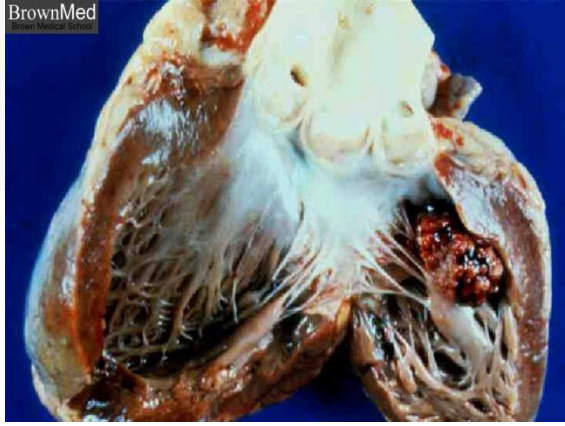


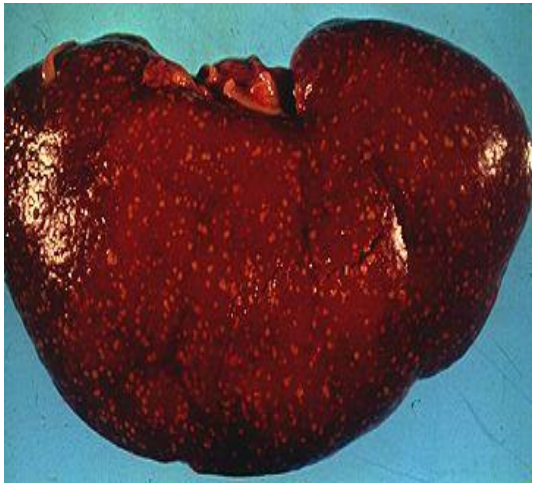
Candidiasis
-clinical picture-

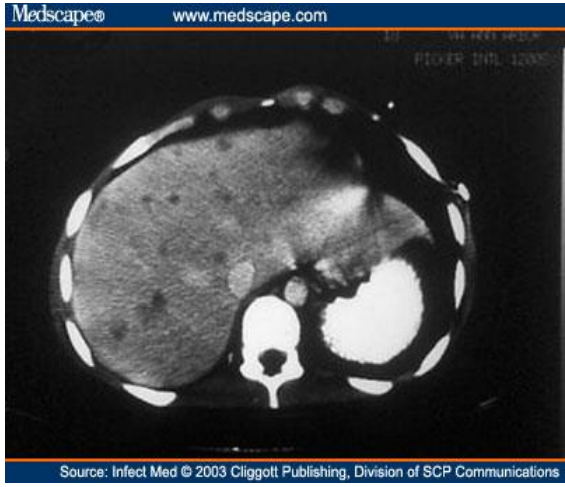
- **Disseminated infection** can be manifested like inexplicable fever, sepsis, or organ dysfunction

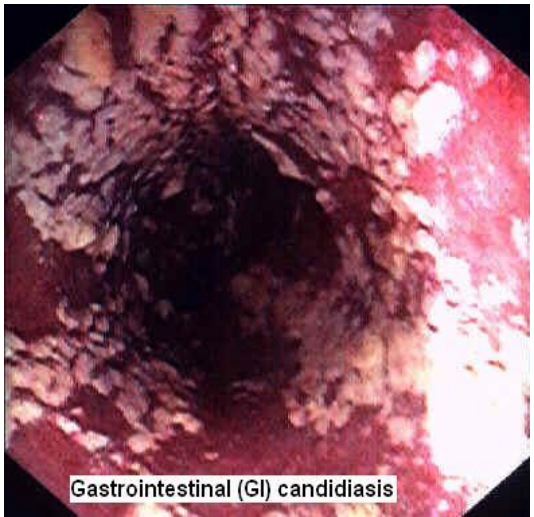
- **Candidemia** is sometimes the only manifestation of the spread of infection, and the clinical manifestations depend on which organs are infected: **meningitis, chorioretinitis with consequent vitritis, hepatosplenic abscesses, osteomyelitis of the spinal column, endocarditis (on artificial valves).**

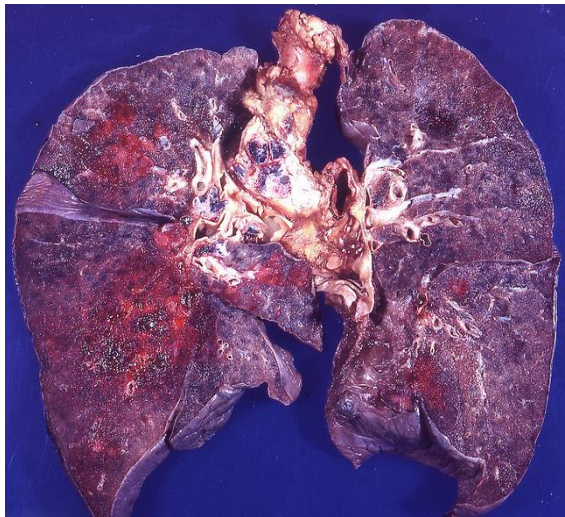
- Hisopathological finding is one or more **microabscesses** in affected organs





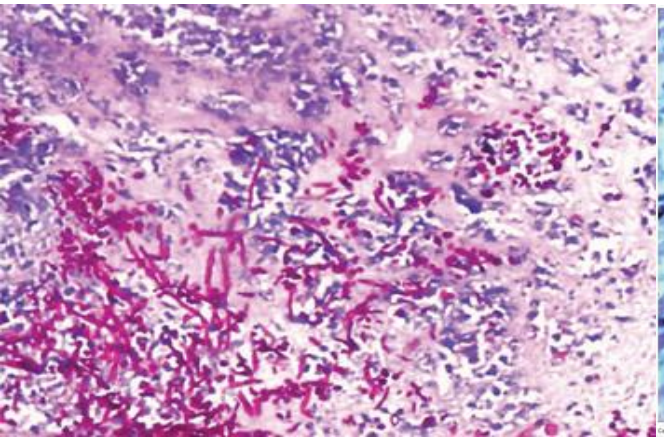


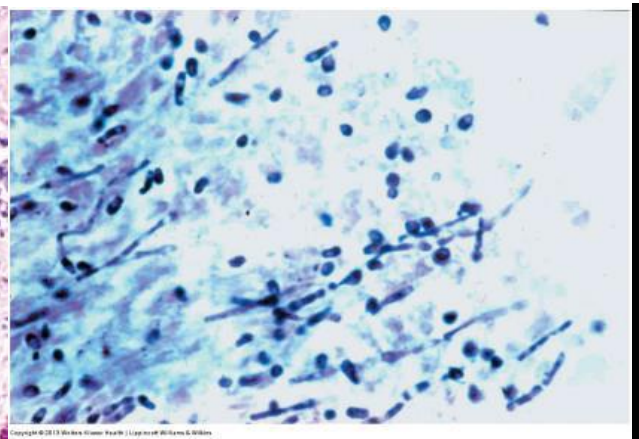




Candidiasis
-diagnosis-

1. **Diagnosis of mucosal candidiasis** is simple. A scraping of the lesions shows yeast buds and often pseudohyphae (elongated buds attached to each other), and culture of the sample shows growth of *Candida*
2. **Invasive candidiasis** is more difficult to confirm. A biopsy of infected tissues shows invasion by a combination of yeast with buds and hyphae, which is characteristic of candidiasis, while the growth of *Candida* in the sample culture confirms the finding
3. *Candida albicans* can be distinguished from other species of *Candida* because within a few hours the so-called germ tubes (elongated yeast buds) in conditions where this yeast is exposed to calf serum





Candidiasis
-therapy and prevention-

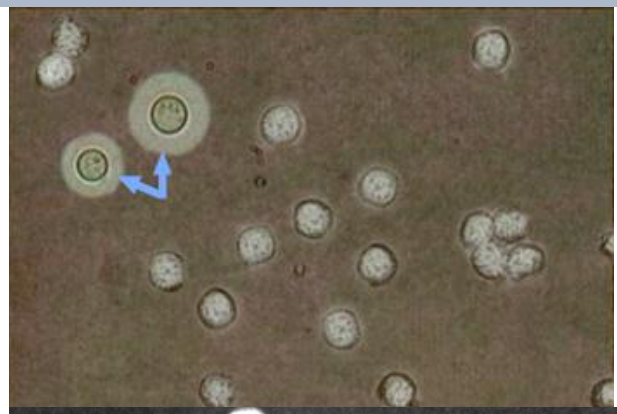
- **Mucosal candidiasis and intertriginous candidiasis** are treated **locally**, using **antifungal ointments and powders**. However, if a large area of the mucous membrane is affected, systemic administration of antifungal drugs is also possible. Candidemia without obvious organ dysfunction is usually treated for a minimum of 2 weeks
- **Invasive infections** should always be treated with **systemic antifungal medication**. Depending on the pathogen, the most commonly used drugs are **fluconazole** and **echinocandin**. **Amphotericin B** is also used for invasive candidiasis treatment
- Invasive candidiasis must be treated for months

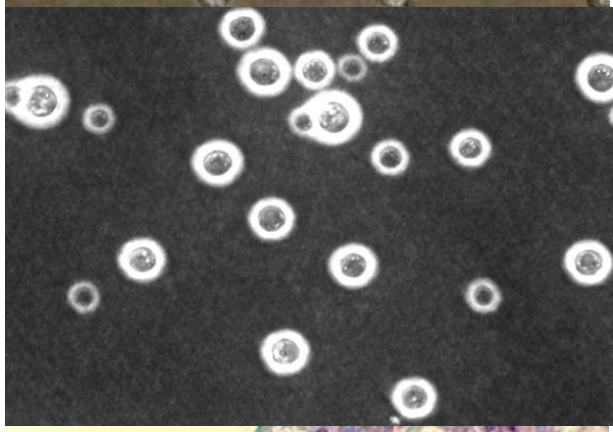
PREVENTION

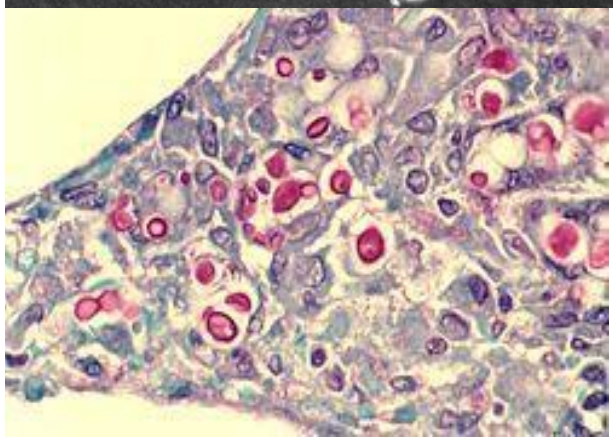
- Mucous membrane infections in AIDS patients can be prevented by **preventive use of antifungal drugs**, but long-term use carries the risk of developing resistance
- Neutropenic and bone marrow stem cell transplant patients, who are at greatest risk for disseminated candidiasis, usually receive azoles prophylactically
- Intensive care: hand and catheter hygiene

Cryptococcosis
-basic characteristics of the pathogen-

- The causative agent of cryptococcosis is a yeast from the external environment named ***Cryptococcus neoformans***
- **In the tissues**, but not in the outer environment, **this yeast is surrounded by a polysaccharide capsule**, which protects it from phagocytosis
- ***Cryptococcus gattii*** is increasingly cited as a cause of human infections, while other species are generally not pathogenic
- *C. neoformans* can be found worldwide in soil contaminated with birds secretions
- Unlike most other opportunistic fungi, about 20% of patients with cryptococcosis are immunocompetent

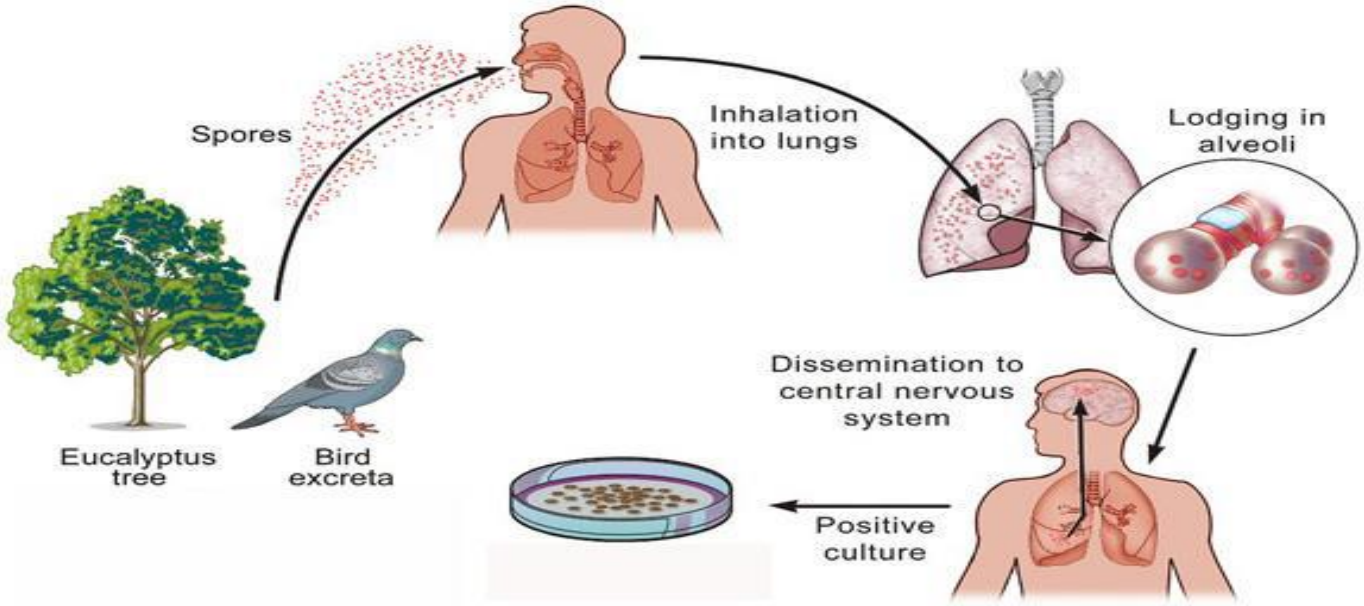






Cryptococcosis
-pathogenesis-

1. **Yeast is inhaled**, goes to the alveoli, where it causes lung infection, often without any symptoms. **In the alveoli**, the yeast begins to **create a polysaccharide capsule**
2. Neutrophils and macrophages are important in the initial stages of the infection, when yeasts are killed by phagocytosis (**the capsule inhibits phagocytosis**)
3. By producing melanin, *C. neoformans* also increases its virulence, forming a kind of tougher "armor" of its cell wall.
4. **Cellular immunity** is crucial for the infection control
5. A striking feature of *C.neoformans* is **neurotropism**

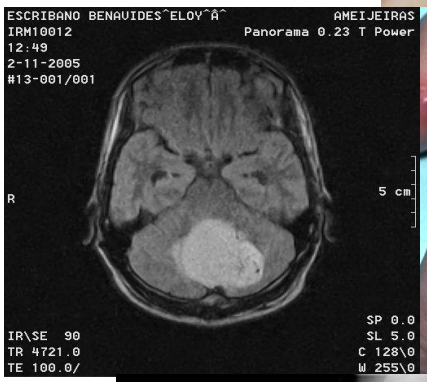


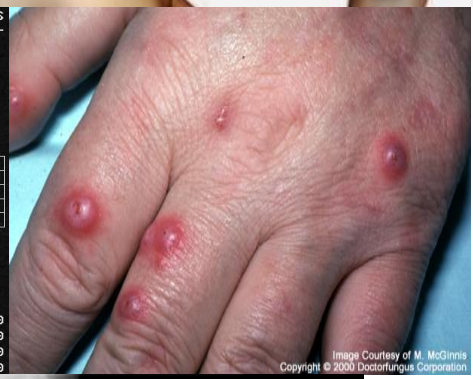
Cryptococcosis
-clinical picture-

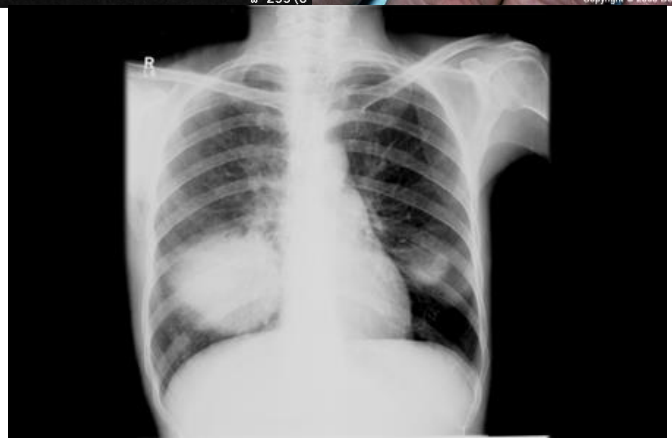
- **Meningitis** (subacute or chronic), which can occur in patients with cryptococcosis, indicates hematogenous spread of the pathogen from an asymptomatic focus of pulmonary infection

- **Symptoms**: headache that worsens as time passes (days to weeks), fever, cranial nerve dysfunction, and altered mental status

- **Dissemination** is common in AIDS patients, in whom it can be manifested by meningitis associated with **diffuse infiltrates in the lungs**, **skin lesions** and **widespread infections of visceral organs**

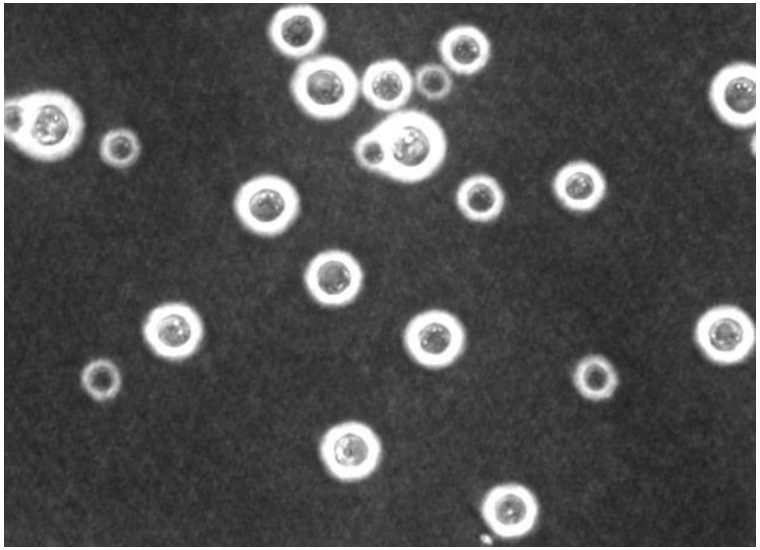






Cryptococcosis
-diagnosis-

- Cerebrospinal fluid analysis after lumbar puncture (encapsulated budding yeast)
- In the cerebrospinal fluid, the predominant presence of lymphocytes, high protein content and reduced glucose concentration are typically observed
- Polysaccharide capsule antigen detection in cerebrospinal fluid and serum
- *C. neoformans* grows on many types of agar media in just a few days and is easily identified in clinical laboratories



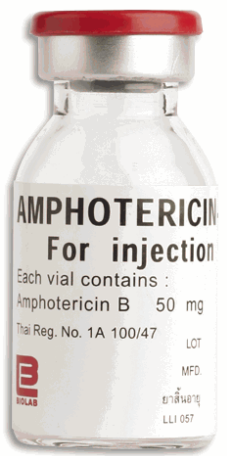
Cryptococcosis
-therapy-

- Initial treatment of meningitis caused by *C. neoformans* is a combination of amphotericin B and flucytosine for several weeks, followed by consolidation therapy with fluconazole for at least several months

- Some patients with impaired cellular immunity require lifelong fluconazole therapy to prevent re-infection

- Other clinical forms of cryptococcosis, such as pulmonary infections, can often be treated with fluconazole as primary therapy

- There are no prescribed prophylactic regimens for cryptococcosis for AIDS patients or other risk groups



Aspergillosis
-basic characteristics of the pathogen-

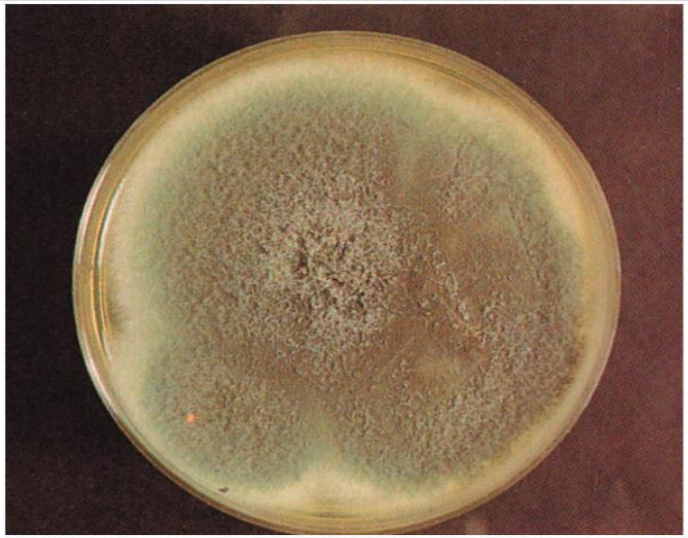
- ***Aspergillus*** fungi form mycelia of septate hyphae and **reproduce by forming conidia on conidiophores**

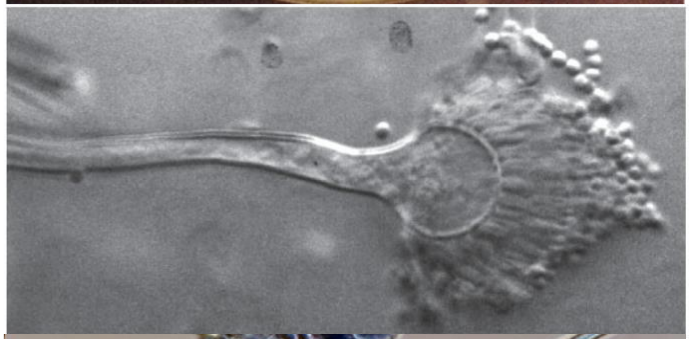
- The main species are the pathogens ***Aspergillus fumigatus*** and ***Aspergillus flavus***, but there are hundreds of other species in the environment that differ from each other in the arrangement of conidia on conidiophores

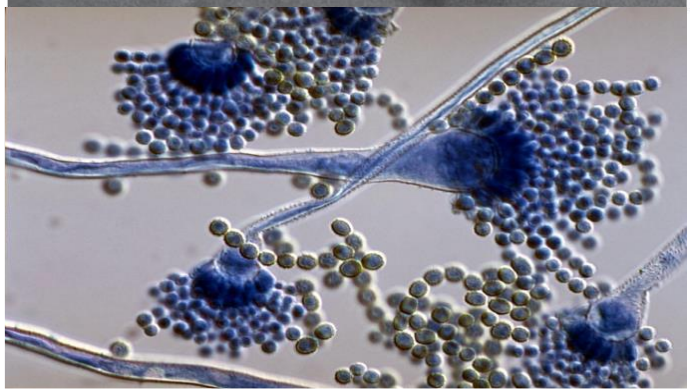
- They are not part of the normal human flora

- **They are ubiquitous,** found in soil, manure and decay products of vegetation

- **Risk: neutropenic and immunocompromised patients**

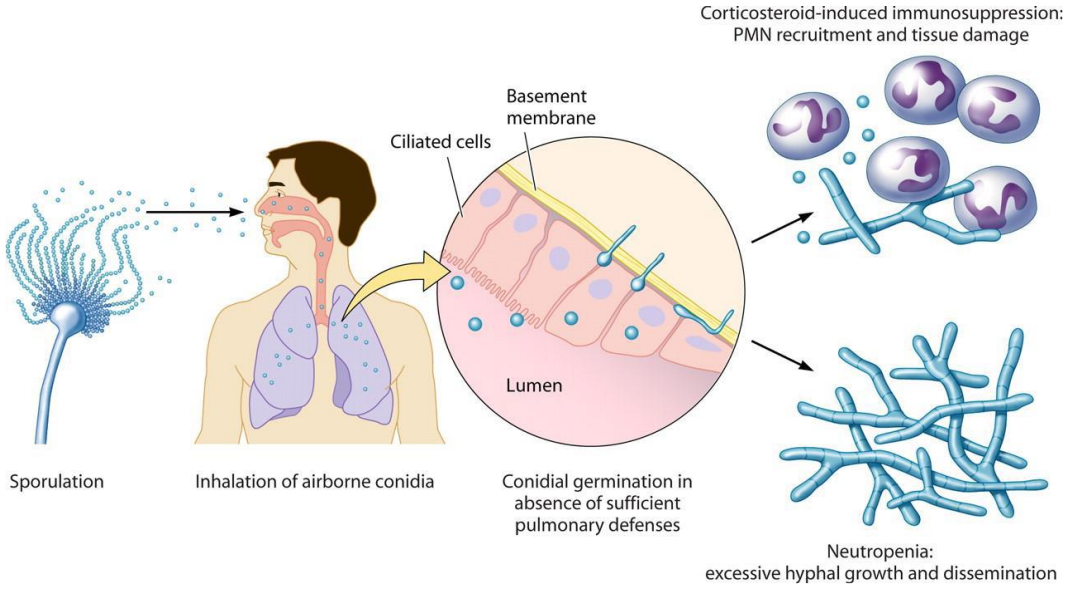


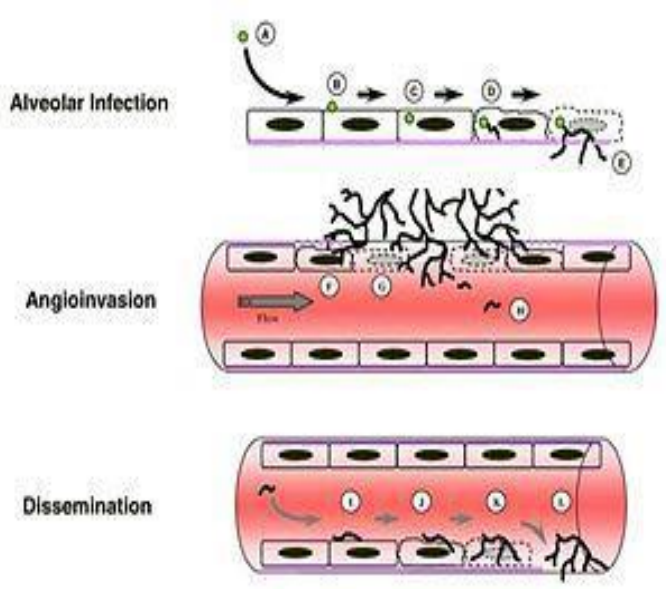




Aspergillosis
-pathogenesis-

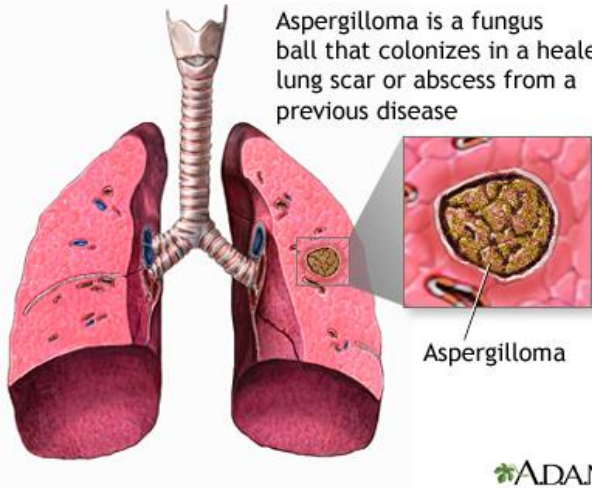
- Conidia are inhaled, conidia germinate into hyphae, which then invade tissues
- **Neutrophils and macrophages** play the most important role in host defense
- **Lung macrophages phagocytose and kill conidia** which have entered the alveoli, but are unable to kill the hyphae
- **Neutrophils are linearly distributed along the hyphae** and secrete reactive oxygen mediators that kill fungi
- **Neither antibodies nor T lymphocytes play a major role in host defense**
- ***Aspergillus* fungi are angioinvasive**, hyphae invade tissues through the walls of blood vessels causing **tissue infarction**, **hemorrhage** and **necrosis**

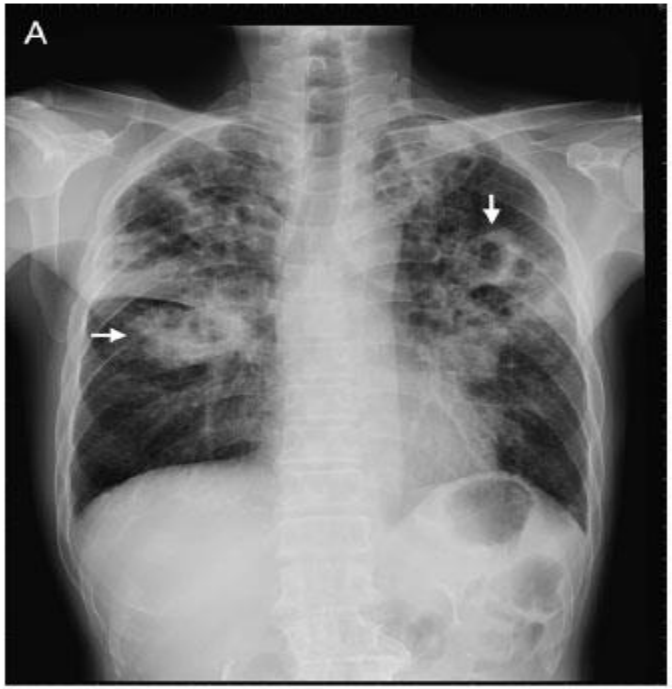


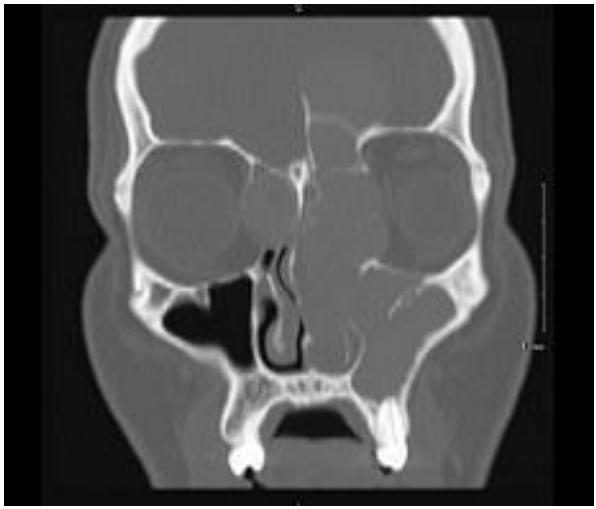


Aspergillosis
-clinical picture-

- Aspergillosis is almost always initially manifested as **lung or sinus infection**
- Clinical manifestations of **invasive pulmonary aspergillosis** are fever, pleuritic chest pain, cough, hemoptysis, and dyspnea
- Acute pain in the facial area is a sign of **sinus invasion**
- Chest radiograph and computed tomography show multiple nodules in the lungs, hemorrhage around the nodules, and cavitation (necrosis)





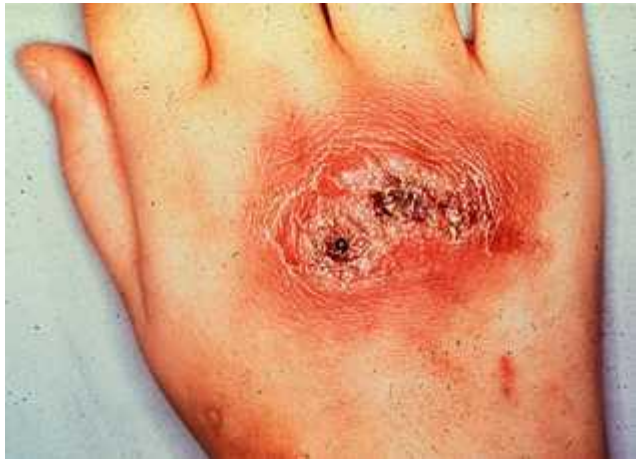


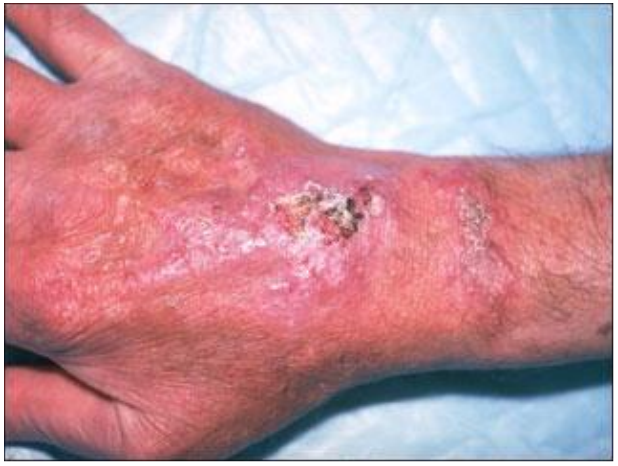
Aspergillosis
-clinical picture-

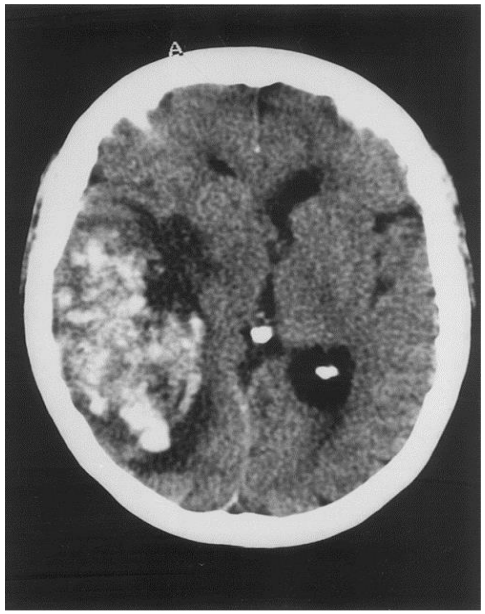
- **Dissemination of infection** is common due to the tendency of these fungi to invade blood vessels

- Common clinical manifestations of disseminated aspergillosis are **necrotic lesions on the skin** and **brain abscess** which manifests as a stroke, epileptic seizures or changes in mental status

- At autopsy, a large number of hemorrhagic infarcts and abscesses can be found in many organs



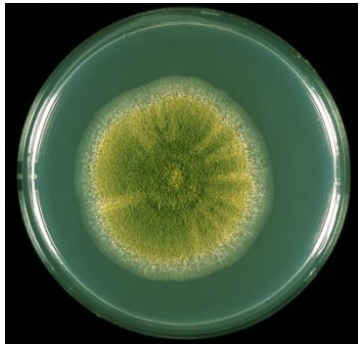


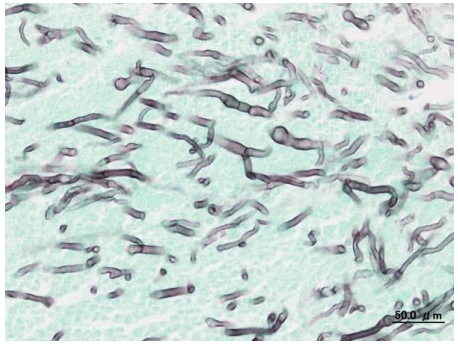


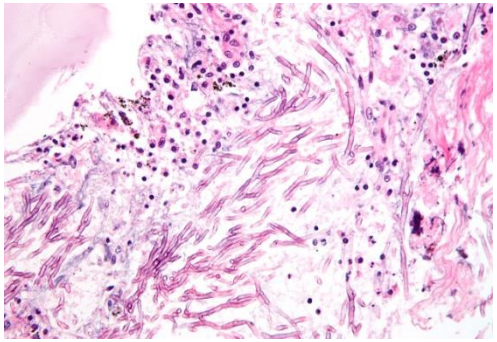
Aspergillosis
-diagnosis and therapy-

Diagnosis

- *Aspergillus* species grow well on *Sabouraud* agar within a few days
- The main problem in diagnostics is to distinguish contamination from infection with these ubiquitous fungi
- Tissue biopsy is important to document tissue invasion, but is not specific for *Aspergillus*







Therapy and prevention

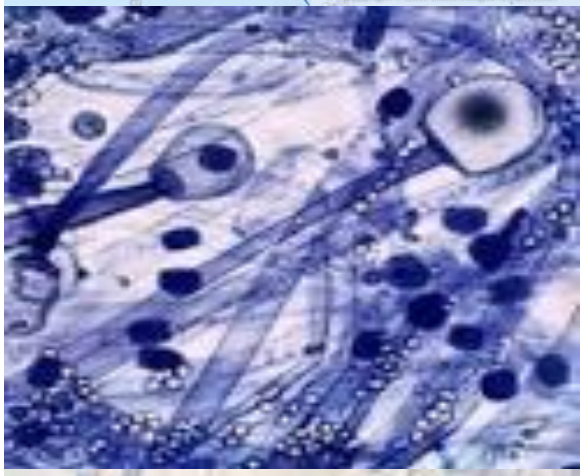
- The drug of choice for invasive aspergillosis is voriconazole, but amphotericin B or an echinocandin are also used in some cases
- In high-risk patients, empiric treatment is often initiated based on clinical manifestations and computed tomography findings
- Prevention in high-risk patients - reducing exposure to these fungi
- Prophylactic use of antifungal drugs (voriconazole or posaconazole) (stem cell recipients)

Mucormycosis
-general characteristics of the pathogen-

- ***Mucorales*** are molds that differ from *Aspergillus* species in that their hyphae are wider and have few or no septa, but they resemble *Aspergillus* fungi in their angioinvasive properties

- The main pathogens from this group are fungi from the genera ***Rhisopus*** and ***Mucor***

- **Immunocompromised patients** and **diabetics** are at risk of infection with these fungi (due to the negative effects of acidosis on chemotaxis and phagocytosis of neutrophils)

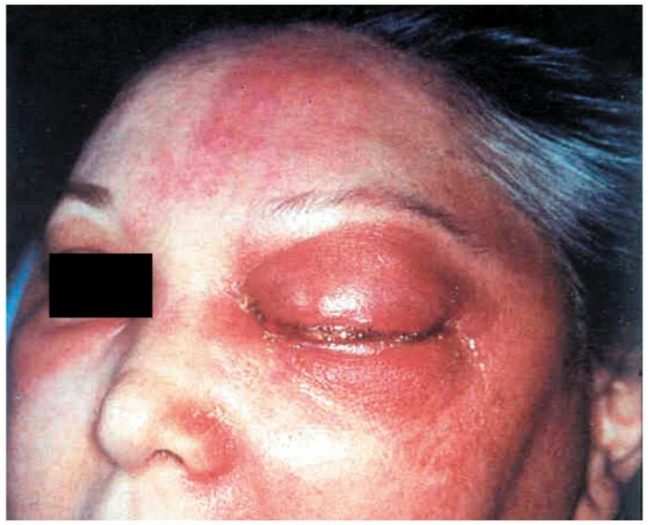


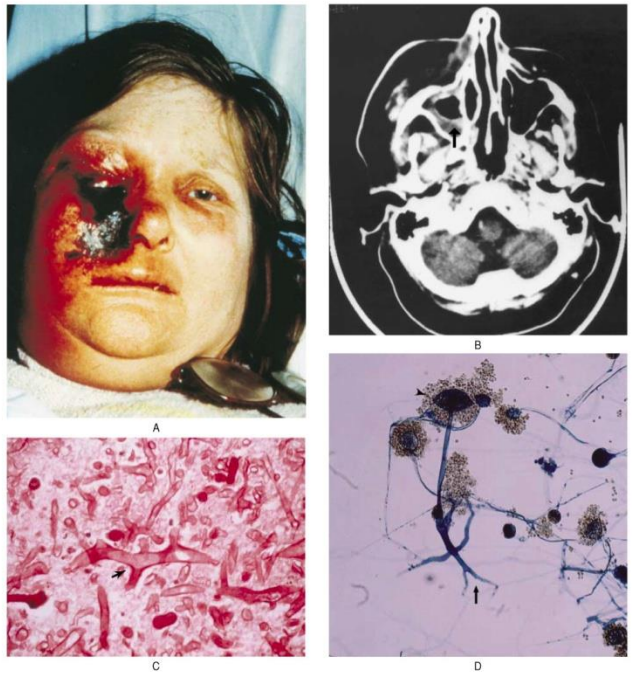
Mucormycosis

- The most common clinical manifestation in diabetics is **rhino-orbital-cerebral mucormycosis**, during which the fungus spreads from the nostrils to the sinuses, palate, orbits and soft tissues of the face, and then the infection can affect the cavernous sinus and the brain

- **Pulmonary** and **disseminated infection** occurs more often in leukemia patients due to neutropenia, and clinically mimics invasive aspergillosis

- Treatment of mucormycosis involves the use of **amphotericin B** and **aggressive surgical removal of infected and necrotic tissue**





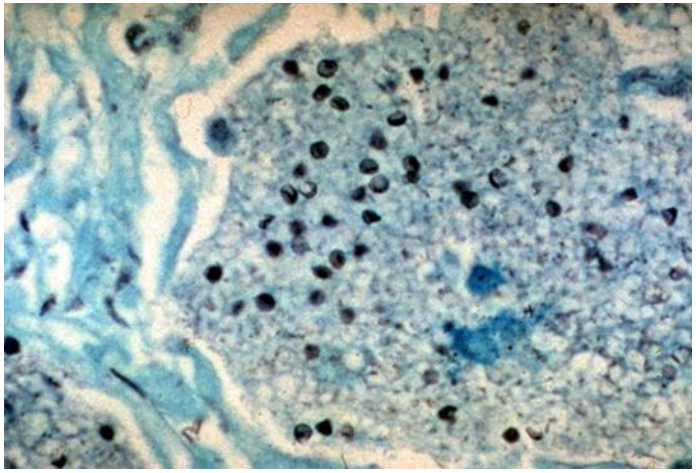
Pneumocystis jiroveci
Pneumocystosis

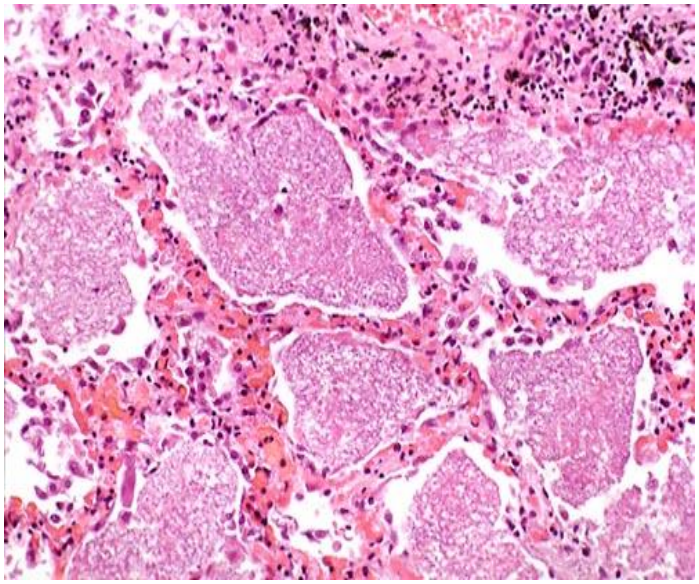
- ***Pneumocystis jiroveci*** is probably introduced into the body by **inhalation from the external environment**, but its ecological niche has not been found

- Most people probably become infected early in life, but the disease manifests only in conditions of immunosuppression

- The most common risk factor is a **deficiency of cellular immunity**, which is demonstrated by the fact that **pneumonia** caused by *Pneumocystis jiroveci* was the most common opportunistic infection in AIDS patients before the advent of anti-HIV therapy

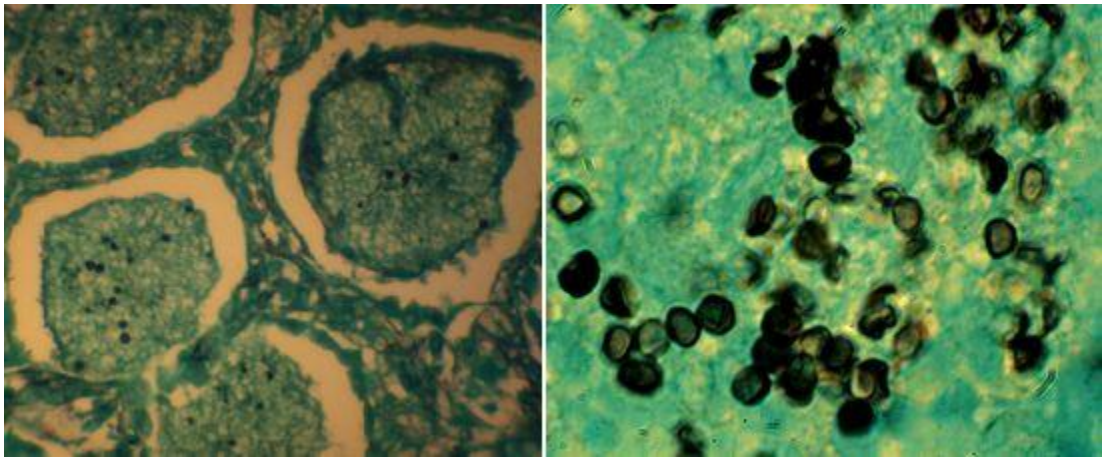
- *P. jiroveci* is very rarely found outside the lungs. Histopathologically, **the alveoli are filled with foamy protein content, desquamated alveolar cells, and fungi**

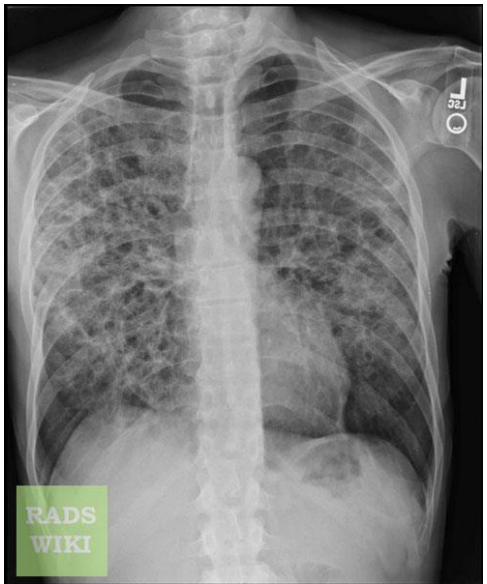




Pneumocystosis

- **Clinical manifestations** are **dyspnea**, **dry cough** and **fatigue**, with or without fever
- **A chest radiograph** shows **bilateral diffuse infiltrates**, and **hypoxemia**, which can be severe, is almost always present
- **Diagnosis**: detection of *P. jiroveci* with "silver colors" by direct immunofluorescence or PCR analysis of a sample obtained by bronchoalveolar lavage or biopsy
- **Drug of choice**: trimethoprim/sulfamethoxazole, which is also very effective in prophylaxis of high-risk patients





Fungal infections of the skin, subcutaneous tissue and skin derivatives

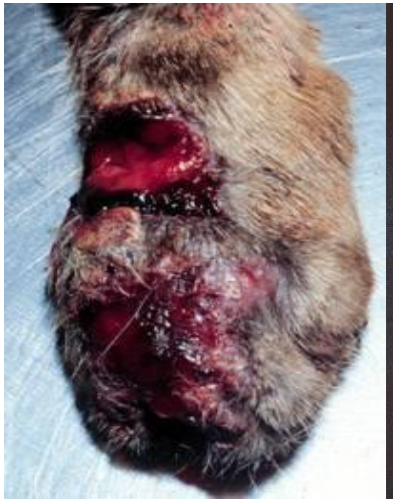
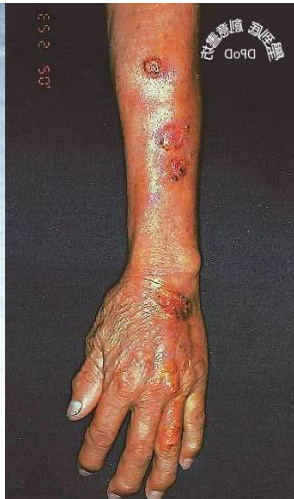
Fungal infections of the skin, subcutaneous tissue and skin derivatives

- **Sporotrichosis** (*Sporothrix schenckii*)
- **Mycetomas and Chromoblastomycosis** (one of the possible causes is *Madurella mycetomatis*)
- **Dermatophyte infections** (*Trichophyton*, *Microsporum* and *Epidermophyton*)
- **Superficial mycoses** (*Malassezia*)

Sporotrichosis
-general characteristics of the pathogen-

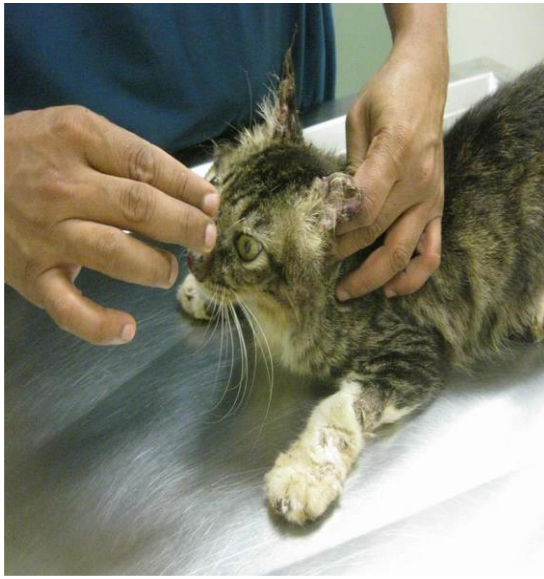
- *Sporothrix schenckii* is **dimorphic fungus**
- In the external environment, *S. schenckii* exists as a mold whose hyphae produce small conidia which are the infectious form
- At body temperature, it changes into yeast form
- It is found in soil, moss, rotting wood and vegetation around the world
- It enters the body through the skin injury
- Risk groups: foresters, farmers and gardeners

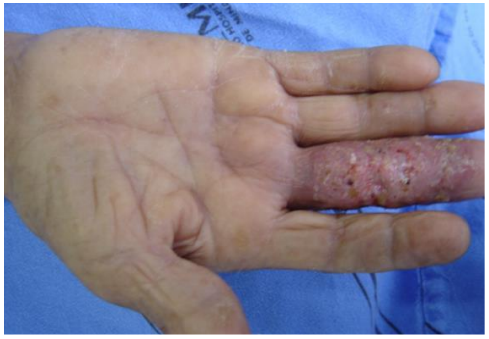


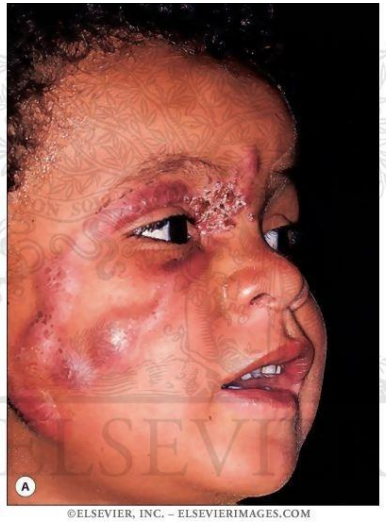



Sporotrichosis
-pathogenesis-

- The fungus is inoculated into the skin or subcutaneous tissue by the prick of a thorn or some other sharp plant
- Fungi can also enter the body after scratching infected animals or even by petting cats that have ulcerated lesions
- **Most infections are seen on the upper extremities or face**
- **Rarely,** the fungus, via aerosols, is inhaled into the body when it cause **pulmonary sporotrichosis**



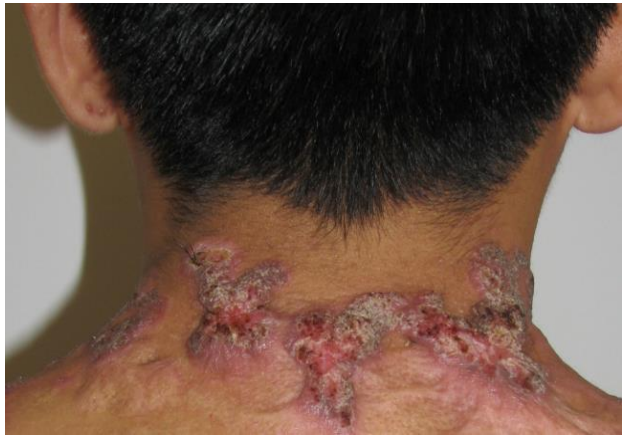


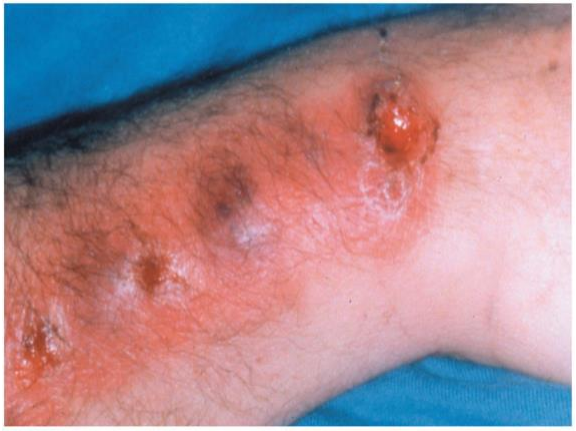


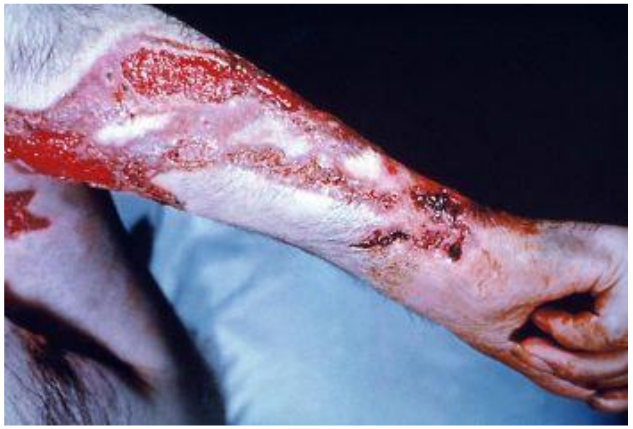
Sporotrichosis
-clinical manifestations-

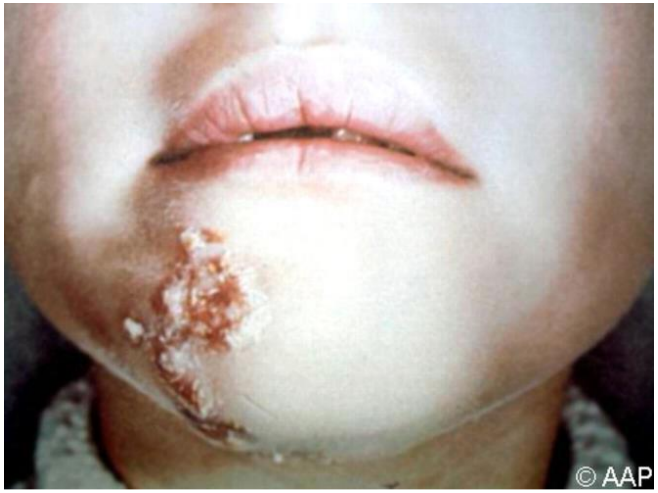
- Sporotrichosis is **usually a localized infection** with few systemic symptoms
- **At the primary site of inoculation, a painless or mildly painful nodular lesion develops over several weeks, which subsequently ulcerates**
- In some patients, a single skin lesion is the only manifestation of the infection (**cutaneous sporotrichosis**), and there is no further spread of the infection
- In others, a larger number of nodules appear distributed along the lymphatic system that drains the contents from the site of inoculation of the causative agent (**lymphocutaneous sporotrichosis**)
- The lesions usually resolve, with minor scarring, after antifungal therapy
- In **immunodeficient patients**, especially those suffering from AIDS, **disseminated cutaneous and/or life-threatening infection of visceral organs may occur**
- Osteoarticular and sporotrichosis of the lungs often occur in alcoholics and have a significant impact on residual tissue damage

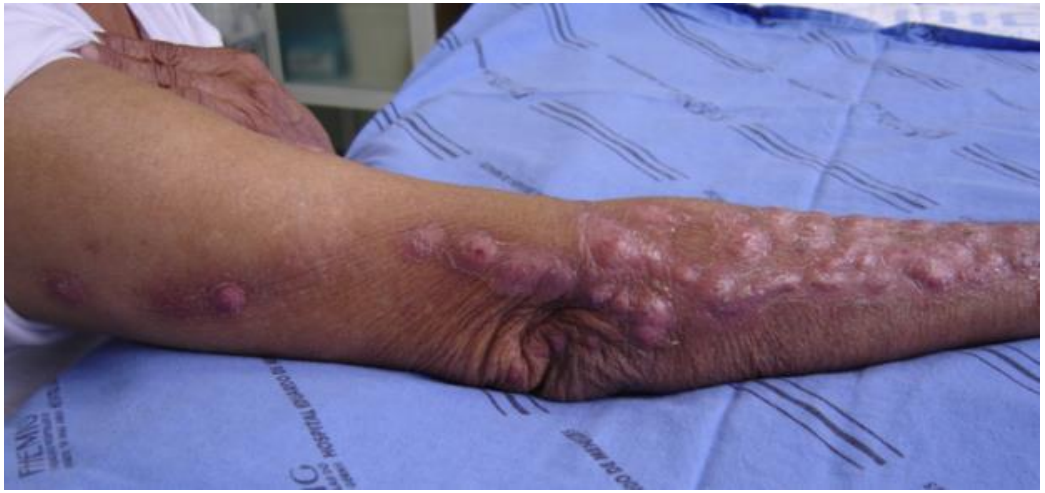
Sporotrichosis
-clinical manifestations-







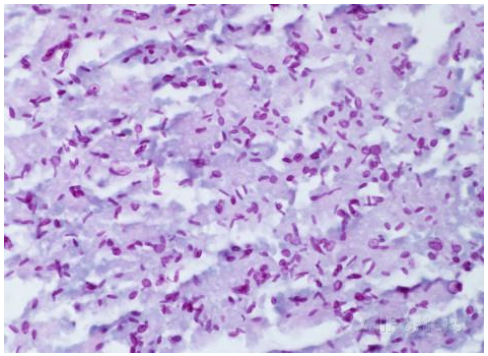




Sporotrichosis
-diagnosis and therapy-

Diagnosis:

- **Skin lesions or subcutaneous nodules should be biopsied** for culture and histopathological examination
- A characteristic finding is the **presence of granulomatous inflammation**
- **Isolation of the causative agent** in culture is the most reliable diagnostic test



Therapy:

- Sporotrichosis rarely goes away without antifungal therapy. Itraconazole is the drug of choice until the lesions are completely healed, usually 3 to 6 months
- For rare cases of osteoarticular, pulmonary or disseminated sporotrichosis, treatment with amphotericin B is started, then treatment with itraconazole is continued for one to two years
- Immunocompromised patients may need to take itraconazole for life

Mycetomas and Chromoblastomycosis

- **Mycetomas** are chronic infections characterized by the appearance of **nodules, sinus involvement** and the presence of **visible cluster masses composed of colonies of microorganisms**

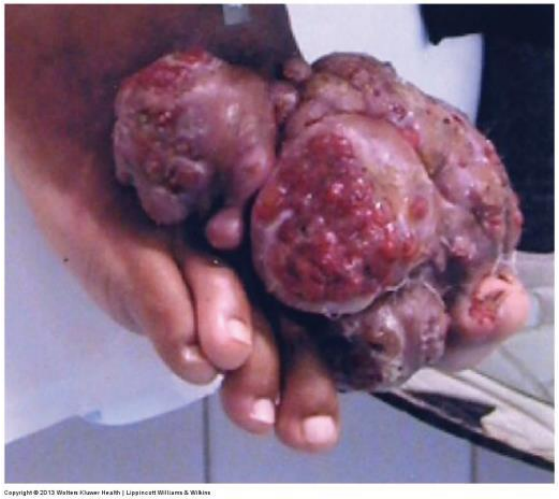
- They are most often caused by mold from the soil, such as ***Madurella mycetomatis***, which is inoculated through the skin

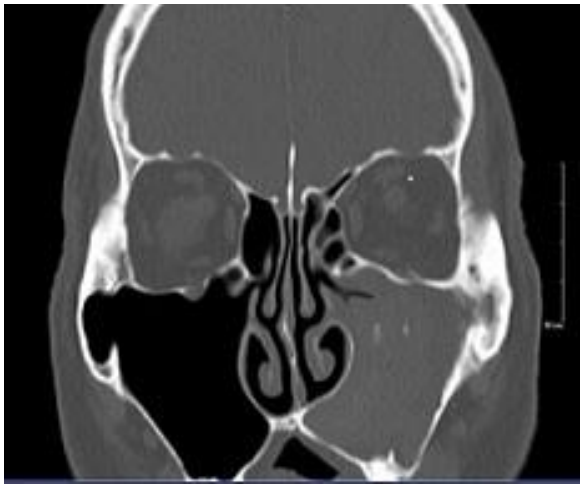
- **Chromoblastomycosis** is characterized by the presence of chronic **nodular, warty lesions** caused by various brown-black-pigmented molds from the soil that are inoculated through the skin

- Mycetomas and chromoblastomycosis occur mainly **on the lower extremities** in people who live **in tropical rural areas**

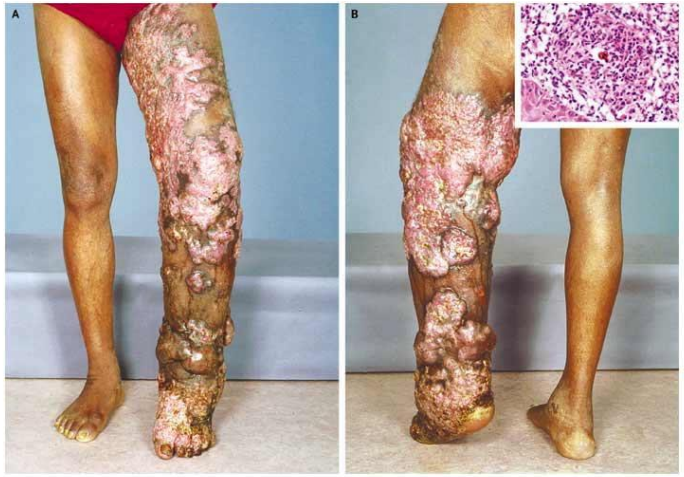
Mycetomas and Chromoblastomycosis

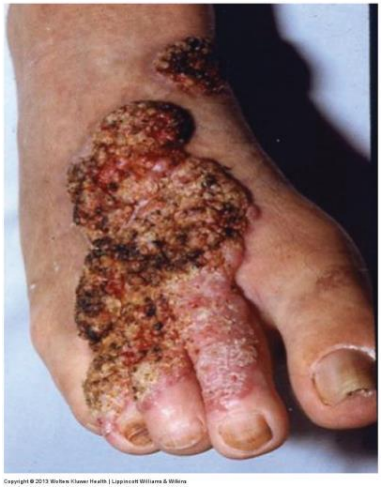
Mycetomas

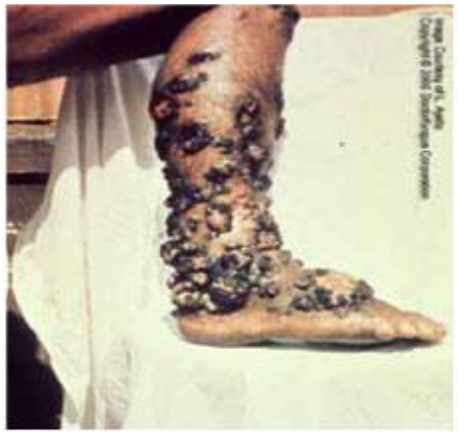




Chromoblastomycosis







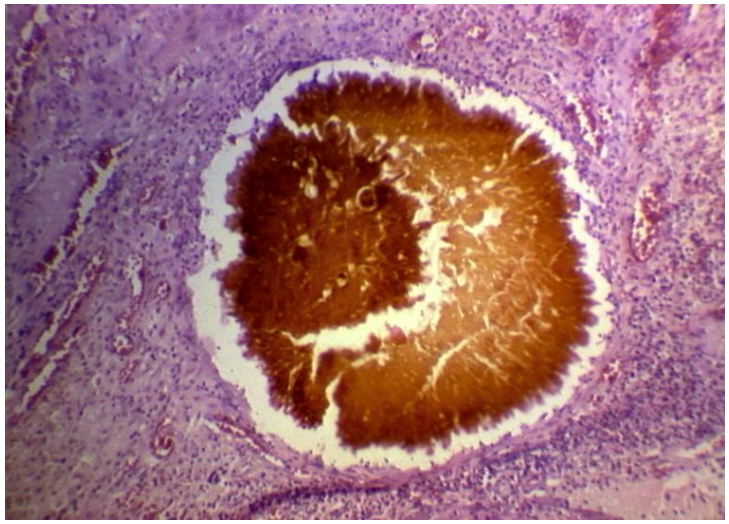
Chromoblastomycosis caused by *F pedrosoi*

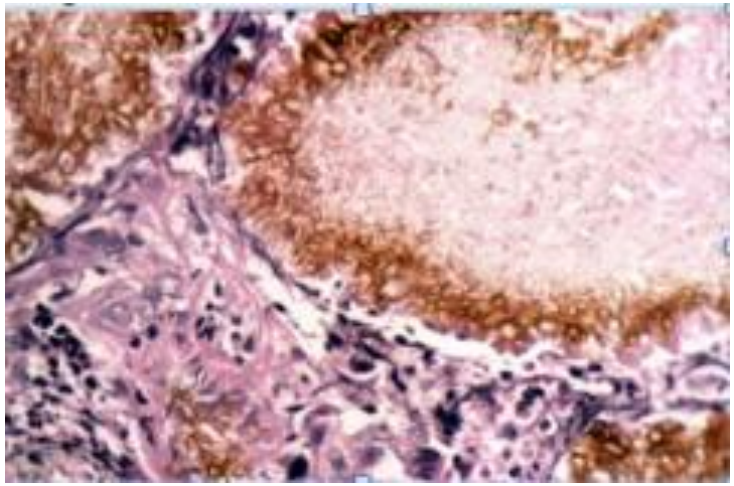
Mycetomas and Chromoblastomycosis

In tissues, fungi are seen as **pigmented, thick-walled septate structures**, named **sclerotic bodies**

Treatment:

- **Itraconazole** is sometimes useful, but rarely effective therapy
- **Surgical debridement** of small lesions is an effective method of treatment, while extended infection may require amputation of the affected limb





Dermatophyte infections
-general characteristics of the pathogen-

Three genera of Dermatophytes, ***Microsporum***, ***Trichophyton*** and ***Epidermophyton*** cause human infections

Infections are called ***tineae*** (Latin word for worm - because of the appearance of the lesion) combined with the Latin words for the infected part of the body:

Tinea capitis (head)

Tinea pedis (foot)

Tinea corporis (body)

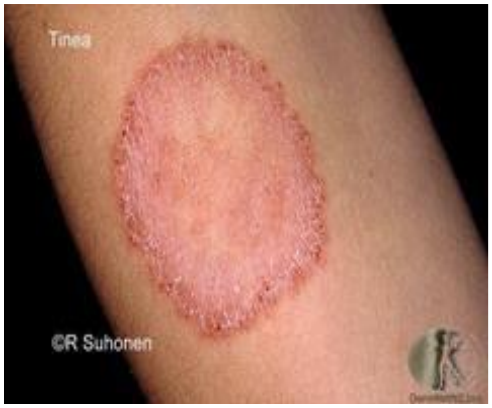
Tinea cruris (groin)

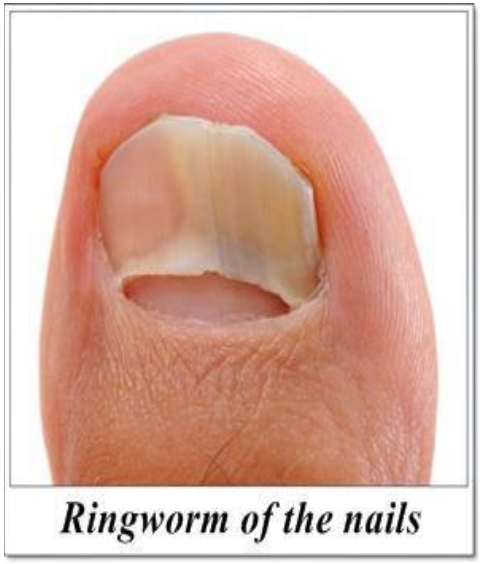
Tinea unguium (nails) or **Onychomycosis**

- Some of these fungi grow in soil, while others are found in association with animals, especially dogs and cats, and others are found almost exclusively in association with humans
- Direct contact is usually required to transmit these fungi

Dermatophyte infections -pathogenesis-

- For infection occurrence, a person must come into contact with the fungus and have lesions on the skin, so that relatively avirulent microorganisms can enter the body.
- Maceration of tissue, especially common on the feet and groin, can significantly contribute to the development of infection
- Dermatophytes spread through the stratum corneum, but rarely invade the dermis
- **The ring shape** that is characteristic of lesions caused by dermatophytes is the result of the growth of the microorganism outwards, **in a centrifugal pattern**
- Viable fungi are found on the edges of the lesion
- The central part of the lesion usually contains little or no viable fungi
- Invasion of the nails by these fungi starts from the lateral edges or from the superficial parts of the nail plate, and then spreads through the nail
- When the hair is infected, the fungus is found either in or around the hair
- **Keratinases and mannans** (cell wall polysaccharides) present in dermatophytes may play **the role in the invasion of keratinizing tissues**



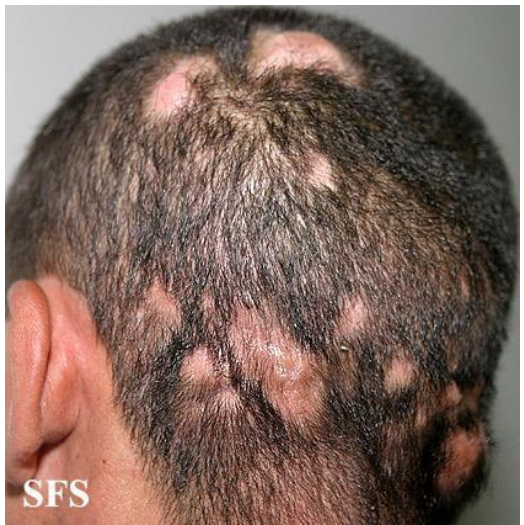

Ringworm of the nails

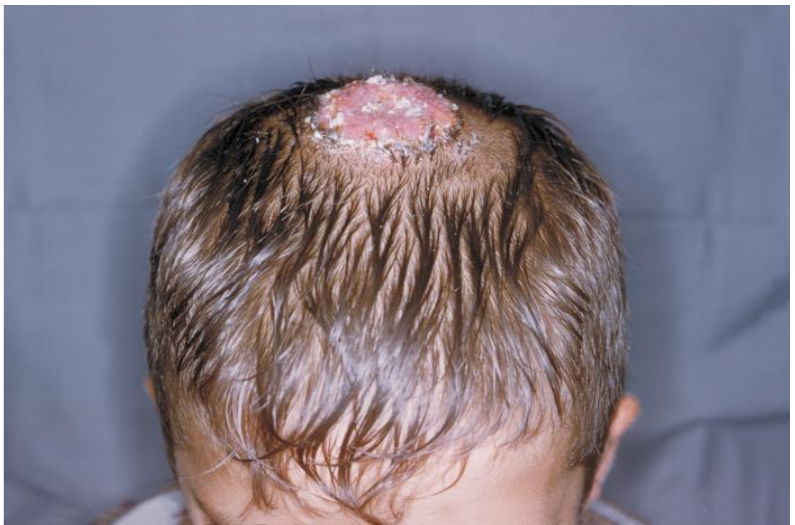
Dermatophyte infections
-clinical picture-

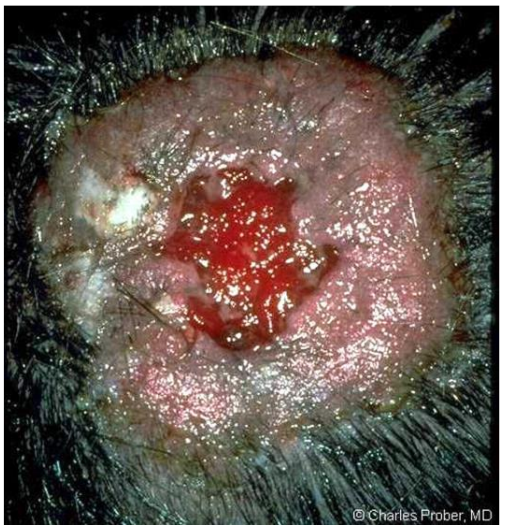
Tineae occur in different anatomical places:

- *Tinea cruris*,*Tinea pedis* and **Onychomycosis** are common in adults
- *Tinea capitis* is most common in children (3-7 years old)

Tinea capitis is manifested by clearly limited areas of peeling skin where the hairs are broken off just above the skin

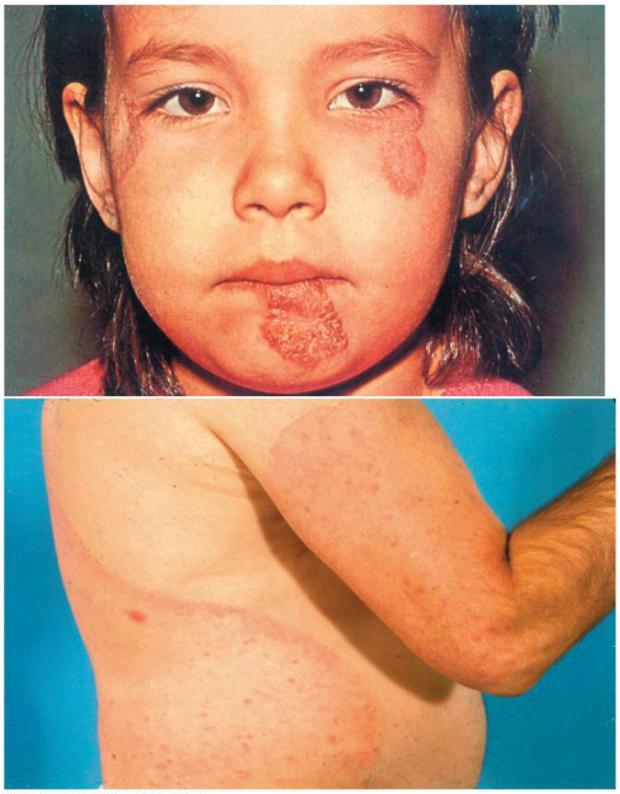


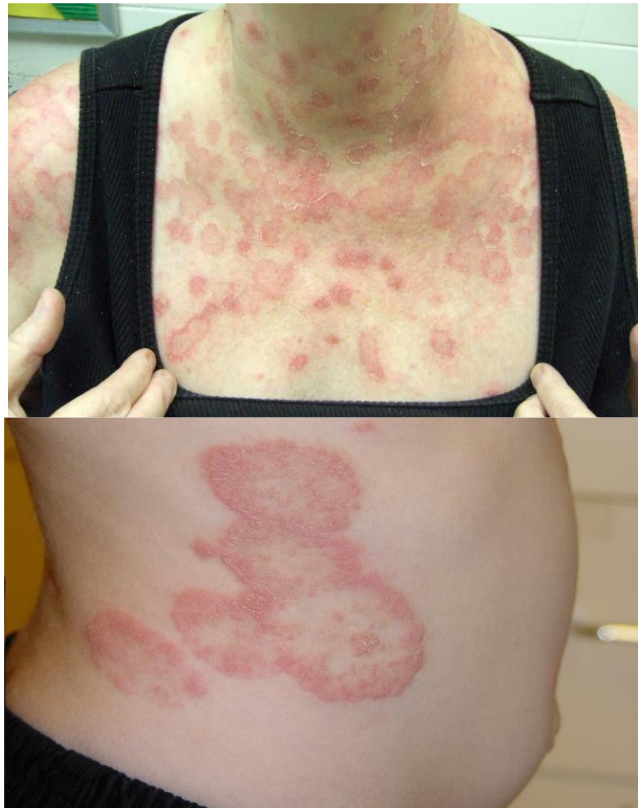




Dermatophyte infections
-clinical picture-

- ***Tinea corporis*** manifests as clearly circumscribed, pruritic, desquamated areas of skin that recede (pass) from the center to the periphery as the lesion spreads
- One or more small lesions are often present, but in rare cases large areas of trunk skin may be affected

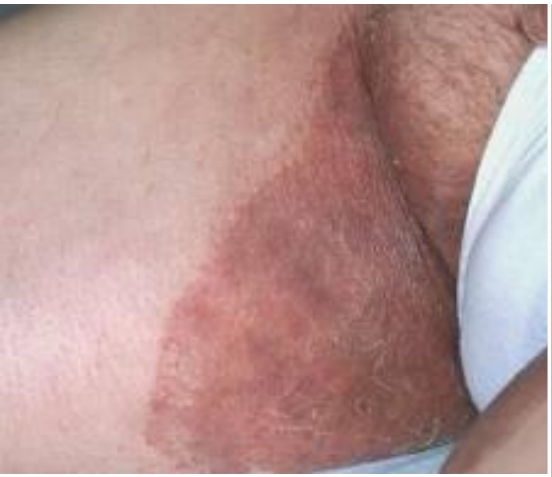




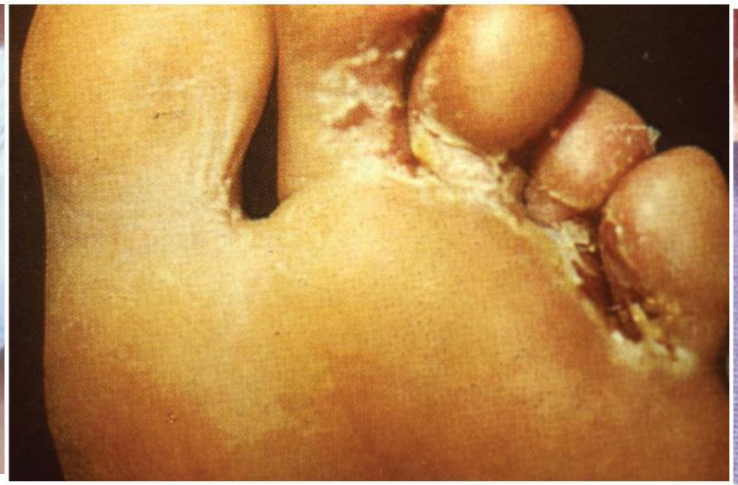
Dermatophyte infections
-clinical picture-

- *Tinea cruris* manifests as a pruritic erythematous rash, with desquamation in the groin area
- *Tinea pedis* (athlete's foot) is manifested by fissures between the toes with desquamation of the skin and the pruritic rash on the sides of the feet and soles
- Nails infected with dermatophytes become thick, colorless, with raised roots (**onycholysis**)

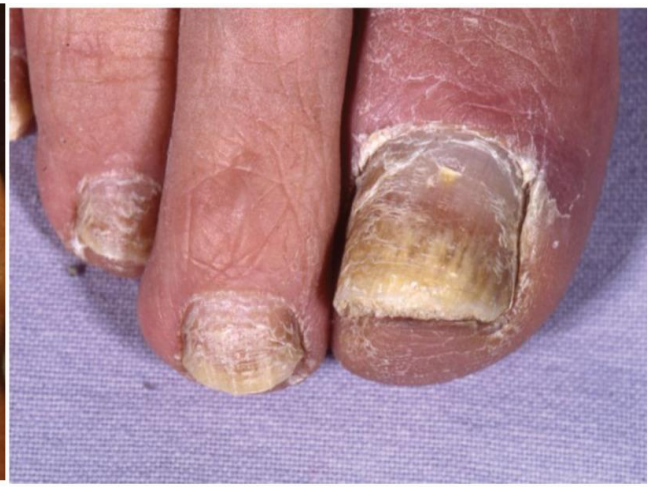
Tinea cruris



Tinea pedis



Onychomycosis



Dermatophyte infections
-diagnosis and therapy-

Diagnosis:

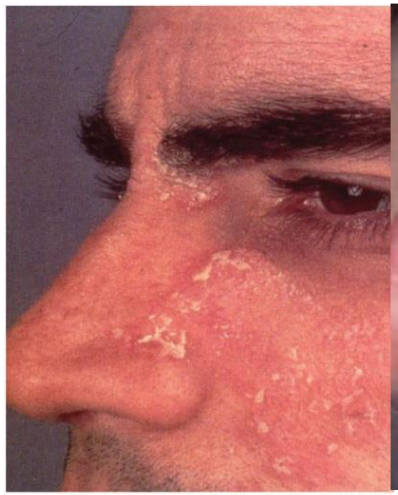
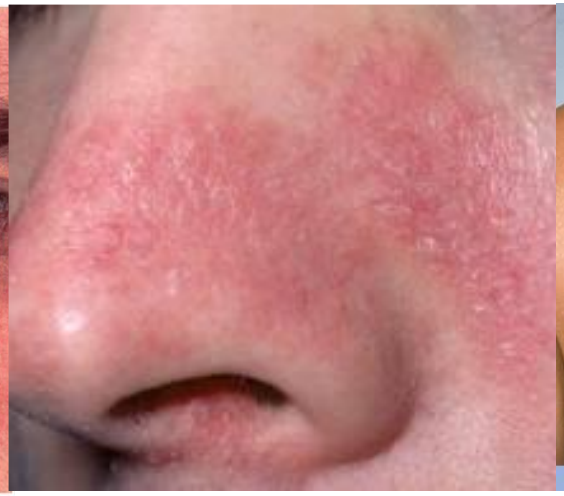
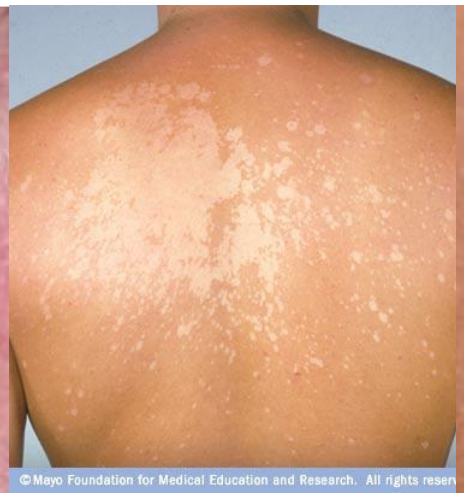
- A sample should be taken from the infected area (from the edge of the skin lesions) by scratching and observed under a microscope after treatment with potassium hydroxide
- The presence of hyaline, septate, branched hyphae confirms the diagnosis of dermatophyte infection, but culture is necessary to identify specific microorganisms

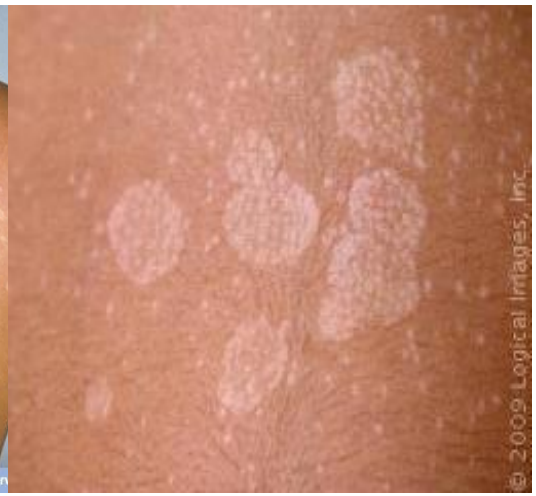
Therapy:

- *Tineae* usually responds to treatment with antifungal creams and lotions, including tolnaftates, allylamines, and azoles
- The exception is onychomycosis, which always requires systemic administration of antifungal drugs for at least 3 to 4 months
- As a rule, recurrences occur in *Tinea pedis* and *Tinea cruris*. Early administration of antifungal drugs, at the first signs of relapse, keeps the infection under control

Superficial mycoses

- Practically all adults have a stratum corneum colonized by yeast ***Malassezia furfur***. There are usually no symptoms of this colonization
- However, this fungus can cause **seborrheic dermatitis**, which is characterized by pruritic, erythematous desquamation and oily flaking of the skin in the area of the eyebrows, mustache and crown of the head
- It also causes ***Tinea versicolor (Pityriasis versicolor)***, which usually appears on the chest and neck, as hypopigmented or hyperpigmented areas of desquamation with mild scaling of the skin
- Superficial mycoses are treated with antifungal creams or shampoos



Endemic mycoses

Endemic mycoses

They appear in **geographically limited areas**

The causative agents of endemic mycoses are:

- **dimorphic fungi**, exist in the environment as molds, or in humans as yeasts or spherules
- **true pathogens** because they can infect healthy people, not just immunocompromised individuals

1. **Histoplasmosis** (*Histoplasma capsulatum*)

2. **Blastomycosis** (*Blastomyces dermatitidis*)

3. **Coccidiomycosis** (*Coccidioides immitis* and *Coccidioides posadasii*)

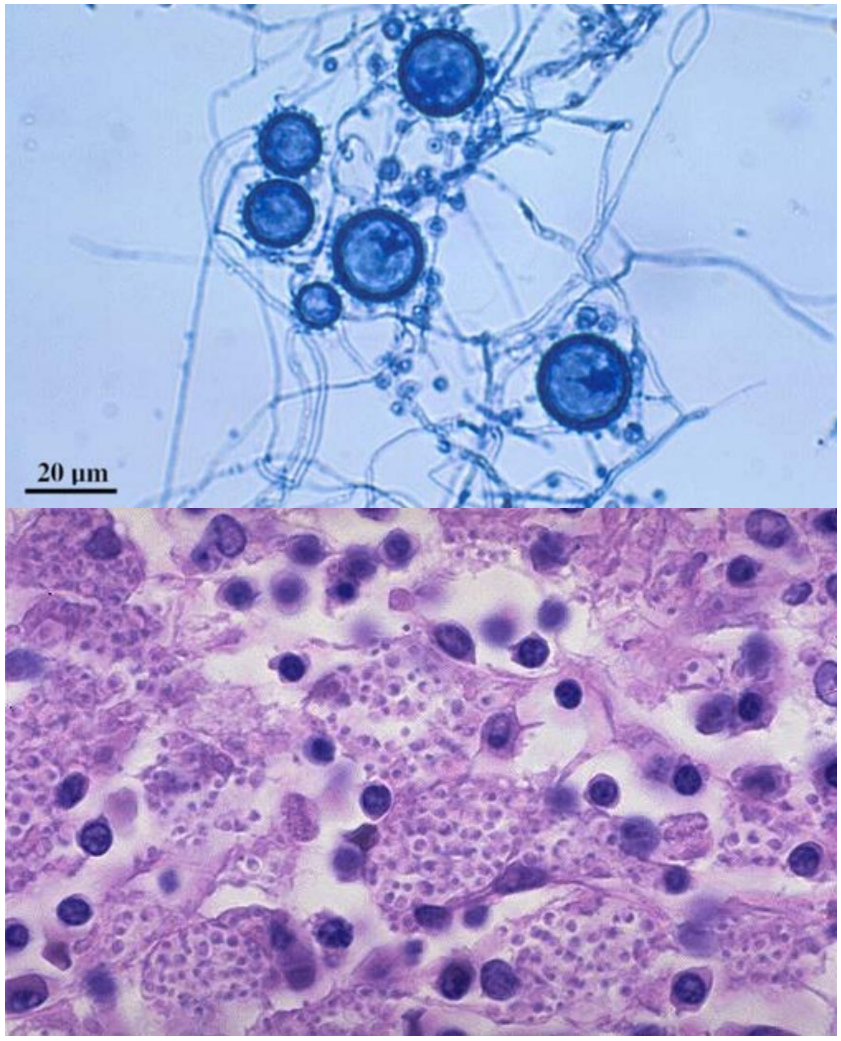
4. **Paracoccidiomycosis** (*Paracoccidioides brasiliensis*)

5. **Penicillosis** (*Penicillium marneffei*)

Histoplasmosis
-general characteristics of the pathogen-

- ***Histoplasma capsulatum*** is **dimorphic fungus** which exists in the external environment as the mold. It produces **macro (tuberculated) conidia and microconidia, infectious forms**

- **In the body**, at 37°C, *Histoplasma capsulatum* **changes into the form of yeast**, which was previously mistakenly thought to have a capsule (hence the name for this fungus)

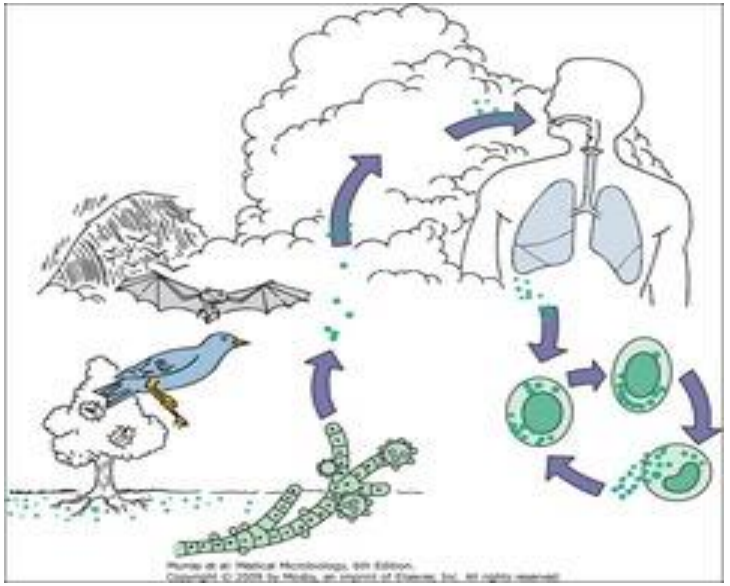


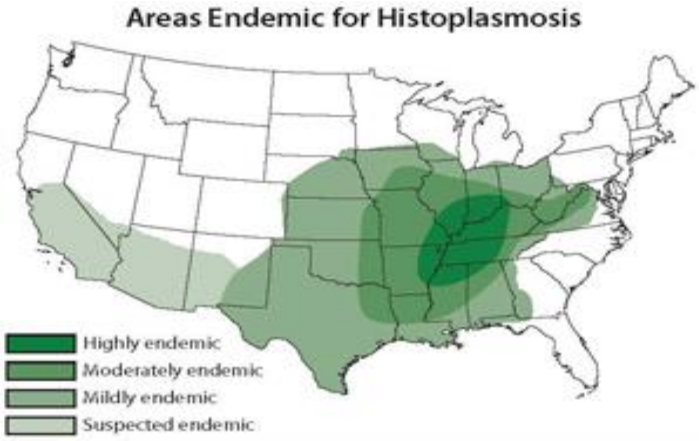
Histoplasma capsulatum
- natural habitat-

Histoplasma capsulatum is a **soil fungus** that grows best in conditions of high nitrogen content, created by birds or bats, in caves and old buildings

The appearance of infection occurs during exploration in caves, after the demolition of old buildings or during construction work that damages the ground

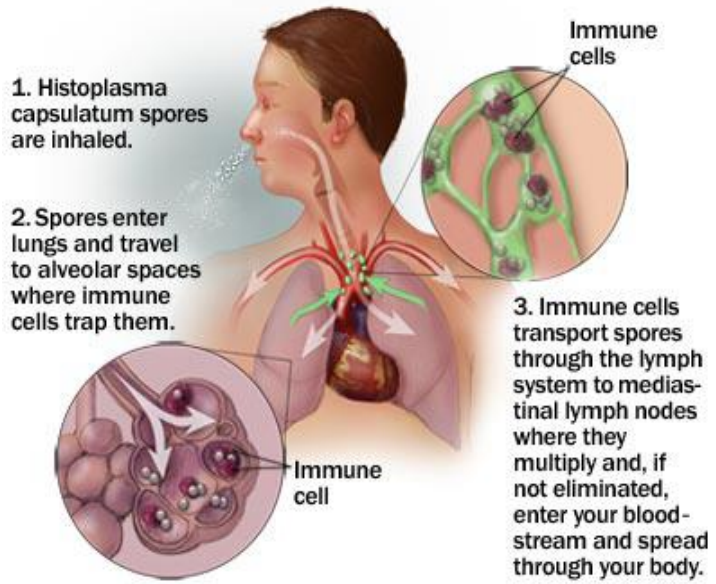
Histoplasmosis is an **endemic mycosis** that occurs primarily in Central America and some areas of South America. In addition, these fungi can also be found in caves in some areas of several eastern states and elsewhere around the world

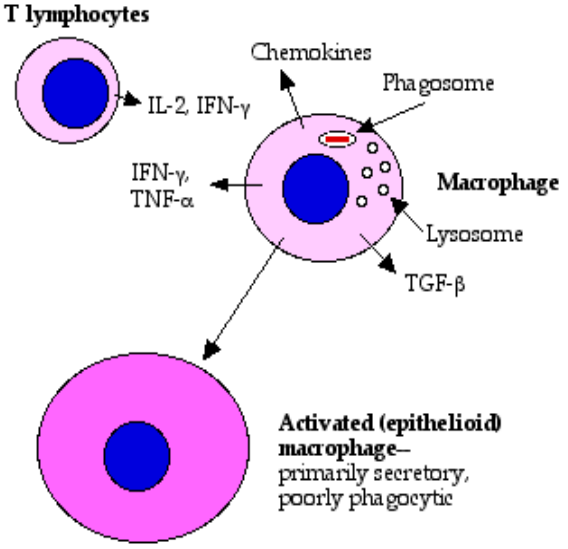




Histoplasmosis
-pathogenesis-

- Entering the lungs and changing into yeast form
- It is phagocytosed by neutrophils and macrophages (fungi remain viable in macrophages because they modulate pH in phagolysosomes and absorb essential growth factors from the cell)
- The immune response is mediated by cellular immunity - **CD4 + T lymphocytes and activated macrophages**: only after activation of T lymphocytes, release of interleukin-2 and interferon-γ, macrophages are able to kill intracellular yeasts
- This usually takes several weeks, and by then, the fungus spreads locally through the lymphatics to the hilar and mediastinal lymph nodes and then hematogenously, within macrophages, through the monocyte-macrophage system
- Possible development of **granuloma** with or without caseous necrosis
- Immunity after previous infection is lifelong, although reinfection is possible after exposure to a large inoculum of *Histoplasma capsulatum*

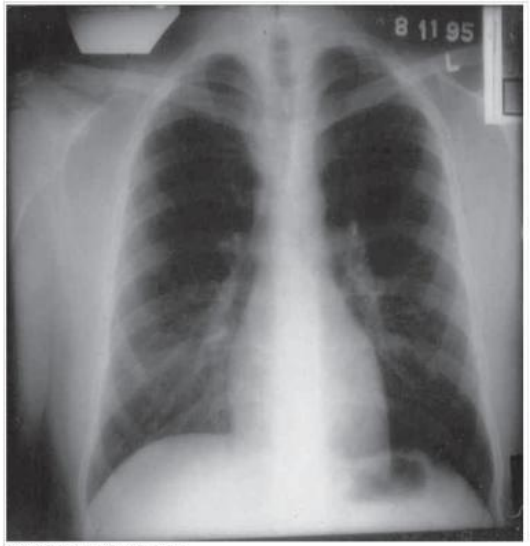




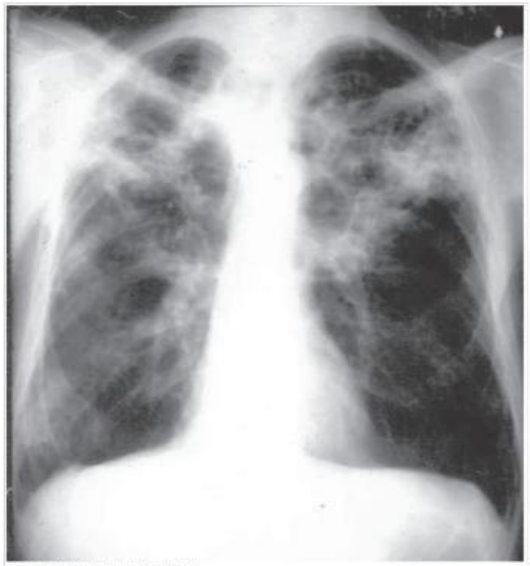
Histoplasmosis
-clinical manifestations-

Clinical manifestations of the disease depend on the number of inhaled conidia and cellular immune response

- **The majority of infected persons** do not have a clinically manifested disease, or the disease manifests itself with **mild symptoms often similar to viral infections of the respiratory tract**. A small percentage of patients will have fever, chills, anorexia, fatigue, and a dry cough, and a chest radiograph may show pneumonia and hilar or mediastinal lymphadenopathy



- **Large exposure to the pathogen**, even in healthy individuals, can cause **severe pneumonia, bilateral diffuse nodular infiltrates, and hypoxemia**

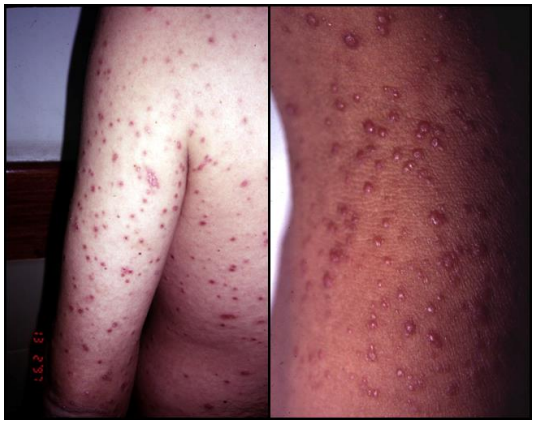


- Patients with **chronic obstructive pulmonary disease** (COPD) are at risk for developing **chronic pulmonary cavitary histoplasmosis**, a progressive and potentially fatal infection that mimics reactivation of pulmonary tuberculosis

Histoplasmosis
-clinical manifestations-

- **Acute disseminated histoplasmosis** is characterized by **fever, chills, fatigue, mucosal ulceration, hepatosplenomegaly and pancytopenia**, and in some cases, adrenal insufficiency, sepsis and disseminated intravenous coagulopathy (most often in immunosuppressed patients, suffering from AIDS)

- **Chronic progressive disseminated histoplasmosis** arises **in older adult patients** who did not have an obvious immunodeficiency before, but for some reason they cannot eliminate *H. capsulatum*



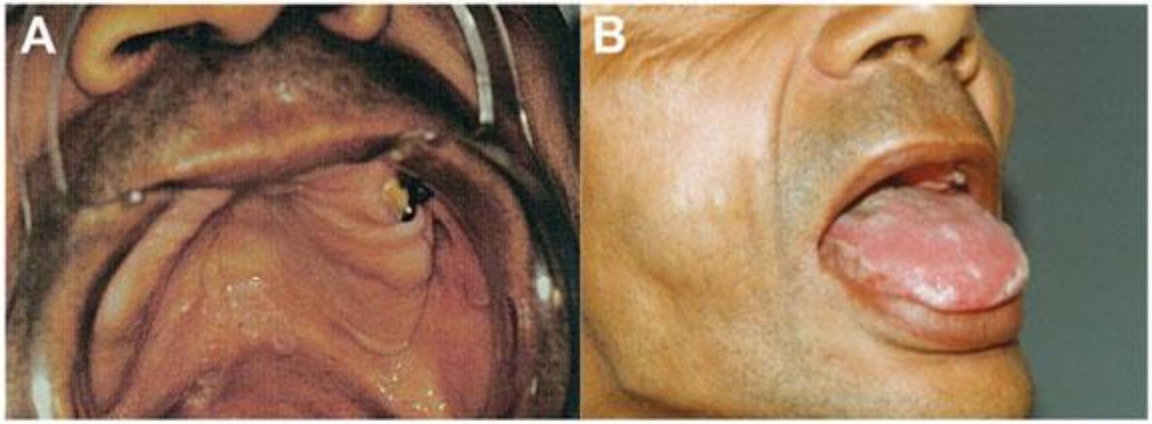
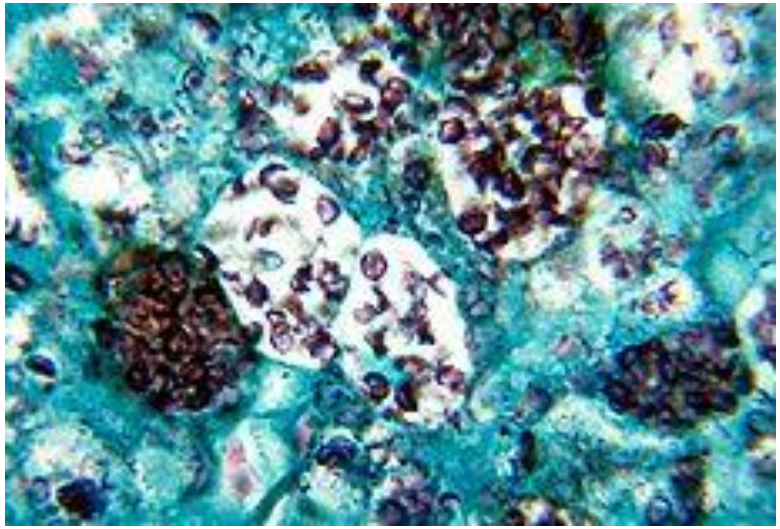
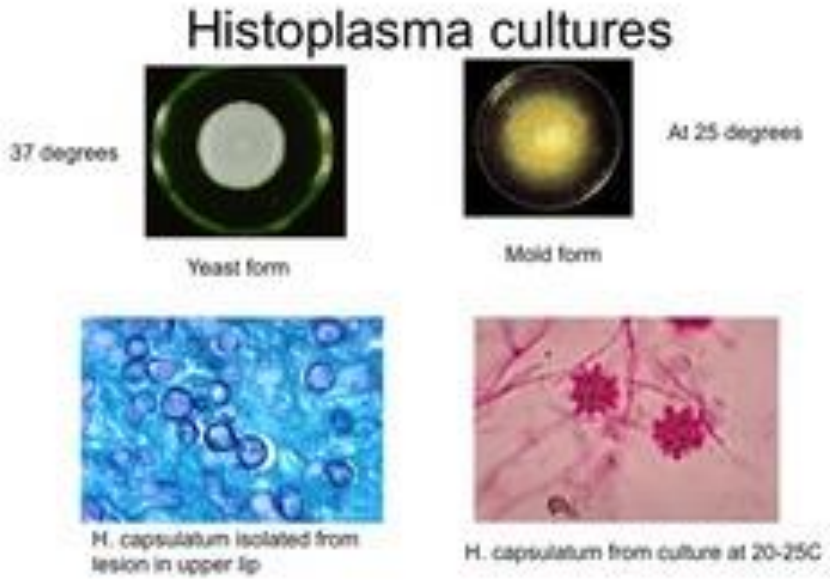


Fig. 1 - Lesions due to *Histoplasma capsulatum* into oral cavity of a HIV negative patient: *A*. palate lesion, *B*. tongue lesion.

Histoplasmosis
-diagnosis-

- Histoplasmosis can be diagnosed by isolating the pathogen from sputum, blood, tissue or body fluids
- Definitive growth *in vitro* can take up to 6 weeks and is not successful in many laboratories
- Histopathologically, using special staining techniques, histoplasmosis is indicated by the presence of small intracellular yeasts in bone marrow, liver, lung, or lymph nodes
- Immunoassays

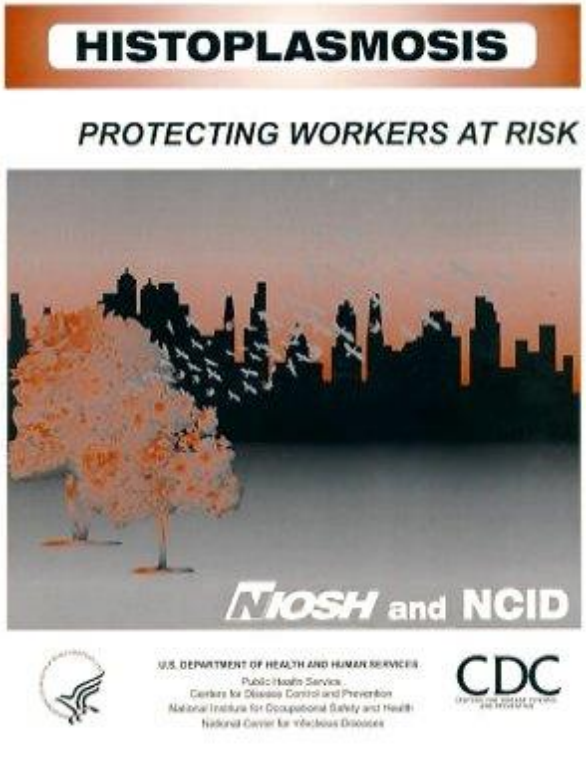


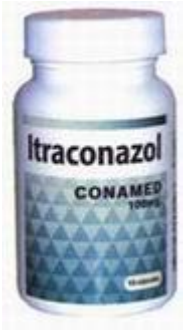


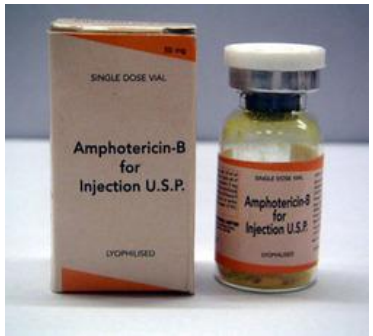
Histoplasmosis
-therapy and prevention-

- Mild to moderate pulmonary or disseminated histoplasmosis is treated with **itraconazole**, usually for 3 to 12 months depending on the clinical presentation
- Patients who have a serious infection, usually **disseminated**, should be treated with **amphotericin B initially and then, once the condition has stabilized, continued with itraconazole**
- **Prevention**: use of respirators when demolishing chicken farms or other buildings inhabited by birds or bats

HISTO
PLASMOSIS

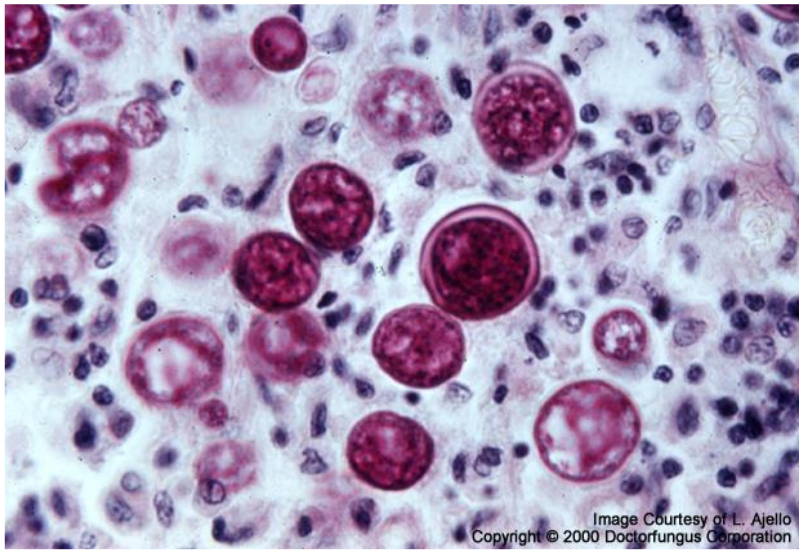


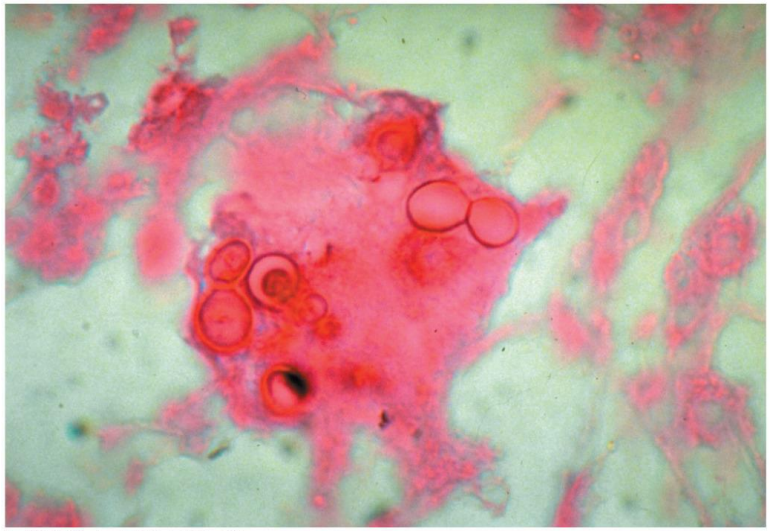




Blastomycosis
-general characteristics of the pathogen-

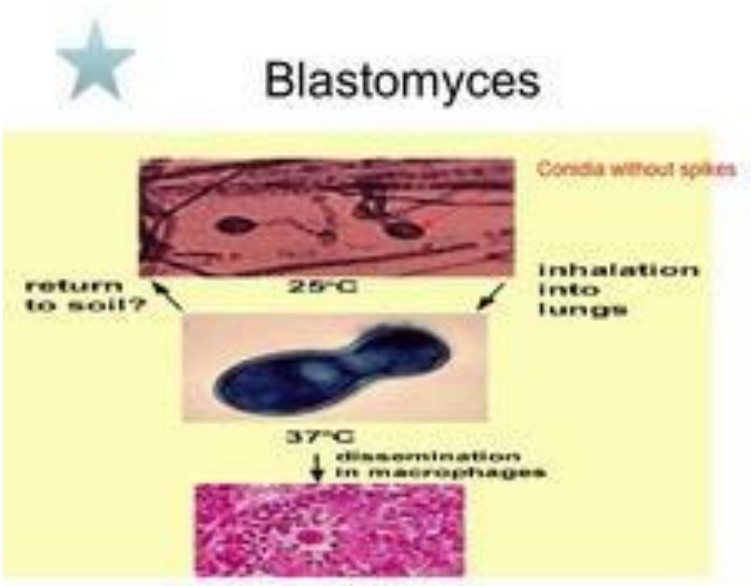
- ***Blastomyces dermatitidis*** is **dimorphic fungus** which is the mold in the external environment, while in the body, at 37°C, it has the form of yeast
- **Yeasts have a thick cell wall**, and daughter cells can be observed microscopically, in the form of buds
- Soil and rotting trees are considered the source of this fungus
- Rare epidemics

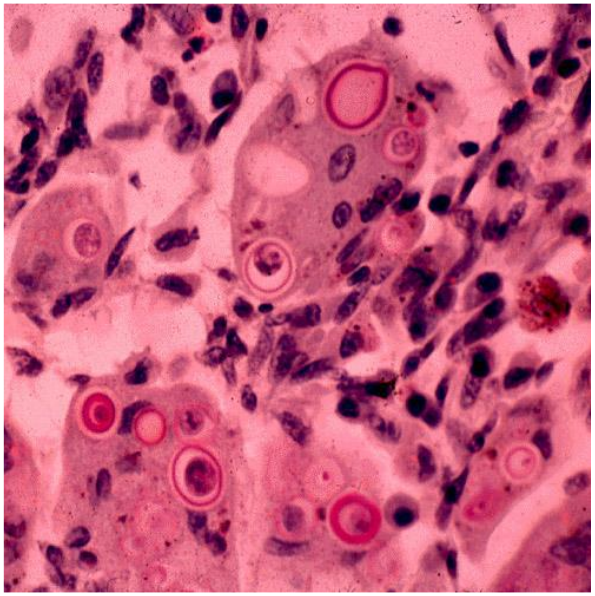




Blastomycosis
-pathogenesis-

- Conidia of *Blastomyces dermatitidis* are inhaled into the lungs, where they change into yeast that are phagocytosed by macrophages and neutrophils
- Cellular immunity and neutrophils play the most important role in fighting infection
- As with histoplasmosis, it appears that yeasts can persist in granulomas for years and can be a source for later reactivation of infection



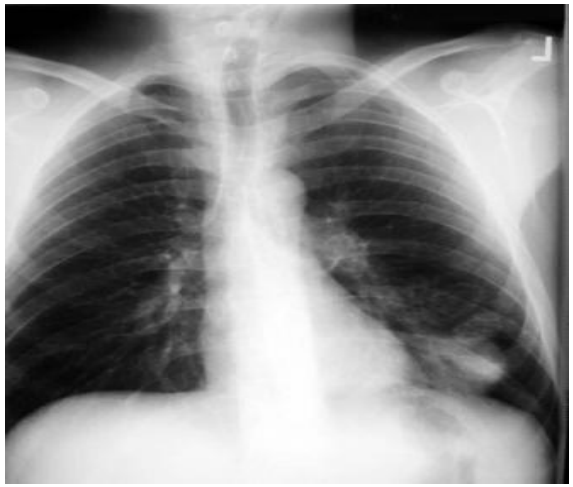


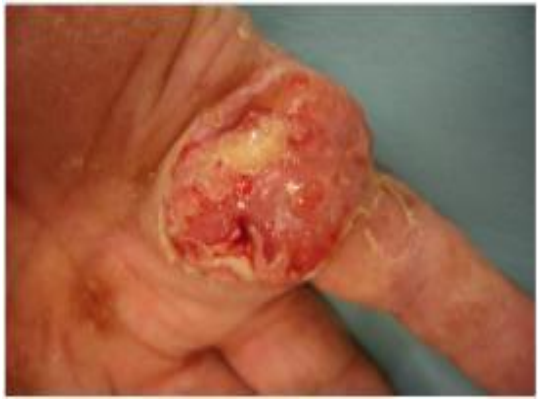
Blastomycosis
-clinical manifestations-

- The majority of infected people have symptoms of **mild pneumonia**, or **skin** or **osteoarticular lesions** may occur after pneumonia

- Patients with more severe pneumonia also have fever, chills, anorexia, fatigue, dry cough, and pneumonia can be seen on a chest radiograph

- **If there is a large exposure** to this fungus, even healthy people may develop **bilateral diffuse nodular infiltrates, hypoxemia and acute respiratory distress syndrome**



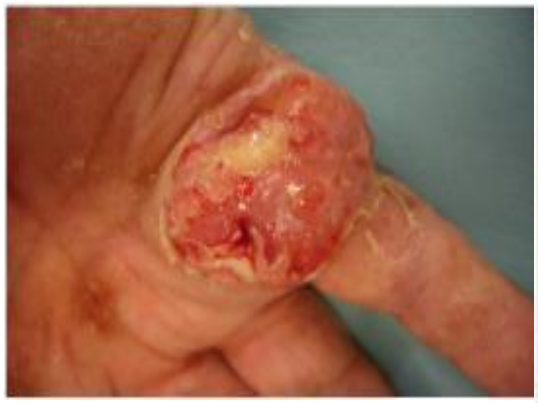


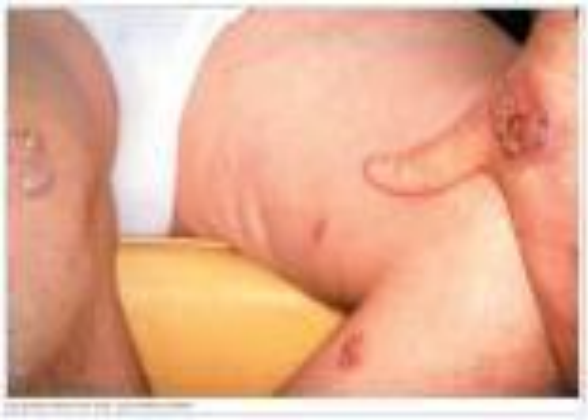
Blastomycosis
-clinical picture of disseminated infection-

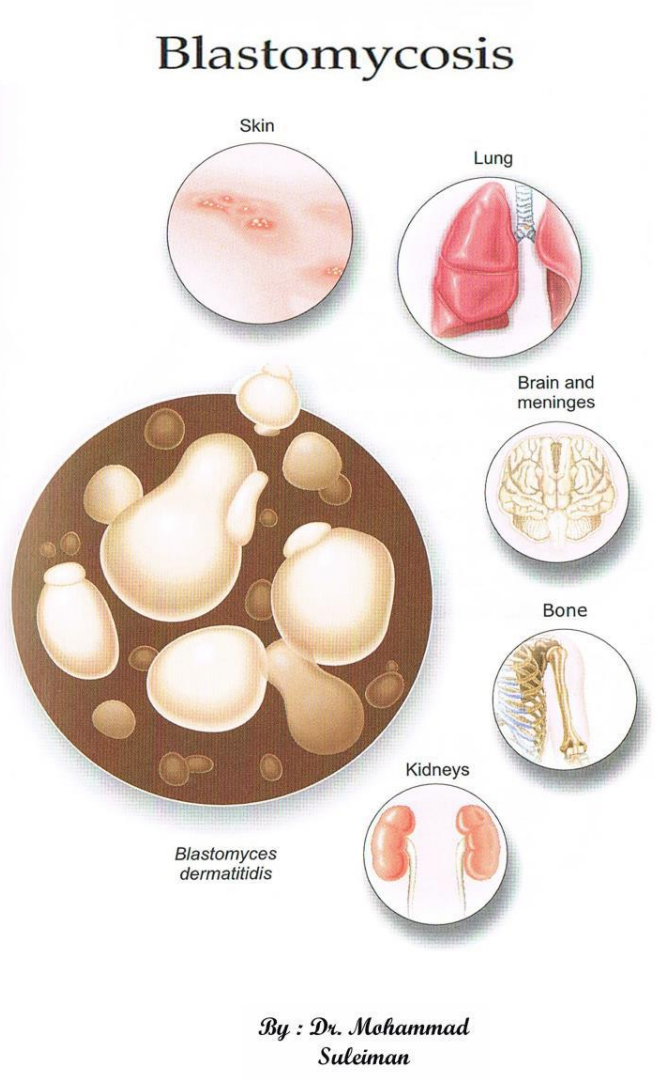
Disseminated infection (in immunocompromised individuals)

Skin lesions (a sign of disseminated infection) can be single or numerous, characterized by the presence of an uneven, wrinkled edge with a small, centrally located microabscess or manifest as skin ulcerations

Other organs can also be affected



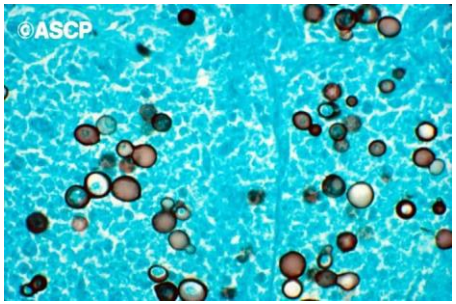


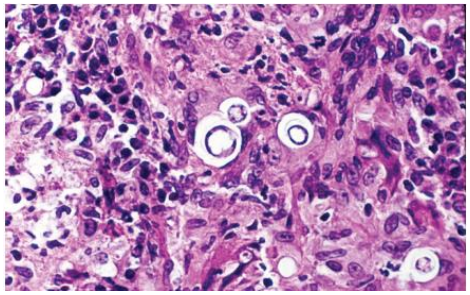


Blastomycosis
-diagnosis and therapy-

Diagnosis:

- **Isolation of *Blastomyces dermatitidis*** from sputum, skin or other tissues
- **Growth *in vitro*** can take weeks
- **Histopathological analysis** indicates blastomycosis if **large, thick-walled yeasts with one broad bud** are observed in the tissues
- The test for the presence of *Blastomyces* antigen is used in the diagnosis of disseminated and more severe blastomycosis





Therapy:

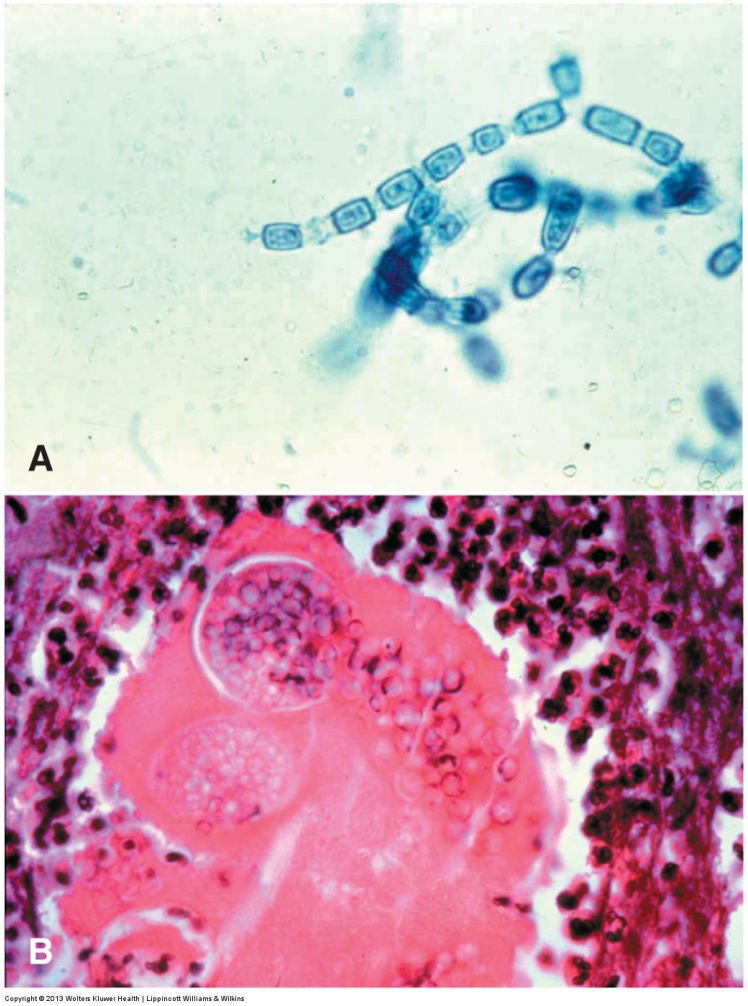
- Mild to moderate pulmonary or cutaneous blastomycosis is treated with itraconazole, usually for 6 to 12 months depending on the clinical presentation

- Patients who have severe pneumonia or disseminated blastomycosis should be treated with amphotericin B initially and then, after the condition has stabilized, continued with itraconazole. There are no preventive measures

Coccidiomycosis
-general characteristics of the pathogen-

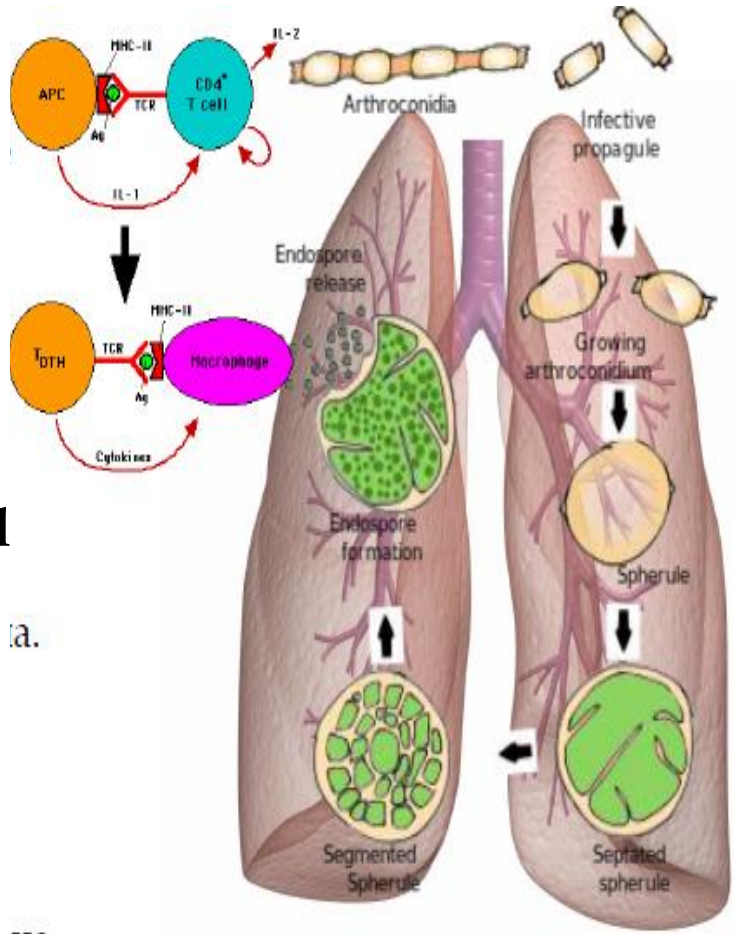
Coccidioides immitis and ***Coccidioides posadasii***

- Both fungi are **dimorphic**, but dimorphism is not dependent on temperature
- In the external environment, *Coccidioides* are molds that form **arthroconidia**, **the infective forms**. In tissues, they form large structures (50 to 100 μm in size) called **spherules**. Inside each spherule are hundreds of **endospores** that, when released, spread the infection
- Semi-moist soil encourages the growth of organisms, most likely growing in the burrows of desert animals



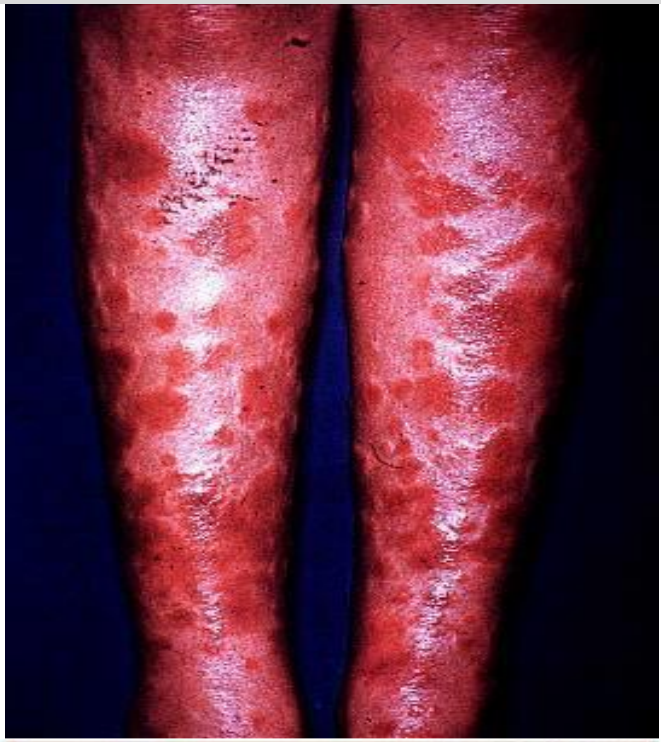
Coccidiomycosis
-pathogenesis-

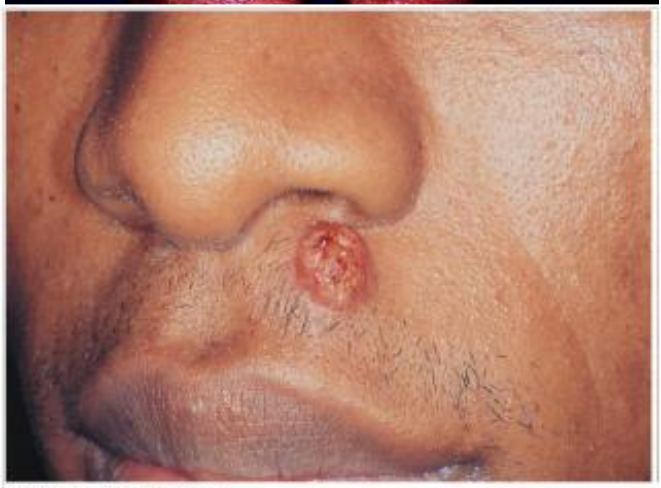
- **Arthroconidia** of *Coccidioides* are highly infectious and easily enter the alveoli by **inhalation**
- In the lungs, arthroconidia transform into characteristic large **spherules** filled with endospores (**resistant to phagocytosis**)
- In some patients, *Coccidioides* spreads hematogenously and infects several different organs
- **Neutrophils, T lymphocytes and activated macrophages** participate in the immune response
- The cellular immune response eliminates the spherules
- Severe disseminated infections often occur in immunodeficient patients with CD4+ T lymphocyte dysfunction



Coccidiomycosis
-clinical manifestations-

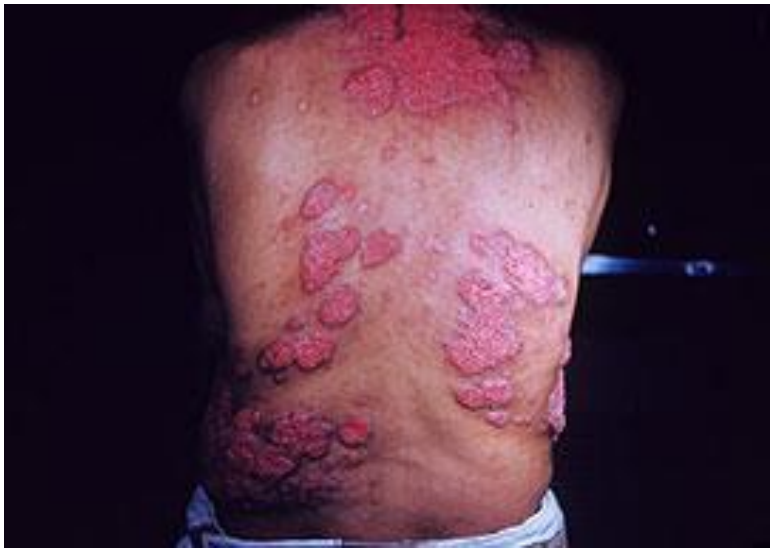
- Most people with coccidioidomycosis have no symptoms or have symptoms similar to a mild viral infection
- **Symptomatic acute lung infection** occurs several weeks after inhalation of this fungus and is manifested by fever, anorexia, fatigue, dry cough and chest pain
- **Arthralgias and subcutaneous nodules (erythema nodosum)** may occur during the course of the disease as a consequence of the immune response to the presence of the fungus. This syndrome is often called **desert rheumatism or valley fever**
- For most patients, the disease resolves spontaneously. However, in a small number of patients, the disease progresses to a chronic lung infection, cavities are often formed, and the application of antifungal therapy is necessary

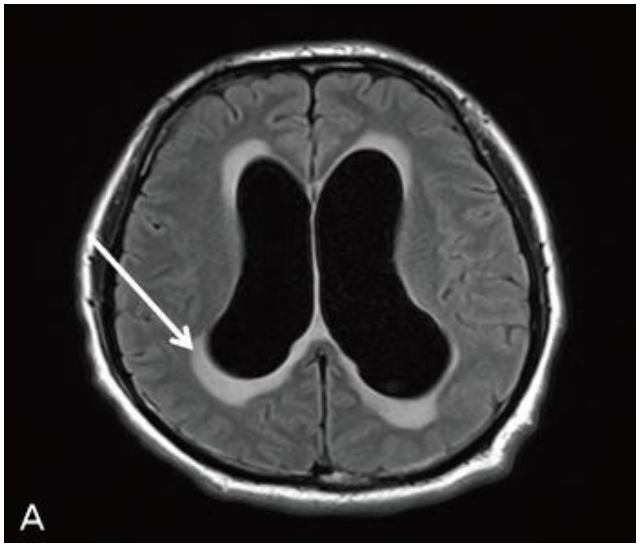




Coccidiomycosis
-clinical manifestations-

- **Disseminated coccidiomycosis** occurs more often in patients with a disorder of cellular immunity
- **Cutaneous, subcutaneous and osteoarticular infections are common**, but any organ can be affected
- **Chronic meningitis** is the most serious complication, because it is fatal if not treated, and patients who have responded to antifungal therapy must receive this therapy continuously due to the possible relapse when treatment is stopped

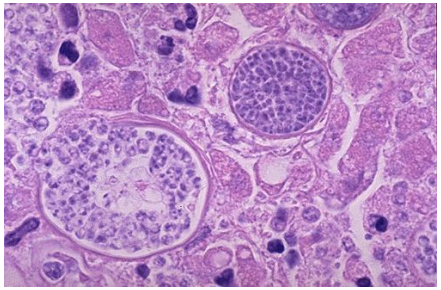


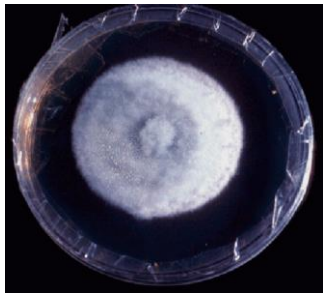


Coccidiomycosis
-diagnosis and therapy-

Diagnosis :

- **Isolation of the pathogen** from infected tissues or body fluids and **cultivation** (grows well on most media in a few days)
- Histopathologically, the disease is diagnosed by **the presence of spherules in the tissues**
- **Immunoassays** for the detection of antibodies directed at *Coccidioides* antigens





Therapy and prevention:

- Mild to moderate coccidiomycosis is treated with **itraconazole or fluconazole**, usually for 12 to 24 months depending on the clinical presentation. Patients who have a serious infection should be treated with **amphotericin B** initially and then, after the condition stabilizes, treatment with an azole should be continued
- Coccidioidal meningitis can be successfully treated with fluconazole, but therapy must be lifelong
- Preventive measures are difficult to implement in an endemic area, because the fungus is easily transmitted

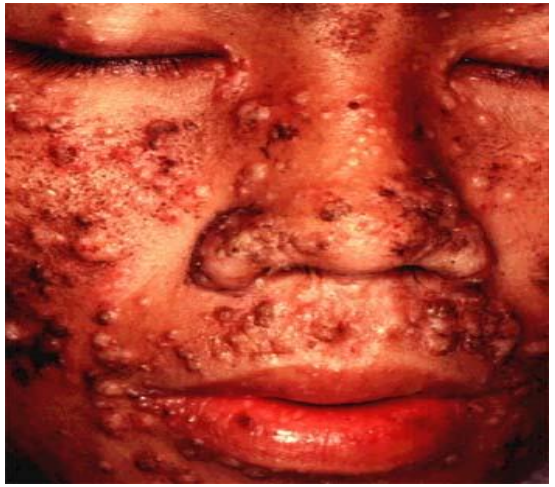
Paracoccidiomycosis

- **Paracoccidiomycosis** is caused by the fungus ***Paracoccidioides brasiliensis*** and occurs mainly in Brazil and surrounding countries in South America
- The most common manifestation is a **chronic progressive infection of the lungs and mucous membranes**, which occurs primarily in older men who are exposed to this fungus in rural areas
- The acute form of disseminated infection in young and adult and immunosuppressed patients is rare
- **Trimethoprim/sulfamethoxazole or itraconazole** are usually used for treatment, while amphotericin B is reserved for severe infections

Geographic distribution of the different genetic groups of *Paracoccidioides brasiliensis* species complex, according to the actual available data. PS2: phylogenetic species 2 from Brazil and Venezuela; PS3: phylogenetic species from Colombia; S1: species 1 from Brazil, Argentina, Paraguay, Peru and Venezuela.

Penicillosis

- **Penicillosis** is caused by the fungus *Penicillium marneffei* and is endemic only in Southeast Asia
- The infection is usually disseminated, involving the lungs, skin, bone marrow, and other organs, and occurs almost entirely in immunosuppressed patients, especially those with AIDS
- Depending on the severity of the infection, either itraconazole or amphotericin B is used for treatment



Antifungal drugs

Antifungal drugs

The main obstacle to the development of antifungal drugs is the common metabolic and physiological pathways of eukaryotic fungal and mammalian cells, which conditions the existence of the risk of toxicity of these drugs.

- **Polyenes** (Nystatin (local) and Amphotericin B (nephrotoxicity)) - bind to ergosterol, but also to cholesterol (toxicity)
- **Allylamines** (Terbinafine) - block the synthesis of ergosterol
- **Azoles** (ketoconazole, itraconazole, fluconazole, voriconazole and posaconazole) - block the synthesis of ergosterol
- **Echinocandins** (caspofungin, micafungin, and anidulafungin) - disrupt the synthesis of the fungal cell wall
- **Pyrimidine inhibitors** (flucytosine) - interfere with DNA and protein synthesis of fungi, toxic (bone marrow and liver)

Other antifungal medications:

- **Griseofulvin** (interferes with microtubule function: treatment of dermatophyte infections)
- **Tolnaftate** (unknown mechanism: treatment of dermatophyte infections)
- **Potassium iodide** (unknown mechanism: treatment of sporotrichosis)

Antifungal drugs
-mechanisms of action-