Medical mycology

Dr. Luma T. Ahmed

Introduction:

The term Mycology derived from the Greek word mykes, a direct counterpart of Latin word fungus, which in turn thought to be a modification of Greek word sponges, from which our word (sponge) is derived. The term anamorph refers to nonsexual fungal reproduction, in while Teleomorph refers to the sexual form of reproduction, in which each new cell is derived from the joining of two separate cells.

Fungi are eukaryotic cells that is each cell possesses a nucleus, nuclear membrane, endoplasmic reticulum, golgi apparatus and mitochondria. they also possess a rigid cell wall composed of chitin (N-acetyl-D-glucosamine linked by β1-4glycoside bonds),mannans (polymers of glucose in α-or β-glycoside bonds), and sometimes cellulose. These cell wall constituents adsorb several dyes, which provide for the application of special stains by which they can be identified in laboratory mounts and tissues sections.

Single cell fungus forms are Known as yeast, those with multiple cells forming a filamentous mycelium are known as molds. Fungi reproduce by spores, either sexually or asexually, that may be derived directly from the vegetative mycelium (arthrospores, chlamydomspores, blastospores), or from the surface of special aerial fruiting bodies (conidia).

Fungal infections may be referred to as either superficial or deep seated (systemic). However, this broad categorization no longer serves the needs of clinical practice, as several fungal species once thought to be (superficial) may cause disseminated disease. The terms deep seated and
systemic classically referred to a group of fungal infections caused by agents that inherently can be highly virulent, that can invade deeply into tissues, and organs. Most of these infections have been caused by dimorphic fungi, which are present in the form of mold in the environment of room temperature but as a yeast when incubated at 35-37°C.

Saprobic: are contaminants which are agents of systemic disease.

Opportunistic fungi: which are non-pathogenic fungi; they usually of inherently low or limited virulence and can cause subcutaneous and disseminated infections widely in those who are immune suppressed or in those who wear intravascular or prosthetic devices e.g. Candida species, Aspergillus species and Zygomycetes species.

1-Zygomycetes: The fungi belonging to the subclass Zygomycetes are widely distributed environmental inhabitants of soil, dung, and vegetative matter. Humans usually become infected in the upper respiratory tract through the inhalation of airborne spores, although ingestion of contaminated foodstuffs may result in primary gastrointestinal disease.

Direct inoculation of traumatic breaks in the skin and mucous membranes may lead to primary mucocutaneous infection. Most members of the Zygomycetes have a proclivity for hyphal invasion of the walls of blood vessels once a primary infection is established, often resulting in the dissemination of mycotic thrombi and the development of metastatic foci in many organs.

The medically important Zygomycetes species.

Medically important fungi within the subclass Zygomycetes include several genera they are (Rhizopus sp., Abisidia sp., Syncephalastrum sp., Circinella sp. and Mucor).

The initial clue to the diagnosis of Zygomycosis is the recovery of a rapidly growing colony on primary fungal recovery culture medium, usually within 48-72hrs, with the surface of the agar covered with a woody mycelium that extends from border to border in the petri dish.
Histopathology of infections caused by the Zygomycetes:

The ribbon like, broad, aseptate hyphae of the Zygomycetes are generally distinct from other hypha-producing fungi in tissue sections. The hyphae range from 3 to 25 µm in width, have nonparallel walls, and often tend to break up into small fragments. The hyphae don't stain well even with periodic acid-schiff (PAS) or Gomorimethenamine silver (GMS) fungal stains. The Zygomycetes also have a predilection for invading blood vessels, causing hemorrhagic infarction. The Zygomycetes can also present as a fungus ball in body cavities and occasionally, the typical fruiting heads, complete with sporangia and sporangiospores may be observed.
fungi belonging to the Zygomycetes are widely distributed environmental inhabitants of soil, dung, and vegetative matter; they usually become infected in the upper respiratory tract through the inhalation of airborne spores, although ingestion of contaminated foods may result in primary gastrointestinal disease, or direct inoculation of traumatic breaks in the skin and mucous membranes may lead to primary mucocutaneous infection. A predisposition for the hyphae to invade the walls of blood vessels or a primary infection is established results in the dissemination of mycotic thrombi and the formation of metastatic infections in many organs.

Zygomycoses most commonly occur as opportunistic infections in immunocompromised hosts. Host risk factors include iatrogenic mortality, particularly during periods of acidosis, neutropenia, sustained immunosuppressive therapy (as may occur with bone marrow transplantation), the prolonged use of antibiotics, and a breakdown in the integrity of the cutaneous or mucous membranes due to trauma, surgical wounds, needle sticks, or burns. These authors also indicate that corticosteroid treatment, common in these patients, results in vascular thrombosis, infarction of the involved tissue, and tissue destruction from the action of proteases, lipases, and mycotoxins. Release of mycotic thrombi from primary sites may lead to disseminated disease. Cerebral, pulmonary, cutaneous, and disseminated forms of disease are most commonly encountered.

In the setting of acute leukemia, bone marrow transplantation, acute leukemia, solid organ transplantation, diabetes mellitus, or without ketoacidosis, overuse of corticosteroids, and dextrose/milk therapy for intravenous hydration are cited as being patients predisposed to infection. Emphasis is placed on reducing the high mortality rate, reaching as high as 50%, depending on underlying disease. Successful outcomes depend on early diagnosis; treatment of the underlying condition, surgery when indicated, and amphotericin B therapy. High-dose lipid formulations of amphotericin B and the use of hyperbaric oxygen are the particular strategies that have shown potential value in the treatment of zygomycosis, as noted by Gonzalez, Renaci, and Sugar.

Athrinopus is the genus of Zygomycetes recovered most frequently in culture from human infections, followed in incidence by other Zygomycetes species. Other Zygomycetes species are less frequently encountered. Cunninghamella species are infrequently cultured in clinical laboratories. Nevertheless, several case reports indicate that this organism has been recovered as the causative agent of each of the more common forms of zygomycosis—cerebral, pulmonary, cutaneous, and disseminated disease. Kontoyiannis et al. described the common clinical predispositions of Cunninghamella species; namely, these corticosteroid therapy, prolonged severe granulocytopenia, and diabetes mellitus. Fever and pneumonia were the most common clinical presentations in this series patients; usually an indication of disseminated disease. Cunninghamellae species are usually rapidly progressive, and the outcome in most cases reported in the literature has been almost uniformly fatal. Aggressive treatment with amphotericin B, a reaction of infected tissues, and control of the underlying disease may reverse this trend.

Cerebral Disease:
Infection often begins as a sinusitis, progressing to focal invasive disease, with edema of the eyes, proptosis, or anemia; and internal and external ophthalmoplegia. In many cases, infection is rapidly progressive, although slowly progressive, chronic forms have also been described. A thick, dark, blood-tipped nasal discharge may be observed; material issued from the sinus may appear blackened and hemorrhagic because of vascular invasion and infarction. Meningitis and brain abscesses may develop by direct extension, and are usually fatal. Localized cerebral disease is uncommon, occurring most frequently among intravenous-drug users. Nienoff et al. reported a case of ascending cerebral infection in a patient after transplantation, in whom bilateral temporal arteritis (tenderness) developed. Cerebral disease has also been reported in patients with presumed drug-related infection. Confusion and mental disturbances are more common presenting signs of cerebral involvement. Space-occupying lesions and brain abscesses are seen in drug addicts. Once cerebral symptoms set in, the disease is often rapidly fatal, as occurred in the Nienoff case cited above. Noninvasive fungal infections of the nasal cavity may also be seen.

Pulmonary Disease:
Invasive, finely nodular or diffuse infiltrates may be seen radiologically. Fungus ball involvement in preexisting natural or infection cavitary lesions may also be seen. Chest pain, hemoptysis, and cough productive of purulent or blood-tipped sputum are common clinical presentations. Subacute pulmonary disease is usually intracranial, with the formation of mucinous exudates. The pleura may occasionally be involved.

CNS Disease:
Invasive disease usually occurs secondary to trauma and soil contamination, primarily in patients with burns and in patients with endocarditis, disseminated intravascular coagulation, and gangrene. Zygomycetes species usually belong to the Order Entomophthorales. Infections are most common in cases of subcutaneous disease. Infections are usually caused by Aspergillus or Fusarium species. Potassium acetate, amphotericin B, and azole drugs have been successfully used in treatment of these cases.
2-**Aspergillus species and Aspergillosis**

Aspergillus species is a hyaline mold, widely distributed in nature, they are found in soil, on decaying vegetation, and on a wide variety of organic matter. The inhalation of spore-contaminated dust is the most common mode of infection in humans, resulting in sinusitis or bronchopulmonary disease.

An increase in the rate of infection occurs during periods of building construction, particularly in zones surrounding hospitals. The report many years ago of an outbreak of aspergillosis among cancer patients, related to the fireproofing operation in the resident hospital is apropos. Surveillance studies should always include sampling of hospital air filters which commonly reveal high fungal spore counts. Ventilation ducts in particular may become contaminated with dirt and fragments of vegetative matter that become airborne from disruption of the soil and vegetative undergrowth. The incidence of nosocomial aspergillosis is in direct proportion to the mean ambient airborne spore count, which is highest when mini-bursts of spores are released into the air via the shaking out of contaminated clothing or from disruption of accumulated contaminated dust or floors or other surfaces during cleanup operations. Patients who are immunocompromised or who are receiving immunosuppressive drugs, notably bone marrow and organ transplant recipients, and those with hematologic malignancies, are particularly susceptible to infection.

**The medically important Aspergillus species.**

The A. species most commonly encountered in clinical laboratories include *A. fumigatus*, *A. flavus*, *A. terrus* and *A. niger*. The majority of serious infections are caused by *A. fumigatus*. *A. nidulants* is also mentioned in this section because most strains readily produce the sexual or telomorphic forms-cleistothecia enclosing species-specific Ascospores.
Fig. 2. Sketch of a generic fruiting head of *Aspergillus* species. Illustrating the swollen vesicle giving rise to phialides from which chains of conidia are produced.

**Histopathology of infections caused by the *Aspergillus* species:**

The hypha of *A*. species are characteristically hyaline, septate, regular in outline and have parallel walls. They average 3 to 6 µm in diameter and divided by transverse septa. The hypha does not stain well in hematoxylin and eosin (H and E) sections, but are well outlined using PAS and GMS stains. The tissue reaction in immunocompetent hosts infected with these fungi may first be purulent and then granulomatous.

A species have a particular predilection to invade blood vessels causing thrombosis and hemorrhagic infarction. When fungus colony grows within a preexisting cavity such as a nasal sinus or within a congenital or inflammatory lung cyst, the lesion is known as a fungus ball; the hypha often appear amorphous and stain poorly.

In bronchopulmonary aspergillosis, bronchi and bronchioles often are dilated and filled with viscid mucinous material in which are trapped cellular debris, many eosinophils, scattered neutrophils, lymphocytes, plasma cells and hyphal fragments.
3-Dermatophytes

Definition. Cutaneous lesions due to dermatophytes, presenting most commonly as athlete's foot (tinea mannum), nail infections (tinea unguium), body infection (tinea corporis), and scalp ringworm (tinea capitis). These pathogenic fungi inhabit the keratinized tissue of skin, hair, and nails, and generally do not invade living tissue. In active infections, they are seen as branched hyphae. They grow down the pilosebaceous follicles towards the hair bulb, but are arrested before reaching the bulb itself and fan out to form multiple hyphal fronds known as Adamson's fringe.

Dermatomycoses due to *Trichophyton mentagrophytes*, *Trichophyton rubrum*, *Microsporum gypseum*, and *Epidermophyton floccosum* occur commonly worldwide and these are one of the most common skin infections in north east region of India. Unlike other superficial fungal infections, the incidence of dermatophytoses, commonly called ringworm or tinea, (Weitzman and Summerbell, 1995; Jessup et al., 2000)

The prevalence of different types of superficial fungal infections of the skin is variable among different age groups, gender, socio-economic levels, and countries. In Iraq, tinea pedis infection age group 15-45 years showed the highest frequency, male:female ratio was 1.67:1, labour and industrial workers formed the largest group "22.4%" of the patients and the rate among military personnel seems to be high. In UK and other Western Europe countries, the prevalence is 5.1% and in USA is 8.1% and in general it is more prevalent in male's children.

Three genera of dermatophyte fungi cause tinea infections (tinea worm):

- Trichophyton (skin, hair and nail infections)
- Microsporum (skin and hair)
• Epidermophyton (skin and nails)

Dermatophytes invade keratin only, and the inflammation they cause is due to metabolic products of the fungus or to delayed hypersensitivity. In general, zoophilic fungi (those transmitted to humans by animals) are

![Image of Trichophyton mentagrophytes](image.jpg)

Fig.3-Trichophyton mentagrophytes, most common species of dermatophytes

Tinea types

1. **Tinea pedis (athlete's foot)**. This is the commonest type of fungal infection in man. Ring worm of the feet it is the most prevalent of all dermatophytoses. It occurs as a chronic infection of the toe webs. Other varieties are the vesicular, ulcerative and moccasin types, with hyper keratosis of the sole, initially there is itching between the toe webs becomes chronic, peeling and cracking of the skin are the principle manifestations, accompanied by pain and pruritus.

Infections are most common during the warm, humid months, *T. mentagrophytes*, *T. rubrum* and *E. floccosum* are the dermatophyte species most commonly recovered. The increased amount of keratin on the soles of the feet and the palms of the hands makes these two sites selectively vulnerable to infection with *T. mentagrophytes* and other dermatophytes.

2. **Tinea cruris**: When the infection occurs in the groin area, it is called tinea cruris, or jock itch. Frequently, the feet are also involved.
such infections involve males mainly the causative agent are *T. rubrum*, *T. mentagrophytes*, *E. floccosum*. The theory is that the feet get infected first from contact with the ground. The fungus spores are carried to the groin from scratching.

**3 Tinea Corporis:** Typically appears as single or multiple annular, scaly lesions with clearing, a slightly elevated, reddened edge and sharp margin on the trunk, extremities, or face. Tinea corporis was a major problem for U.S. troops during the Vietnam conflict, particularly those assigned to combat units exposed to wet terrain. In the United States, the most common organism recovered is *T. rubrum*; however, during the Vietnam conflict, the most common isolated species recovered from lesions of tinea corporis and tinea cruris was a zoophilic strain of *T. mentagrophytes* that accounted for 73% of fungal infections in combat servicemen.

**4 Tinea capitis:** Hair infected with one of the following fungi *Microsporum ferrugineum*, *Microsporum audouinii* and cause tinea capitis. *Microsporum canis* var. *distortum* is a zoophilic fungus known to cause infections in cats, dogs, and other animals. It is a rare cause of tinea capitis in New Zealand, Australia, and North America. Clinical disease is similar to *M. canis*. Invaded hairs show an ectothrix infection and fluoresce a bright greenish-yellow under Wood’s ultraviolet light.

Infected hair shaft are broken off just at the base, leaving a black dot just under the surface of the skin. Scraping these residual black dot will yield the best diagnostic scrapings for microscopic examination.

**5 Tinea unguium**

It's the infection of the nails usually toe nail infection associated with tinea pedis. The initial changes occur at the free edge of the
nail which becomes yellow and crumbly. Subungual hyperkeratosis, separation of the nail from its bed, and thickening may then follow. Usually only a few nails are infected but rarely all are. Finger nail lesions are similar, but less common, and are seldom seen without a chronic *T. rubrum* infection of the skin of the hands. Onychomycosis, its caused by members of the fungal triad, namely dermatophytes, yeasts and other molds. It is estimated that fungi cause 50% of all nail disorders, and onychomycosis accounts for 30% of all superficial fungal infections.

6 *Tinea mannum*: it's the infection of the hands this is usually asymmetrical and associated with tinea pedis. *T. rubrum* may cause a barely perceptible erythema of one palm with characteristic powdery scales in the creases.
The Dimorphic Fungi

A subset of hyaline molds, the dimorphic fungi are usually considered separately because they have unique characteristics. First, they are dimorphic, that is, they exist in the mold form in the environment (room-temperature incubation), but as yeasts when incubated at 35-37°C. The natural habitat for the dimorphic fungi is the soil, where under ambient conditions, they exist as molds and undergo sporulation. The mold form is the infective form. Humans and animals become infected either through inhalation or by direct traumatic implantation of material contaminated with conidia or hyphal elements when incubated at 35-37°C or on access to the body temperature of human tissues. The conidia transform into a yeast form (or spherule form for *Coccidioides immitis*). Secondly, the dimorphic fungi are pathogens, causing “deep-seated” infections in humans. As a group, these fungi can be highly virulent in susceptible hosts and can invade deeply into tissues and organs and have the capability of spreading widely throughout the body.

The species of medical importance:

A. *Blastomyces dermatitidis*
B. *Coccidioides immitis*
C. *Histoplasma capsulatum*
D. *Sporothrix schenckii*
E. *Paracoccidioides braziliensis*

The colonies typically grow slowly (10-30) days when recovered in primary culture from clinical specimens. In cases in which the spore concentration in a clinical specimen is high, particularly in sputum, growth may be observed within 4-7 days.

Rarely, a fine delicate growth may be observed in 14-27 hrs on routine blood agar plates incubated at 35°C. The colonies typically are gray-white or buff, although a few strains may show light pastel yellow shading into pink pigmentation.
A- *Blastomyces dermatitidis*

is a soil mold that is endemic in the states adjacent to The Mississippi and Ohio river valleys. The regions of infection with blastomycosis are determined only on the basis of individual case findings because of the lack of a sensitive skin test. Humans are presumed to become infected from inhalation of dust-contaminated spores.

![Image of Blastomyces dermatitidis spores](image)

B- *Coccidioides immitis* and Coccidioidomycosis

*Coccidioides immitis* is a dimorphic soil fungus native to valley of California. The mycelia form grows beneath the hot desert sands in which the elevated subsurface temperatures are ideal for propagation. The hyphae are branched and fragment into individual arthroconidia when the soil is disturbed. These arthroconidia are tiny, light and easily wind born in clouds of blowing sand and dust.

Hyphal forms may be found in tissue sections, particularly if the affected site has been exposed to air. It was reported that five cases of coccidioidomycosis in which hyphae were found in brain tissue or spinal fluid. Recent reports indicate that coccidioidomycosis remains a growing problem in the southwestern United States. Related is the parallel increase in individuals with depressed cellular immunity, particularly those with HIV infections, those who have undergone allogenic transplantation, and others on immunosuppressive medications.
In endemic areas, particular attention should be paid to ranchers, farmers, constructing workers, and others engaged in outdoor activities requiring intimate exposure to dust and soil.

**C-Histoplasma capsulatum and Histoplasmosis**

Histoplasmosis, caused by the dimorphic fungus Histoplasma capsulatum is a common systemic fungal disease the world. Its also is the most common fungal infection in patients with AIDS. Isolated indigenous cases have been reported from Europe, in Germany, Belgium, Holland and Denmark. Histoplasmosis is known as an "exo-European" disease, Although a few cases have been reported from Italy. The mycelia form of Histoplasma capsulatum is present in warm, moist soil rich in organic content, such as that produced by heavy accumulation of bird or bat excreta.

The mold form of Histoplasma capsulatum typically grows slowly (10-30) days, although from specimens with a heavy concentration of organisms growth as early as 5 days may be observed. Microscopically, the diagnostic structures seen in the mold form are large, roughened or spiked macroconidia measuring 10-20µm in a diameter.

**D-Sporothrix schenckii**

Is a fungus that is found world wide in soil and decaying vegetative matter, particularly plants, wood splinters, and rosebush thorns. Its the causative agent of sporotrichosis, a chronic infection of humans and animals. It also may be carried by certain wild and domestic animals and by rodents. Humans become infected when the organism penetrates the skin of individuals handling the contaminated substances Systemic spread may occur with bone, muscle, central nervous system and pulmonary involvement.

An outbreak of sporotrichosis occurred at a tree nursery in Florida, lymphocutaneous sporotrichosis developed in 9-65 (14%) of workers involved in the production of sphagnum moss topiaries. The incidence of sporotrichosis in Peru was calculated at between 48 to 60 cases per 100,000 persons with highest incidence among children aged 7-14 years. The skin of the face was the most commonly affected site. The disease was clinically confined to the skin and subcutaneous tissue in all patients.
E-Paracoccidioides immitis and paracoccidioidomycosis

Paracoccidioidomycosis is a progressive subacute to chronic systemic granulomatous fungal infection caused by the thermally dimorphic fungus, *Paracoccidioides brasiliensis*. The mycelia form of this fungus resides in the soil and pulmonary infection develops in humans by inhalation of the small (4µm diameter) conidia or skin infections by direct inoculation of spore contaminated dirt. In south America 80% of cases have been reported from Brazil, Colombia and Venezuela, endemic area also exist in southern Mexico. Although the majority of patients are agriculturists, cases have been reported in individuals with rare direct exposure to soil and vegetation. Whites are more prone to infections than Native Americans, more severe in infections tend to develop in immigrants coming to endemic areas.

The colonies are similar in appearance to those of *Blastomyces dermatitidis*. They are slow-growing at 30°C, requiring 10-20 days to mature, are gray-white and have a delicate silky or hair-like mycelium.

5-Dematiaeous Fungi

In contrast to the hyaline group of fungi, a second large group of rapidly growing saprophytic molds produce a melanin-like pigment resulting in darkly pigmented hyphae, visually recognized as dark gray or black colonies, both on the surface and on the reverse side. The term *phaeohyphomycetes* has been applied to this dematiaceous group of fungi. The concept of *Phaeohyphomycetes* was first proposed Ajello *etal*. in 1986 to cover all infections of cutaneous, subcutaneous and systemic nature caused by dematiaceous fungi that develop in the host tissues in the form of dark-walled dematiaceous septate mycelia elements are characteristically accompanied by granulomatous inflammatory reactions when observed in tissue sections. Thus as originally described, *Phaeohyphomycetes* was a term used describe a histopathologic entity rather than representing any particular clinical disease or fungal species as identified in laboratory culture. Nonetheless, the term *Phaeohyphomycetes* currently applies to several clinical entities: sinusitis, keratitis, endocarditis and pneumonia, among others. Yet many Mycologists now recommend that the generic term be replaced with
reports such as "keratomycosis" caused by Bipolaris species or Mycetoma caused by phialophorarichardsiae".

The species of medical importance

A. Alternaria species: The formation of short chains of large, smooth-walled, multicelled, macroconidia separated by both cross and longitudinal septa (muriform) are characteristic of Alternaria sp.. The macroconidia are shaped like drumsticks, with the elongated beak of one conidium butting against the rounded, blunt end of the next.

B. Ulocladium species: Also produce muriform macroconidia, however they are more spherical than those of Alternaria sp., do not arrange in chains and are borne from short, twisted "bent-knee" or geniculate, conidiophores.

C. Stemphylium species: Muriform macroconidia that appear similar to those of Ulocladium are produced, however they are borne singly at the apex of a short, straight non-geniculate conidiophore.

D. Epicoccum species: The hyphae typically form focal repeated branching and rebranching of certain threads, forming masses known as sporodochia. Short conidiophores arise from these masses bearing multicelled, muriform, spherical to slightly club shaped macroconidia.
Chromomycosis and Mycetoma

Chromomycosis is the term originally used to describe a cutaneous and subcutaneous infection characterized by the formation of elevated, roughened multicoloured verrucous vegetations, most commonly spreading over the dorsal surfaces of the feet and lower leg, caused by a group of slow-growing, dematiaceous fungi belonging to the genera Cladophialophora, Phialophora, Cladosporium and Fonseceae.

The term Mycetoma refers to a condition in which the infection is located primarily in the subcutaneous tissue, forming an abscess or granulomatous mass with the formation of sinus tracts that reach the surface of the skin. Purulent material containing grains or granules of fungal elements are often discharged from these sinus tracts and are also observed in histologic sections of the mass.

These agents gain entrance to the skin through traumatic wounds and penetrating injuries. Microabscesses granulomatous nodules, extreme acanthosis, and pseudoepitheliomatous hyperplasia with varying degrees of fibrosis and scarring are the common histologic changes.

The species of medical importance

A. Cladophialophora (Cladosporium) carrionii
B. Cladophialophora (Xylohypha) bantiana
C. Phialophora verrucosum
D. Phialophora richardsiae
E. Fonsecaea pedrosoi
F. Exophiala species
G. Wangiella species.

A-Cladophialophora (Cladosporium) carrionii

Freely branching hyphae give rise to long chains of dark-staining, elliptical conidia. The conidia often show scars or dysjunctors at the sites of attachment. Cladophialophora bantiana is a closely related species that also produces spores of a cladosporium type. Cladophialophora bantiana differ from Cladophialophora (Cladosporium) carrionii in two essential characteristics they are:
a) Produce very long chains of conidia.
b) Grows at 43°C and doesn’t liquefy gelatin.

**B-Phialophora verrucosum:**

Flask shaped or urn-shaped phialides, ranging from 4 to 7 µm in length. Spherical to oval-shaped, yellow pigmented conidia are produced from within each phialide, and aggregate in ball-like clusters at the terminal opening.

**C-Phialophora richardsiae**

Is a common agent recovered from phaeohyphomycotic cysts. Spherical to elliptical, hyaline conidia are borne in tight clusters at the tips of these phialides, held together by mucinous material.

**D-Fonsecaea pedrosoi**

Conidia arise from short denticles attached laterally to the sides of conidiogenous cells which periodically swell, turn sympodially, and produce additional conidia that arrange in short chains at points of septations.

**7-Candida and Candidiasis.**

They are members of the normal flora of the skin mucous membranes, and gastrointestinal tract.

The risk of indigenous infection is ever-present. Candidiasis is the most common systemic mycosis, and the most common agents are *C. albicans*, *C. tropicalis*, *C. parapsilosis*, *C. glabrata*

*Candida* species grow as oval, budding yeast cells (3-6mm in size).

*C. albicans* is dimorphic, produce soft, cream-colored colonies a yeasty odor.

*C. albicans*, the most common pathogen from other species of candida: after incubation in serum for about 90 minutes at 37°C, yeast cells of *C. albicans* will begin to form true hyphae or germ tubes and on nutritionally deficient media *C. albicans* produces large, spherical
chlamydospores. sugar fermentation and assimilation tests can be used to confirm the identification.

Factors predisposing to high frequency of yeast infections include:

1. Increase in chemotherapy and in bone marrow and other organ transplantations.
2. Prolonged stays in hospitals.
3. Vascular catheterizations.
4. Prolonged administration of broad-spectrum antimicrobial agents.
5. Extensive use of prophylactic antifungal drugs.

In a review of patients with nosocomial candidiasis, cite burns, artificial respiratory assistance, colonization with Candida species and repeated transfusions a additional risk factors. Patients with cancer particularly those with leukemia and lympho proliferative disorders.

The species of medical importance

A. Candida albicans
B. Candida tropicalis
C. Candida parapsilosis
D. Candida kefyr

A-Candida albicans:

Two patterns of growth on cornmeal agar helpful in identifying C. albicans

a) The production of chlamydospores.

b) Blastocconidia that arrange in dense clusters evenly distributed along the pseudohyphae. A review for these cornmeal agar patterns is particularly helpful in making an identification for strain that are germ tube –negative. If the germ tube test is negative and chlamydospores are not observed in cornmeal agar mount a yeast other than Candida albicans has probably been isolated.

B-Candida tropicalis:
Produce pseudohyphae with blastoconidia either borne singly or in small irregular clusters along the pseudohyphae at points of constriction.

**Candida parapsilosis**:

Identification of *C. parapsilosis* in cornmeal agar preparations is the observation of multiple focal areas of satellite growth forming (cross matchstick) patterns.

**Types of Candidiasis according to the site of action**

A. Mucocutaneous
B. Cutaneous candidiasis
C. Disseminated candidiasis
D. Candidiasis of the urinary tract
E. Endocarditis
F. Candida Meningitis

**Factors affecting the pathogenesis of the fungal infections**:

1. Hydrolysis enzymes

Virulence factors of molds and dermatophytes, allowing the hydrolysis of structural components of the epidermal tissue and the invasive character of these pathogens.

Among the wide variety of enzymes secreted by dermatophytes, proteolytic enzymes are the most studied, and the importance of keratinolytic proteases to the pathogenicity is well established.

Keratin is a fibrous protein molecule of high molecular weight, rich in cysteine, whose disulfide bridges and acetamide bonds guarantee its stability. This protein is produced by humans and other animals and is the main component of skin, nails, having the function to protect and cover.

The keratinases secreted by dermatophytes catalyse the degradation of the keratin present in the host tissue into oligopeptides or amino acids that may be then assimilated by the fungus.
It is thought that proteolytic enzymes degrade the protein components of the skin, aiding in the process of penetration in the stratum corneum.

Some authors suggest that the proteases secreted by dermatophytes facilitate and are even necessary for an efficient adhesion of these pathogens to the host tissue.

\textbf{pH of the tissue}

pH signaling and monitoring pathways could be considered fungal and dermatophyte virulence factor, allowing the development and maintenance of the infection. Regulated by the pacC gene, interfering with the secretion of proteases with optimal activity in alkaline pH.

They proposed a model of regulation of proteolytic enzymes by neutral pH during the infectious process of dermatophytoses. In the early stages of the infection and in response to the acidic pH of human skin, the pathogen unsuppressed the synthesis of non-specific keratinases and proteases that have optimal activity in acidic pH. They act in substrates, keratinous or not, producing peptides that are hydrolyzed to amino acids, which are used by the fungus as a source of carbon, nitrogen and sulphur.

The metabolization of some aminoacids promotes the alkalinization of the host's microenvironment, making it suitable to the action of keratinases with optimal activity in alkaline pH, which allows the maintenance of the infection. It was shown that \textit{T. rubrum} rapidly responds to changes in neutral pH by modulating its gene expression profile. This metabolic machinery allows dermatophytes to use proteins as a source of nutrients in a wide pH spectrum. This makes the complete installation, development and permanence of the dermatophyte in the host tissue possible. For example, \textit{T. rubrum} codifies a protein homologous to the transcriptional regulator pacC (\textit{Aspergillus nidulans})/Rim101p (\textit{Candida albicans}), which is part of the signaling pathway of neutral pH. In candidiasis one should be avoid the
breads, cheese, mushrooms, vinegar which give arise to decrease pH of the stomach and small intestine that will enhance the growth of Candida species. Milk and milk products as well as avoided because of their high levels of milk sugar as yeast grows freely in a high-sugar environment.

3-Lipid content of the tissue

Other important components found in the host tissue are lipids, which are also the target of fungal extracellular enzymes in the pathogenesis of fungal and dermatophyts species. Studies have demonstrated that Aspergillus species grows widely in corn and weigh, peanuts due to their content of lipid and consider a major contaminants of the food stuff which will cause digestive tract problems in human. The dermatophytes Epidermophyton floccosum, Microsporum canis, Trichophyton mentagrophytes and Trichophyton rubrum show lipolytic activity when cultured in different lipid agar sources.

Yeast also prefer the lipid environment and seborrhic skin e.g. pityriasis versicolor, tinea piedra and tinea nigra they widely distributed in highly lipid area of the body and cause brown color infection which is consider a cosmetic problem e.g.( chest, upper back, abdomen, arms).

4-Drugs

The medication affect the growth of yeast e.g. Candidiasis, including antibiotics, cortisone, hormones (birth control pills), ulcer drugs(zantac).

They reversely enhance the growth of the yeast and fungal species by killing the bacterial species so the area will be suitable for fungal growth, in addition the cortisone and hormones make the area of low pH (acidic) which consider a good factor in activating yeast and fungal species.
Antifungal chemotherapy

There are a limited but growing no. of antibiotics that can be used to treat mycotic infections. The classes of currently available drugs include the polyenes (amphotericin -B and nystatin), flucytocine, a pyrimidine analog, the azoles and other inhibitors of ergosterol synthesis and griseofulvin which interferes with microtubules assembly. Currently under investigation are inhibitors of cell wall synthesis e.g. nikomycin which inhibits the synthesis of chitin and pneumocadin which inhibits the synthesis of B-glucan.

1-Amphotericin B

The major polyene antibiotic is amphotericin B, a metabolite of streptomyces. It has a broad spectrum and the development of resistance is rare. The mechanism of action of polyenes involves the formation of complexes with ergosterol in fungal cell membrane resulting in membrane damage and leakage.

Mechanism of action:

Amphotericin B is giving intravenously as micells with sodium deoxycholate dissolved in dextrose solution. Though the drug is widely distributed in tissues, it penetrates poorly to the cerebrospinal fluid. Amp. B firmly binds to ergosterol in the c.m. this interaction alters the membrane fluidity and perhaps produces pores in the membrane through which ions and small molecules are lost. Unlike other antifungals amph. B is cidal. Mammalian cells lack ergosterol and relatively resistant to these actions.

Indications:
Amphotericin B has a broad spectrum with demonstrated efficacy against most of the major systemic mycoses including coccidiodomycosis, blastomycosis, histoplasmosis and Candidiasis. The response to amphotericin B is influenced by the dose and rate of administration, the site of mycotic infection, the immune status of the patient and the inherent susceptibility of the pathogen.

**2-Azoles:**

The antifungal imidazoles e.g. (ketoconazole) and triazoles (fluconazole and itraconazole) are oral drugs used to treat a wide range of systemic and localized fungal infection. It supplement with amphotericin B in many less severe mycoses because they can be administered orally and are less toxic.

**Mechanism of action:**

The synthesis of ergosterol. They block the cytochrome p450-dependant 14-α demethylation of lanosterol which is a precursor of ergosterol in fungi and cholesterol in mammalian cells. Fungal cytochrome p 450 are approximately (100-1000) times more sensitive to the azoles than mammalian systems.

**Indications:**

The indications for the use of antifungal azoles will broaden as the results of long term studies as well as new azoles become available. Ketoconazole is useful in the treatment of chronic mucocutaneous Candidiasis, dermatophytosis and nonmeningeal blastomycosis. It offers the best penetration of the central nervous system, oropharyngeal Candidiasis in AIDS patients and Candidemia in immunocompetent patients.

4-Griseofulvin

5-Terbinafine
6-Flucytosine

Topical antifungal agents

1-Nystatin
2-Clotrimazole,Miconazole
3-Naftifine,Undecylenic acid