Medical mycology

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Contents

Introduction to mycology

The term "mycology" is derived from Greek word "mykes" meaning mushroom. Therefore mycology is the study of fungi. The ability of fungi to invade plant and animal tissue was observed in early 19th century but the first documented animal infection by any fungus was made by Bassi, who in 1835 studied the muscardine disease of silkworm and proved the that the infection was caused by a fungus *Beauveria bassiana*. In 1910 Raymond Sabouraud published his book Les Teignes, which was a comprehensive study of dermatophytic fungi. He is also regarded as father of medical mycology.

The isolation and identification of fungi is an often-neglected area of medical microbiology. The science known as medical mycology began in the early 19th century in Italy with the discovery of *tinea favosa*. The discipline concerns those infections in humans and animals that occur because of pathogenic fungi. Fungi cause a range of diseases ranging from skin infections such as athlete's foot, ringworm, dandruff, superficial cutaneous infections with dermophytes, to the more serious and invasive *Candida* and *Aspergillus* in severely immunocompromised hospital patients. Many important fungal pathogens seen in the immunocompromised also comprise part of the normal flora and this can lead to difficulties in detection.

It might seem surprising to learn that the global annual death toll due to fungal infections is greater than that for malaria, breast, or prostate cancer and more like those rates seen in tuberculosis (TB) and HIV (Gow, 2018). This toll runs to over a million people. In addition, around 10 million suffer from a severe fungal allergy; 100 million women annually fall foul to recurrent vulvovaginal infections and more than a billion people are afflicted by skin infections each year.

Importance of fungi: Fungi inhabit almost every niche in the environment and humans are exposed to these organisms in various fields of life.

Beneficial effects of fungi:

1. Decomposition - nutrient and carbon recycling.

2. Biosynthetic factories. The fermentation property is used for the industrial production of alcohols, fats, citric, oxalic and gluconic acids.

3. Important sources of antibiotics, such as Penicillin.

4. Model organisms for biochemical and genetic studies. Eg: *Neurospora crassa*

5. *Saccharomyces cerviciae* is extensively used in recombinant DNA technology, which includes the Hepatitis B Vaccine.

6. Some fungi are edible (mushrooms).

7. Yeasts provide nutritional supplements such as vitamins and cofactors.

8. *Penicillium* is used to flavour Roquefort and Camembert cheeses.

9. Ergot produced by *Claviceps purpurea* contains medically important alkaloids that help in inducing uterine contractions, controlling bleeding and treating migraine.

10. Fungi (*Leptolegnia caudate* and *Aphanomyces laevis*) are used to trap mosquito larvae in paddy fields and thus help in malaria control.

Harmful effects of fungi:

1. Destruction of food, lumber, paper, and cloth.

2. Animal and human diseases, including allergies.

3. Toxins produced by poisonous mushrooms and within food (Mycetism and Mycotoxicosis).

4. Plant diseases.

5. Spoilage of agriculture produce such as vegetables and cereals in the godown.

6. Damage the products such as magnetic tapes and disks, glass lenses, marble statues, bones and wax.

Products of fungi

A- Mycotoxins:

Definition:

Mycotoxins are toxic secondary metabolites produced by fungi. One species may produce many different mycotoxins and/or the same mycotoxin as another species. These products cause mycotoxicocis following ingestion, inhalation or direct contact.

NB: mycotoxicocis is the ingestion of food contaminated with toxin producing fungus.

Mycetismus: is the ingestion of food containing preformed toxins.

Significance:

They are not necessary for growth or development of the fungi but mycotoxins weaken the receiving host so the fungus may use them as a strategy to better the environment for further fungal proliferation.

Mycotoxins can appear in the food chain as a result of fungal infection of crops, either by being eaten directly by humans or by being used as livestock feed. Mycotoxins greatly resist decomposition or being broken down in digestion, so they remain in the food chain in meat and dairy products.

Factors affecting the presenting symptoms of mycotoxicosis:

- Type of mycotoxin.
- Amount of mycotoxin.
- Duration of exposure.
- Route of exposure.
- Age, sex and general health state of exposed individual.
- Other factors e.g. malnutrition, alcohol intake ….etc.

Major groups:

1- Aflatoxins:

Produced by:

Aspergillus species such as *A. flavus and A. parasiticus*. Aflatoxins are largely associated with commodities produced in the tropics and subtropics, such as cotton, peanuts and maize.

Subtypes:

The term aflatoxin refers to 10 different types of mycotoxins produced, which are B1, B2, B2a, G1, G2, G2a, M1, M2, GM1, and aflatoxicol.

Health effects:

Aflatoxin B1 is the most toxic. Toxicity is either acute or chronic.

Acute aflatoxicosis is presented in the form of acute hepatitis that may be fatal.

Chronic aflatoxicosis is associated with increased risk of hepatocellular carcinoma due to activation of proto oncogenes and mutation of tumor suppressor gene P53. Co infection with HBV increases the risk.

2- Ochratoxin:

It is a mycotoxin that comes in three secondary metabolite forms, A, B, and C. All are produced by *Penicillium* and *Aspergillus* species. The three forms differ in that Ochratoxin B (OTB) is a non chlorinated form of

Ochratoxin A (OTA) and that Ochratoxin C (OTC) is an ethyl ester form Ochratoxin A. *Aspergillus ochraceus* is found as a contaminant of a wide range of commodities including beverages such as beer and wine. *Aspergillus carbonarius* is the main species found on vine fruit, which releases its toxin during the juice making process. OTA has been labeled as a carcinogen and a nephrotoxin, and has been linked to tumors in the human urinary tract.

3- Citrinin:

It is a toxin that was first isolated from *Penicillium citrinum*, but has been identified in over a dozen species of *Penicillium* and several species of *Aspergillus*. Citrinin is associated with yellow rice disease in Japan and acts as a nephrotoxin in all animal species tested. Although it is associated with many human foods (wheat, rice, corn, barley, oats, rye, and food colored with Monascus pigment) its full significance for human health is unknown. Citrinin can also act synergistically with Ochratoxin A to depress RNA synthesis in murine kidneys.

4- Ergot Alkaloids:

They are compounds produced as a toxic mixture of alkaloids in the sclerotia of species of Claviceps, which are common pathogens of various grass species. The ingestion of ergot sclerotia from infected cereals, commonly in the form of bread produced from contaminated flour, cause ergotism. There are two forms of ergotism gangrenous affecting blood supply to extremities and convulsive that affects the central nervous system. Modern methods of grain cleaning have significantly reduced ergotism as a human disease; however it is still an important veterinarian problem.

4- Patulin:

It is a toxin produced by the P. expansum, Aspergillus, Penicillium, and Paecilomyces fungal species. Although patulin has not been shown to be carcinogenic, it has been reported to damage the immune system in animals.

5- Fusarium toxins:

They are produced by over 50 species of Fusarium and infect the grain of developing cereals such as wheat and maize. They include a range of mycotoxins such as:

fumonisins which affect the nervous systems of horses and may cause cancer in rodents.

trichothecenes which are most strongly associated with chronic and fatal toxic effects in animals and humans due to potent inhibitionof protein, DNA and RNA synthesis.

zearalenone, which has estrogen like activity.

Detection of mycotoxins:

Many techniques have been employed for detection of mycotoxins as flouoroimmuonoassy, ELISA, chromatography and detection of cytotoxicity in cell culture.

Treatment of mycotoxicosis:

For most mycotoxins there is no specific treatment or antidote. Stopping further exposure and supportive care are the only available lines of treatment.

Prevention of mycotoxicosis:

- Avoid ingestion of moldy foods or grains.
- Cleaning of the grains to reduce the load of mycotoxin.
- Testing of moldy grains to role out the presence of known mycotoxin.
- Storage of foods and grains at dry environment to decrease the incidence of fungal growth.

Detoxificationof mycotoxins:

Contaminating mycotoxins in foods should be removed, inactivated or detoxified by physical, chemical and biological means depending on the conditions. However, the treatment has its own limitations, since the treated products should be health safe and their essential nutritive value should not be deteriorated. The following methods are suggested to be applied for effective decontamination of some mycotoxins.

I- Physical treatment:

- Fungi-contaminated seeds can be removed by hand picking or photoelectric detecting machines. This method is time consuming and expensive.
- Organic solvents (chloroform, acetone, hexane and methanol) have been used to extract aflatoxins from agricultural products, but mainly in vegetable oil refining process.
- Heating and cooking under pressure can destroy nearly 70% of aflatoxin in rice compared to under atmospheric pressure only 50% destroyed.

- Ionizing radiation such as gamma-rays can stop growth of food spoilage organisms, including bacteria, molds and yeasts. It also inactivates pathogenic organisms including parasitic worms and insect pests. However, it may not destroy the toxin completely and it has a mutagenic effect. In our laboratory, only about 30% of total 600 ppb at aflatoxin B1, either

II- Chemical treatment:

It has been used as the most effective means for the removal of mycotoxins from contaminated commodities. The method should be sure that the detoxification system is capable of converting the toxin to a nontoxic derivative (s) without deleterious change in the raw product. Mutagenicity of the treated products should be assessed. The toxicity may be checked by feeding animals including bouts, egg embryos, chicken, ducklings and rats. Many common chemicals have been used in detoxification of aflatoxin e.g.

- Acetic acid (C2H5OH).
- Ammonia gas (NH3) or NH4OH or ammonium salts 3-5%.
- Calcium hydroxide (Ca (OH) 2).
- Formaldehyde.
- Hydrogen peroxide H2O2.

The chemical reactions of detoxification of aflatoxin are primary addition of the double bond of the furan ring and oxidation involving phenol formation and opening of the lactone ring.

III- Biological treatment:

It means enzymatic degradation of contaminating mycotoxin or the use of biocompetitive agents for these mycotoxins e.g. *falvobacterium aurantiam* remove aflatoxins specially B1.

B- Phytotoxins:

Some fungi produce products that are toxic to plants i.e. phytotoxins e.g. alternariol and alternic acid produced by *alternaria tenuis.*

C- Antibiotics:

Several antibacterial agents e.g. penicillins and cephalosporins are produced by fungi specially penicillium species. Also many antifungal agents are produced by fungi e.g. griseofulvin, candidulin…etc.

D- Pigments:

E.g. ergochrome, indigo, cladin…etc.

Classification of fungi:

Fungi were initially classified with plants and were a subject of interest for botanists; hence the influence of botany can be seen on their classification. In 1969 R.H Whittaker classified all living organisms into five kingdoms namely Monera, Protista, Fungi, Plantae and Animalia. Traditionally the classification proceeds in this fashion: Kingdom - Subkingdom - Phyla/phylum - Subphyla - Class - Order - Family - Genus- Species This classification is too complicated to be dealt here. There are alternate and more practical approaches, one based on sexual reproduction and the other based on morphology of the thallus (vegetative structure).

Based on Sexual reproduction:

1. Zygomycetes: which produce through production of zygospores.

2. Ascomycetes: which produce endogenous spores called ascospores in cells called asci.

3. Basidiomycetes: which produce exogenous spores called basidiospores in cells called basidia.

4. Deuteromycetes (Fungi imperfecti): fungi that are not known to produce any sexual spores (ascospores or basidiospores). This is a heterogeneous group of fungi where no sexual reproduction has yet been demonstrated.

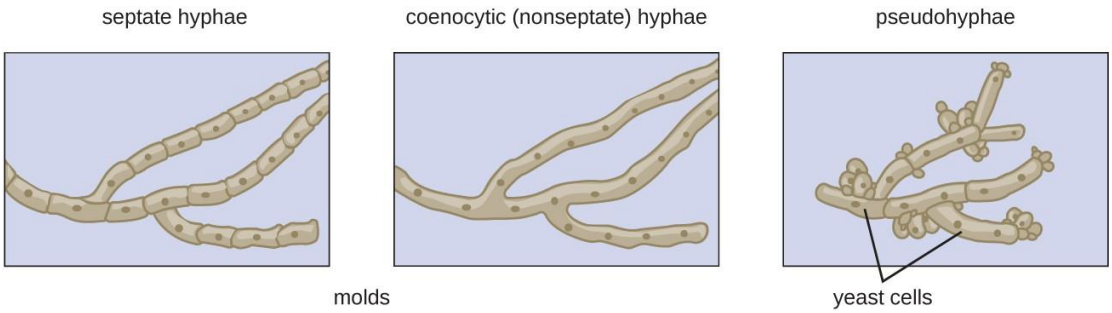
Based on Morphology:

1. Moulds (Molds): Filamentous fungi Eg: *Aspergillus* sps, *Trichophyton rubrum*

2. Yeasts: Single celled cells that buds Eg: *Cryptococcus neoformans*, *Saccharomyces cerviciae*.

3. Yeast like: Similar to yeasts but produce pseudohyphae Eg: *Candida albicans*

4. Dimorphic: Fungi existing in two different morphological forms at two different environmental conditions. They exist as yeasts in tissue and in vitro at 37o C and as moulds in their natural habitat and in vitro at room temperature. Eg: *Histoplasma capsulatum*, *Blastomyces dermatidis*, *Paracoccidiodes brasiliensis*, *Coccidioides immitis.*



Blastomyces dermatitidis

The conversion of the mycelial form of *Blastomyces dermatitidis* to the large, globose, thick-walled, broadly based budding yeast form requires only increased temperature. Hyphal cells enlarge and undergo a series of changes resulting in the transformation of these cells into yeast cells. The cells enlarge, separate, and then begin to reproduce by budding. The yeast cell wall contains approximately 95 percent (α1–3)-glucan and 5 percent (β1–3)-glucan. In contrast, the mycelial cell wall contains 60 percent (β1–3)-glucan and 40 percent (α1 -3)-glucan .

Reproduction in fungi:

Fungi reproduce by asexual, sexual and parasexual means.

Asexual reproduction is the commonest mode in most fungi with fungi participating in sexual mode only under certain circumstances. The form of fungus undergoing asexual reproduction is known as anamorph (or imperfect stage) and when the same fungus is undergoing sexual reproduction, the form is said to be teleomorph (or perfect stage). The whole fungus, including both the forms is referred as holomorph. (Taxonomically, the teleomorph or the holomorph is used, but practically it is more convenient to use the anamorph.)

Asexual reproduction:

Asexual propagules are termed either spores or conidia depending on their mode of production. Asexual spores are produced following mitosis where as sexual spores are produced following meiosis. The asexual spores of zygomycetes, which are known as sporangiospores form within sac like structure known as sporangia. The sporangios pores result from the mitotic cleavage of cytoplasm in the sporangium. The sporangia are borne on special hyphae called sporangiophore. This endogenous process of spore formation within a sac is known as sporogenesis.

Conidia arise either by budding off conidiogenous hyphae or by differentiation of preformed hyphae. These develop following mitosis of a parent nucleus and are formed in any manner except involving cytoplasmic cleavage. This exogenous process is known as

conidiogenesis, a process that occurs both in yeasts and moulds. Conidia are borne on specialised structures called conidiophore. Conidia production may be blastic or thallic. In blastic development the conidium begins to enlarge and a septum is formed. Here the conidium originates from part of parent. In thallic mode of development the conidium is differentiated by a septum before its differentiation.

Thus the conidium results from the conversion of entire parent cell into the conidium. The cell that gives rise to a conidium is called a conidiogenous cell. Conidiophores are specialised hyphae that bear conidia or conidiogenous cells. In many cases conidiogenous cells are referred as phialides.

Conidiogenesis

There are two main types of conidium development:

- *Blastic* conidiogenesis, where the spore is already evident before it separates from the conidiogenic hypha which is giving rise to it,
- *Thallic* conidiogenesis, where first a cross-wall appears and thus the created cell develops into a spore.

Sexual Reproduction:

Sexual propagules are produced by the fusion of two nuclei that then generally undergo meiosis. The first step in sexual methods of reproduction involves plasmogamy (cytoplasmic fusion of two cells). The second step is karyogamy (fusion of two compatible nuclei), resulting in production of diploid or zygote nucleus. This is followed by genetic recombination and meiosis. The resulting four haploid spores are said to be sexual spores, e.g. zygospores, ascospores and basidiospores.

If a sexual spore is produced only by fusion of a nucleus of one mating type with a nucleus of another mating type (+ and - strains), the fungus is said to be heterothallic. In contrast, homothallic moulds produce sexual spores following the fusion of two nuclei from the same strain. For sexual reproduction to occur, two compatible isolates are required.

Zygospores, which are the sexual spores of zygomycetes are round, thick walled reproductive structures that result from the union of two gamentagia. Ascomycetes produce sexual spores called ascospores in a special sac like cell known as ascus. In basidiomycetes the basidiospores are released from basidium, which is the terminal cell of a hyphae.

Parasexual reproduction:

Parasexual reproduction, first seen in *Aspergillus* is known to occur in basidiomycetes, ascomycetes and deuteromycetes. The process involves genetic recombination without the requirement of specific sexual structures. Relating to or being reproduction that results in recombination of genes from different individuals but does not involve meiosis and formation of a zygote by fertilization as in sexual reproduction

Importance of Spores:

A. Biological

1) Allows for dissemination

2) Allows for reproduction

3) Allows the fungus to move to new food source.

4) Allows fungus to survive periods of adversity.

5) Means of introducing new genetic combinations into a population

B. Practical

1) Rapid identification (also helps with classification)

2) Source of inocula for human infection

3) Source of inocula for contamination

Zygomycetes

Commonly known as bread moulds, these are fast growing, terrestrial, largely saprophytic fungi. Hyphae are coenocytic and mostly aseptate. Asexual spores include chlamydoconidia, conidia and sporangiospores. Sporangiophores may be simple or branched. Sexual reproduction involves producing a thick-walled sexual resting spore called a zygospore.

The class Zygomycetes includes two fungal orders: Mucorales and Entomophthorales, with extremely different pathogenic potentials. Mucorales affect only the immunocompromised patient causing mortality in excess of 60% in those affected, while entomophthorales, which include *Basidiobolus* and *Conidiobolus* genera, affect the immune competent individual, causing principally chronic infection of the subcutaneous tissue

Medically important orders and genera include:

1. Entomophthorales: Conidiobolus and Basidiobolus are involved in subcutaneous zygomycosis

2. Mucorales: Rhizopus, Mucor, Rhizomucor, Absidia and Cunninghamella are involved in subcutaneous and systemic zygomycosis (formerly called Mucormycosis).

Conidiobolus coronatus is a saprotrophic fungus, first described by Costantin in 1897 as *Boudierella coronata*. Though this fungus has also been known by the name *Entomophthora coronata*, the correct name is *Conidiobolus coronatus*.

In humans, *C. coronatus* infections likely occur due to inhalation of the fungal spores which imbed into the nasal *mucosa*; subsequently, as a result of enzymatic activity, they can penetrate into the subcutaneous area of the face as well as the nasal cavity and sinuses. Swelling inside the nasal cavity is usually localised to the lower turbinate and nasal *mucosa*. More fulminant progression has been reported in immunocompromised hosts, with invasion into the blood vessels; however, in otherwise healthy patients, the infection is non-fatal and localised to the subcutaneous and mucocutaneous tissues.

Basidiobolus ranarum is a filamentous fungus with worldwide distribution. The fungus was first isolated by Eidam in 1886. It can saprophytically live in the intestines of mainly cold-blooded vertebrates and on decaying fruits and soil. The fungus prefers glucose as a carbon source and grows rapidly at room temperature. *Basidiobolus ranarum* is also known as a cause of subcutaneous zygomycosis, usually causing chronic inflammatory or granulomatous infections on a host's limbs. Granulomatous disease generally restricted to the subcutaneous tissue of the limbs, chest, back or buttocks, primarily occuring in children with male predominance . Subcutaneous zygomycosis caused by *B. ranarum* is a rare disease and predominantly affects children and males.

Cutaneous Zygomycosis (Mucormycosis, Phycomycosis)

Zygomycosis is the term for infection caused by fungi in the class Zygomycetes. There are six fungal genera that cause disease in humans: *Rhizopus*, *Cunninghamella*, *Mucor*, *Rhizomucor*, *Saksenea*, and *Absidia*.[72] These fungi are found in soil, decaying food, and other organic matter. Although infections may follow ingestion or inhalation of spores, contamination of wounds with conidia from environmental sources or direct inoculation into skin is the cause of primary cutaneous zygomycosis, which is seen predominantly in premature infants, as well as those who are immunocompromised from immunosuppressive drugs or underlying disease.

Primary cutaneous infection generally occurs due to direct implantation of fungal elements following major or minor skin trauma, such as skin abrasion, or tattoo, or in hospital following surgery, IV-line placement, or contaminated wound dressing. Secondary cutaneous involvement follows haematogenous dissemination.

Mucormycosis

Mucormycosis (sometimes called zygomycosis) is a serious but rare fungal infection caused by a group of molds called mucormycetes. These fungi live throughout the environment. They live in soil and in decaying organic matter, such as leaves, compost piles, or rotten wood.[1]

People get mucormycosis by coming in contact with the fungal spores in the environment. For example, infections involving the lung or sinus can occur after someone breathes in spores. These forms of mucormycosis usually occur in people who have health problems or take medicines that lower the body's ability to fight germs and sickness.

Types of mucormycosis

- **Rhinocerebral (sinus and brain) mucormycosis** is an infection in the sinuses that can spread to the brain. This is most common in people with uncontrolled diabetes and in people who have had a kidney transplant.
- **Pulmonary (lung) mucormycosis** is the most common type of mucormycosis in people with cancer and in people who have had an organ transplant or a stem cell transplant.
- **Gastrointestinal mucormycosis** is more common among young children than adults. Premature and low-birth-weight infants less than 1 month of age are at risk if they have had antibiotics, surgery, or medications that lower the body's ability to fight germs and sickness.
- **Cutaneous (skin) mucormycosis** occurs after the fungi enter the body through a break in the skin. This type of infection might occur after a burn, scrape, cut, surgery, or other types of skin trauma. This is the most common form of mucormycosis among people who do not have weakened immune systems.
- **Disseminated mucormycosis** occurs when the infection spreads through the bloodstream to affect another part of the body. The infection most commonly affects the brain, but also can affect other organs such as the spleen, heart, and skin.

Symptoms and signs

In the primary cutaneous form, the lesions are usually painful and necrotic, with black eschar, accompanied by a fever. Patients will usually present with a history of poorly controlled diabetes or malignancy. Myocutaneous infections may lead to amputation. Pulmonary tract infections seen with lung transplant patients, who are at high risk for fatal invasive mycoses. Rhinocerebral infection is characterized by paranasal swelling with necrotic tissues. Patient may have hemorrhagic exudates (tissue fluid from lesions tinged with blood) from the nose and eyes as the fungi penetrate through blood vessels and other anatomical structures.

Mucormycosis presents itself as either a respiratory or a skin infection. Signs of a related sinus or respiratory infection may include:

- cough
- fever
- headache
- nasal congestion
- sinus pain

With a skin infection, mucormycosis can develop within any part of your body. It may initially occur at the site of skin trauma, but it can quickly spread to another area. Be on the lookout for symptoms such as:

- blackened skin tissue
- blisters
- fever
- redness
- swelling
- tenderness
- ulcers

Basidiomycetes

They exist as saprobes and parasites of plants. Hyphae are dikaryotic and can often be distinguished by the presence of clamp connections over the septa. Sexual reproduction is by the formation of exogenous basidiospores, typically four, on a basidium. Occasional species produce conidia but most are sterile.

Genera of medical importance include:

1. Teleomorph of *Cryptococcus neoformans*, which is *Filobasidiella neoformans*

2. Agents of basidiomycosis such as Coprinus and Schizophyllium

3. Mushroom poisoning by Aminita, Lepiota, Coprinus and Psilocybe etc.

Cryptococcus neoformans

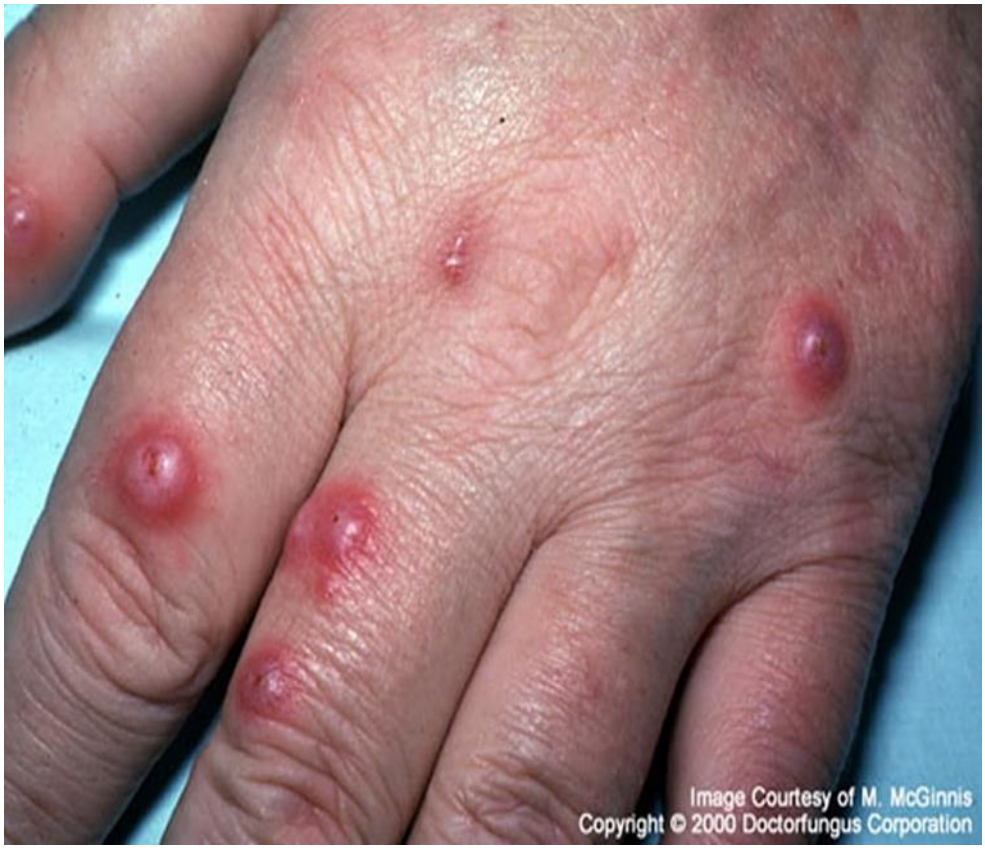
Cryptococcus neoformans (abbreviated *C. neoformans*) is a fungus that lives in the environment throughout the world. People can become infected with *C. neoformans* after breathing in the microscopic fungus, although most people who are exposed to the fungus never get sick from it.Infection with the fungus *Cryptococcus* (either *C. neoformans* or *C. gattii*) is called cryptococcosis. Cryptococcosis usually affects the lungs or the central nervous system (the brain and spinal cord), but it can also affect other parts of the body. Brain infections due to the fungus *Cryptococcus* are called cryptococcal meningitis.*C. neoformans* infections are rare in people who are otherwise healthy. Most cases of *C. neoformans* infection occur in people who have weakened immune systems, particularly those who have advanced HIV/AIDS.

Lungs

Many patients with cryptococcal pulmonary infection are asymptomatic. Those with pneumonia usually have cough and other nonspecific respiratory symptoms. However, AIDS-associated cryptococcal pulmonary infection may manifest as severe, progressive pneumonia with acute dyspnea and an x-ray pattern suggesting *Pneumocystis* infection.

Skin

Dermatologic spread can manifest as pustular, papular, nodular, or ulcerated lesions, which sometimes resemble acne, molluscum contagiosum, or basal cell carcinoma.



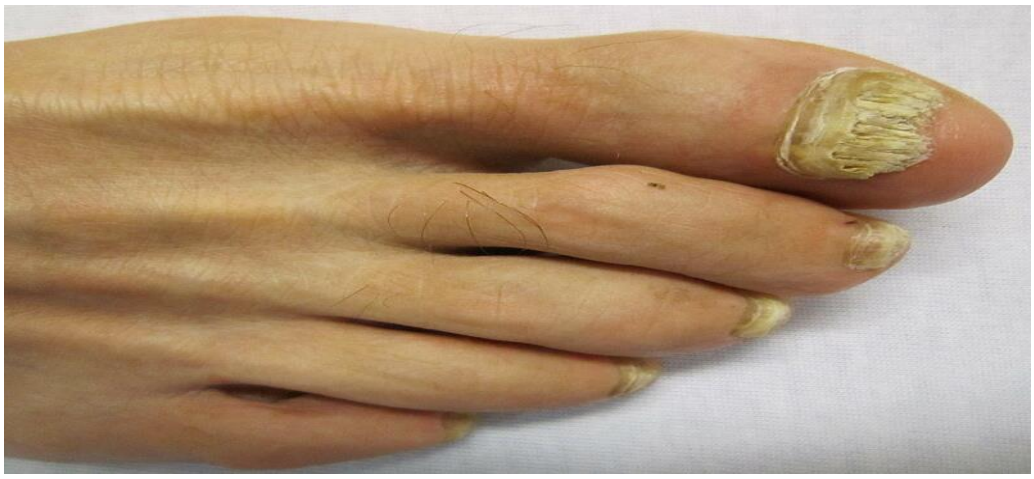
Basidiomycosis such as Coprinus and Schizophyllium

The basidiomycosis, fungal infections provoked by basidiomycetes or agaric fungi have been recorded at growing frequencies in the medical literature, especially after the advent of AIDS in 1991. The basidiospores of these fungi, scattered in the atmosphere and transported by winds or air currents, reach the maxillary sinuses through the nasal route, most of the times causing signs and symptoms of chronic sinusitis. Basidiomycetes have also been isolated from sputum, especially Schizophyllum commune. Lesions of the buccal mucosa, brain abscesses, onychomycosis and endocarditis have been described, with a growing interest in this type of deep mycosis on the part of mycologists and infectologists. The present paper reports descriptions of mycetism as well as infectious processes caused by basidiomycetes, such as Schizophyllum commune, Ustilago maydis (= Ustilago zeae) and Coprinus cinereus.

Onychomycosis

Onychomycosis is a fungal infection of the nail unit. When onychomycosis s caused by dermatophytes, it is called tinea unguium. The term onychomycosis encompasses not only the dermatophytes but the yeasts and saprophytic molds infections as well.Onychomycosis is a fungal infection of the nails that causes discoloration, thickening, and separation from the nail bed. Onychomycosis occurs in 10% of the general population, 20% of persons older than 60 years, and 50% of those

older than 70 years. It is caused by a variety of organisms, but most cases are caused by dermatophytes



Ascomycetes

They exist as saprophytes and parasites of plants. Hyphae are septate with simple septal pores. Asexual reproduction is by conidia. Sexual reproduction is by the formation of endogenous ascospores, typically eight, in an ascus.

Medically important genera include the:

1. Teleomorphs of known pathogenic fungi e.g. Arthroderma (of Trichophyton and Microsporum), Ajellomyces dermatitidis (of Blastomyces dermatitidis), Pseudallescheria boydii (of Scedosporium apiospermum)

2. Agents of mycetoma, like Leptosphaeria

3. Agents of black piedra, like Piedraia hortae.

Pseudallescheria Boydii

Pseudallescheria boydii (anamorph *Scedosporium apiospermum*) has a worldwide distribution in soil and contaminated water. This fungus is also known as *Monosporium apiospermum* or *Scedosporium apiospermum* when it is in the asexual state.

Infection

Pseudallescheria boydii is the species responsible for human scedosporiosis, a fungal infection with a high mortality rate and which is difficult to treat. Usually found in stagnant and contaminated water, it is thought to be responsible for infection in immunocompromised and immunocompetent individuals. Infections arising therefrom can be both

localized and disseminated. It was reportedthat solid organ transplant and hematopoietic stem cell transplant patients are a significant proportion of those at risk of *Scedosporium* mycoses.Human infection takes one of two forms. One is mycetoma, a chronic subcutaneous disease (99% of infections), and the other is pseudoarthropathy, which includes all other forms of disease commonly found in the central nervous system, lungs, joints, and bones.

Diagnosis

Pseudallescheria boydii is a ubiquitous ascomycetous fungus that causes a wide array of human infections that can affect practically all the organs of the body . These infections have been known for a long time, but in recent years, a marked increase in severe invasive infections has been noticed, mainly in immunocompromised hosts. The treatment of these infections has not yet been resolved, and the mortality rate is very high. Recently, it has been demonstrated that high genetic variation exists within this species. We have performed a morphological and molecular study involving numerous strains of clinical or environmental origins and from different countries.

Treatment

One of the most typical features of this species, which is very rare in other pathogenic fungi, is its ability to develop sexual structures on routine culture media. The presence of spherical ascomata (cleistothecia) and fusiform or ellipsoidal ascospores allows easy identification of this species and its differentiation from the other species of *Scedosporium*, *Scedosporium prolificans*, whose sexual state still remains unknown. In mycetoma-type infections, diagnosis requires a convergence of symptoms such as swelling, sinus drainage, and grain discharge. In addition, *P. boydii* grains and hyphae should be stained with H&E, periodic acid-Schiff stain, histogram or Grocott's methenamine silver stain, cultured and examined microscopically.

Scedosporiosis

Scedosporiosis is the general name for any mycosis - i.e., fungal infection - caused by a fungus from the genus *Scedosporium*. Current population-based studies suggest *Scedosporium prolificans* (also known and recently more commonly referred to as *Lomentospora prolificans*) and *Scedosporium apiospermum* to be among the most common infecting agents from the genus.

Localized mycosis

Localized scedosporiosis can occur in a vast range of internal organs and in joints and limbs. It can commonly be found on the surface of the skin in a form of white and yellow papules. Among the other most common manifestations would be mycetoma, specifically, eumycetoma (a mycetoma caused by a fungus), affecting subcutaneous tissue, joints and even muscles and bones, although foot or leg is a common location of such an infection.

A typical cause could be an open wound or surgery and both immunocompetent and immunocompromised patients can develop the infection. **Eumycetoma** grows in a granular fashion, is usually painless at first and grows steadily, causing complications and even disability if left untreated. **Osteomyelitis**, particularly, sternal and lower rib bone infection, caused by *S. apiospermum* was reported in a successfully cured lung transplant patient in 2016. Scedosporal eye infection, specifically, keratitis, arises usually after an injury of the cornea, both *S. apiospermum* and *S. prolificans* are known to be able to cause it. It presents itself in a form of painful lesions within the retina accompanied by symptoms like photophobia and blurred vision.

Disseminated mycosis

Severely immunocompromised patients, patients on immunosuppressive therapy, as well as those suffering from cancers including leukemia, have a risk of developing an infection that would constitute a spread of the extant localized infection throughout the organism. Additional and highly significant risk factor is neutropenia, found especially in leukemia patients.

Disseminated infections present a significant challenge to manage and result in consistently high mortality. Some studies suggest overall mortality rates for disseminated infections to be within 58-75%. A review of 25 cases published in 2006 reported mortality rates of disseminated infections with *S. apiospermum* and *S. prolificans* to be 70 and 100%, respectively. A 2002 review of 72 cases of disseminated phaeohyphomycosis reported poor outcomes for the antifungal treatment using amphotericin B with the overall mortality being 79% among all patients, with a likewise 100% mortality for infections by *S. prolificans*. The culmination of disseminated scedosporiosis would be a highly fatal infection (>90% mortality rate of the central nervous system. This development is possible in both immunocompromised and

immunodeficient individuals. Studies report the former group develops the condition after a near-drowning experience in water contaminated with the pathogen's conidia. An extreme manifestation of this highly lethal case of scedosporiosis would be a brain abscess.

Mycetoma

Mycetoma is a progressive chronic granulomatous infection of the skin and subcutaneous tissue. The disease can occur due to true fungi, referred to as eumycetoma, or by bacteria, referred to as actinomycetoma. Eumycetoma is, therefore, a deep fungal infection of the skin and subcutaneous tissue caused by filamentous fungi. Morphologically and histologically, eumycetoma is characterized by deep granulomatous inflammation and the formation of grains which lead to the destruction of deep tissue, muscle, bone, joints, and tendons.

Mycetoma is a WHO-recognized neglected tropical disease with a significant disease burden. It primarily affects those in tropical and subtropical climates who are in direct contact with soil. The most common site of infection is the foot, followed by hands. Less frequently, other areas may be involved.

Diagnosis

The most common organism causing a eumycetoma is *Madurella mycteomatis*. These organisms are present in soil and are implanted in the skin after minor trauma. Slow progressive subcutaneous swelling then develops, followed by multiple nodules that evolve into suppurative lesions with multiple draining sinus tracts. The sinuses then discharge colonies of causative organisms.

Pathology

Initially, a nodule, or abscess over months to years progresses to chronic infection with the formation of granulomatous nodules drained by sinuses connecting with the skin. Superimposed bacterial infection may result in larger open ulcers.These changes eventually lead to deformity. The changes on imaging are remarkable with the bones being destroyed and remodeled.

Treatment

The treatment course is often protracted, challenging, and consists of systemic antifungal therapy combined with surgical procedures. Severe tissue destruction is an undesired consequence of neglected infections. Eumycetomas are chronic and deep skin infections that carry a medical significance and pose a treatment challenge. In endemic areas,

eumycetomas lead to socio-economic consequences involving affected patients, their families.

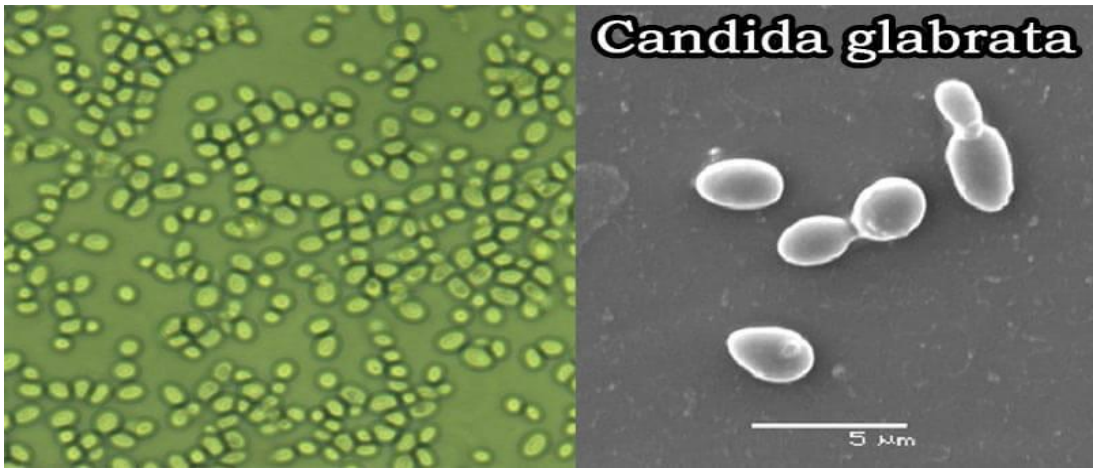
Deuteromycetes

Deuteromycetes are also known as Fungi Imperfecti because of absence of sexually reproducing forms (teleomorph or perfect stage). As their teleomorph continue to be discovered, they would be classified among the previous categories, until then this remains an artificial and heterogeneous group.

There are three classes of Fungi Imperfecti.

1. Blastomycetes: These include asexual budding forms of Cryptococcus, Candida, Torulopsis Candida (Torulopsis) glabrata and Rhodotorula. Depending on the presence of melanin in their cell walls, they may be non-dematiaceous or

dematiaceous.

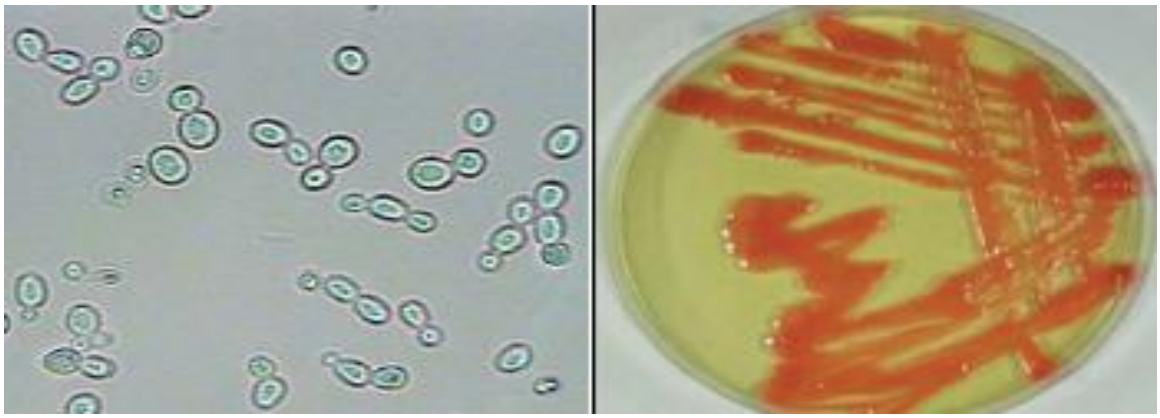


Rhodotorula

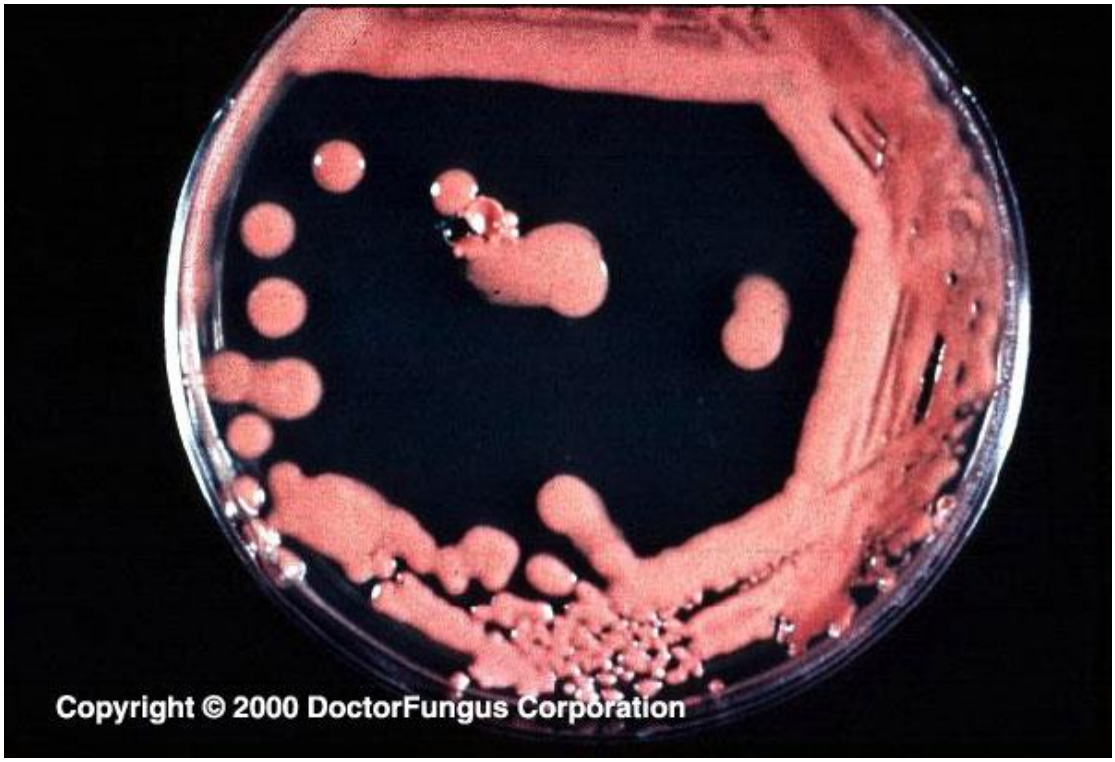
Rhodotorula is a common environmental yeast that is found in air, soil, lakes, ocean water, milk, and fruit juice. The genus Rhodotorula includes eight species, of which *R. mucilaginosa*, *R. glutinis*, and *R. minuta* are known to cause disease in humans. *Rhodotorula mucilaginosa* is a common airborne contaminant of skin, lungs, urine and faeces. *R. mucilaginosa* is a known cause of fungal peritonitis in patients on continuous ambulatory peritoneal dialysis (CAPD). This is usually due to saprophytic colonisation of catheters or dialysis machinery and removal of the source of contamination usually leads to clearing of the symptoms.

Rhodotorula produces pink to red colonies and blastoconidia that are unicellular lacking pseudohyphae and hyphae. *Rhodotorula* species have

emerged as opportunistic pathogens with the ability to colonise and infect susceptible patients. Recent studies have demonstrated that the incidence of fungemia caused by *Rhodotorula* was between 0.5% and 2.3% in the USA and Europe. Most cases of infection with *Rhodotorula* fungemia are associated with central catheters in patients with haematologic malignancies.



Microscopic image and streak plate of Rhodotorula glutinis



Fungemia

Fungemia is the presence of fungi or yeasts in the blood. The most common type, also known as candidemia, or systemic candidiasis, is caused by *Candida* species; candidemia is also among the most common bloodstream infections of any kind. Infections by other fungi,

including *Saccharomyces*, *Aspergillus* and *Cryptococcus*, are also called fungemia. It is most commonly seen in immunosuppressed or immunocompromised patients with sever neutropenia, cancer patients, or in patients with intravenous catheters. It has been suggested that otherwise immunocompetent patients taking infliximab may also be at a higher risk for fungemia. Symptoms can range from mild to extreme—often described as extreme flu-like symptoms. Many symptoms may be associated with fungemia, including pain, acute confusion, chronic fatigue, and infections. Skin infections can include persistent or non-healing wounds and lesions, sweating, itching, and unusual discharge or drainage.

Invasive candidiasis

is an infection caused by a yeast (a type of fungus) called *Candida*. Unlike *Candida* infections in the mouth and throat (also called "thrush") or vaginal "yeast infections," which are localized to one part of the body, invasive candidiasis is a serious infection that can affect the blood, heart, brain, eyes, bones, or other parts of the body. *Candida* normally lives inside the body (in places such as the mouth, throat, gut, and vagina) and on the skin without causing any problems. However, in certain patients who are at risk, *Candida* can enter the bloodstream or internal organs and cause an infection. A *Candida* bloodstream infection, also called candidemia, is the most common form of invasive candidiasis. In the United States, candidemia is one of the most common causes of bloodstream infections in hospitalized patients, and it often results in long hospital stays and death. It is also responsible for high medical costs.

Systemic candidiasis

Candidiasis is a fungal infection due to any type of *Candida* (a type of yeast). When it affects the mouth, in some countries it is commonly called thrush. Signs and symptoms include white patches on the tongue or other areas of the mouth and throat. Other symptoms may include soreness and problems swallowing. When it affects the vagina, it may be referred to as a yeast infection or thrush. Signs and symptoms include genital itching, burning, and sometimes a white "cottage cheese-like" discharge from the vagina. Yeast infections of the penis are less common and typically present with an itchy rash. Very rarely, yeast infections may become invasive, spreading to other parts of the body. This may result in fevers along with other symptoms depending on the parts involved.

2. Hyphomycetes: A class of mycelial moulds which reproduce asexually by conidia on hyphae. Hyphae are septate. This class contains the majority of medically important fungi. Dematiaceous hyphomycetes are those conidial fungi that produce dark brown, green-black, or black colonies and are the causative agents of phaeohyphomycosis. Hyaline hyphomycetes include those conidial fungi, which are not darkly pigmented; colonies may be colourless or brightly coloured. These include the agents of hyalohyphomycosis, aspergillosis, dermatophytosis and the dimorphic pathogens, like Histoplasma capsulatum.

3. Coelomycetes: These produce acervuli, which are tightly bound mats of hyphae on which conidia are produced.

Dematiaceous fungi

Dematiaceous fungi are usually defined as having melanin or melanin-like pigment in the wall of their hyphae and/or spores . Though they represent a very heterogeneous group of fungi, the distinguishing characteristic common to all these various species is the presence of melanin in their cell walls, which imparts the dark color to their conidia or spores and hyphae. The colonies are typically brown to black in color as well. As the number of patients immunocompromised from diseases and medical therapy increases, additional species are being reported as causes of human disease, expanding an already long list of potential pathogens. They are widely distributed in nature found in soil or associated with plants and distributed worldwide.

The genera most frequently involved in human infections include *Bipolaris*, *Curvularia*, *Exserohilum*, and *Alternaria* . Many of the fungi are common allergens growing indoors. Besides causing hypersensitivity reactions in susceptible individuals that sometimes lead to acute exacerbation of asthma, they are also important opportunistic pathogens in immunocompromised patients. Although many of the cutaneous, subcutaneous, and corneal infections associated with dematiaceous fungi have been reported to be common in tropical and subtropical countries

The spectrum of diseases associated with dematiaceous fungi ranges from with high superficial skin and soft tissue infections to disseminated sepsis mortality. The most common infections are phaeohyphomycosis , chromoblastomycosis , and eumycetoma. The major infections caused by dematiaceous human pathogens are classified into two groups of disease: chromoblastomycosis and pheohyphomycosis . Chromoblastomycosis is a chronic infection of cutaneous and subcutaneous tissues.

Dark-pigmented microscopic fungi are worldwide-spread soil saprophytes often found on plant remnants. In chromoblastomycosis,

infectious particles of these fungi enter the human body at the site of injury and may cause chronic infection, mainly in tropical and subtropical endemic areas. Chromoblastomycosis is almost exclusively diagnosed in patients with fully functioning immunity, with typically muriform (sclerotic bodies) cells present in infected tissue distinguishing this condition from phaeohyphomycosis.

Definition genera

- Heterogeneous molds characterized by dark pigmentation of hyphae Hundreds of species known to cause disease in humans.
- **Phaeohyphomycosis:** invasion of tissue by pigmented hyphae
- **Chromoblastomycosis:** chronic subcutaneous infection characterized by pigmented round structures termed copper pennies
- **Mycetoma:** subcutaneous collection of pigmented hyphae that expands within the tissue (tumor-like growth)

Clinical features

- Phaeohyphomycotic cyst: well circumscribed subcutaneous nodule with pigmented hyphae
- Phaeohyphomycosis: pigmented hyphae invading within tissue (typically skin, lung, brain)
- Chromoblastomycosis: psoriasis-like chronic skin inflammation and hyperkeratinization with pigmented round sclerotic bodies (copper pennies) in tissue; no hyphae present
- Mycetoma: a focal subcutaneous collection of pigmented hyphae (fungus ball)
- All lesions are characterized by pyogranulomatous inflammation

Treatment

- No standardized treatment; however, itraconazole, voriconazole and posaconazole have been used successfully
- Infection with chromoblastomycosis can be treated with combination itraconazole and terbinafine but may require surgery, chemotherapy or thermotherapy Treatment often occurs over an extended period of time; months to years

Microscopic (histologic) description

- Phaeohyphomycosis: pigmented septate hyphae with occasional globose swellings
    - Black yeasts like *Exophiala dermatitidis* form pigmented pseudohyphae in tissue Chromoblastomycosis: dark sclerotic bodies with thick walled septations

- Mycetoma: black mycotic granules or grains surrounded by dense extracellular matrix

Chromoblastomycosis

Chromoblastomycosis is a chronic fungal infection in which there are raised crusted lesions affecting the skin and subcutaneous tissue. It usually affects the limbs.

Chromoblastomycosis may be due to several fungi found in soil, wood and decaying plant material. It is usually a threat to male adults, globally considered an occupational disease affecting farmers, gardeners, loggers, agricultural commodity traders and other workers exposed to contaminated soil or handling materials of plant origin.

The organism is inoculated into the skin by a minor injury, for example, a cut with a splinter when barefoot. It is exceedingly rare in New Zealand, but relatively common in warmer areas such as the Pacific Islands.

The most common organisms are:

- *Phialophora verrucosa*
- *Fonsecaea pedrosi*
- *Fonsecaea compacta*
- *Cladophialophora carrionii*

Rhinocladiella aquaspersa (*Ramichloridium cerophilum*)

Clinical features of chromoblastomycosis

Chromoblastomycosis generally presents as a single lesion on an exposed site such as the foot or hand.

- It starts as a small firm red or grey bump.
- It grows very slowly: only about 2mm per year.
- Eventually, a warty dry nodule or plaque develops.
- There may be at least partial clearing with scarring in the centre of the lesion.
- The affected limb can enlarge generally (elephantiasis).
- New lesions may develop in time as satellites around the first one or the infection may be scratched into a new site.
- It may cause no discomfort but is frequently very itchy.

- Rarely, squamous cell carcinoma (SCC) develops within longstanding chromoblastomycosis.

Chromoblastomycosis diagnosed

Histopathology of chromoblastomycosis may show typical thick-walled dark-brown 'sclerotic' cells on skin biopsy confirming the presence of a dematiaceous fungus. It is dark coloured due to melanin in the walls of the organism.

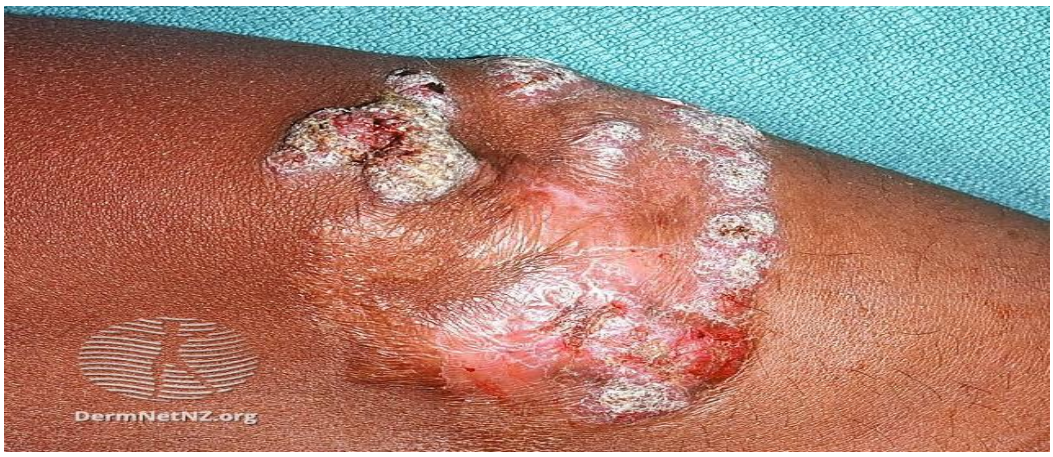
Culture in Sabouraud medium with antibiotics at 25–30 degrees celsius grows olive-green to black fungal colonies after one or two weeks. Naming the responsible fungus can be difficult. Phaeohyphomycosis is the name given to an infection caused by dematiaceous fung

Treatment for chromoblastomycosis

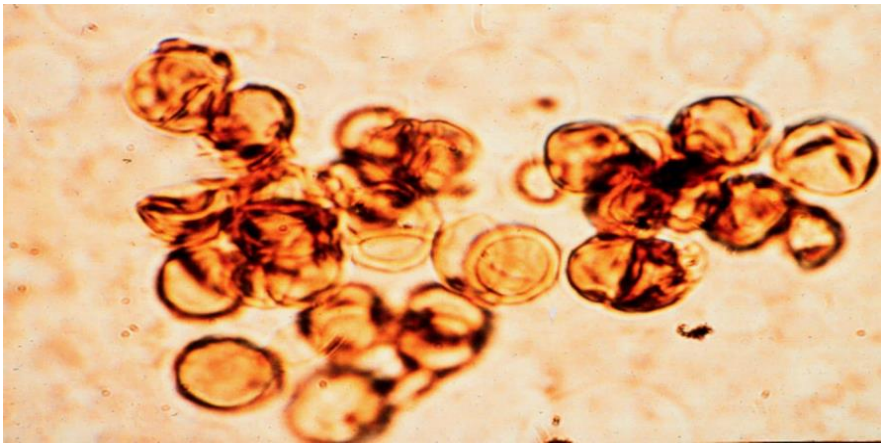
Rarely, chromoblastomycosis resolves spontaneously leaving a scar.

Treatment is difficult and prolonged. It may include:

- Itraconazole, posaconazole or voriconazole, possibly in combination with terbinafine
- Flucytosine
- Thiabendazole
- Local heat
- Cryotherapy
- Surgery to remove the affected tissue completely.



Macro image of chromoblastomycosis



Sclerotic cells on a potassium hydroxide preparation.

Pheohyphomycosis

Phaeohyphomycosis refers to a group of mycoses (fungal infections) that are dematiaceous, which means they are pigmented. The pigment is due to their ability to deposit melanin in their cell walls

Pheohyphomycosis is a primary or opportunistic infection that ranges from the superficial tissue to deep organs. Phaeohyphomycoses have different clinical manifestations, e.g. subcutaneous phaeohyphomycosis. The initial subcutaneous cyst from this infection can ulcerate locally and/or become systemic and spread rapidly to renal, pulmonary and cerebral systems in an immunocompromised host.
Phaeohyphomycosis is caused by fungi of genus

- *Alternaria,*
- *Bipolaris*
- *Cladophialophora*
- *Cladosporium*
- *Exophiala*
- *Fonsecaea*
- *Phialophora*

They have a wide range of presentations from subcutaneous nodules or abscesses, invasive sinusitis, keratitis, mycotic arthritis, brain abscess to disseminated infections. Subcutaneous cyst-like lesions, so-called phaeomycotic cysts, are characterized by central necrosis, fibrin and a neutrophilic infiltrate surrounded by epithelioid histiocytes and fibrosis

The etiologic agents are present in host tissues with melanized yeast-like cells, pseudohyphae-like elements, hyphae or any combination of these forms.

Histology of Phaeohyphomycosis

1-Scanning power view of phaeohyphomycosis shows a deeply extending granulomatous pattern (Figure 1) which may show areas of necrosis (Figure 2).

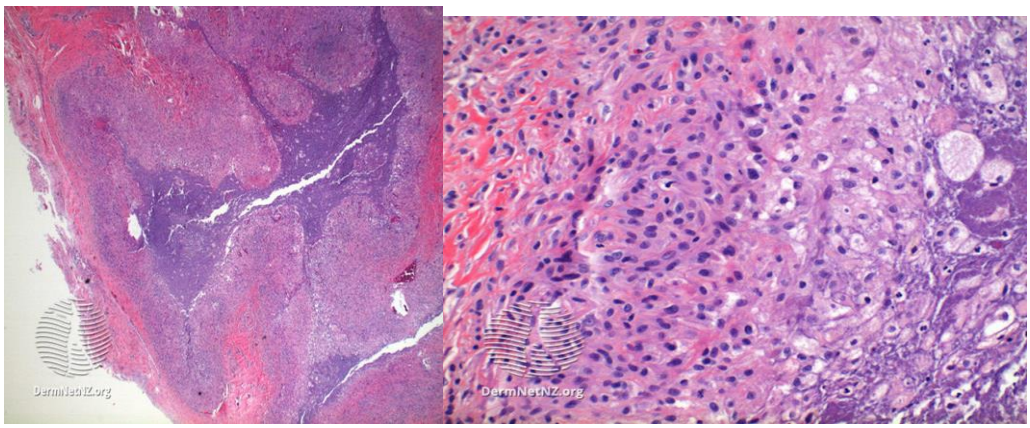
2- Centrally an abscess or cystic nodule may form.

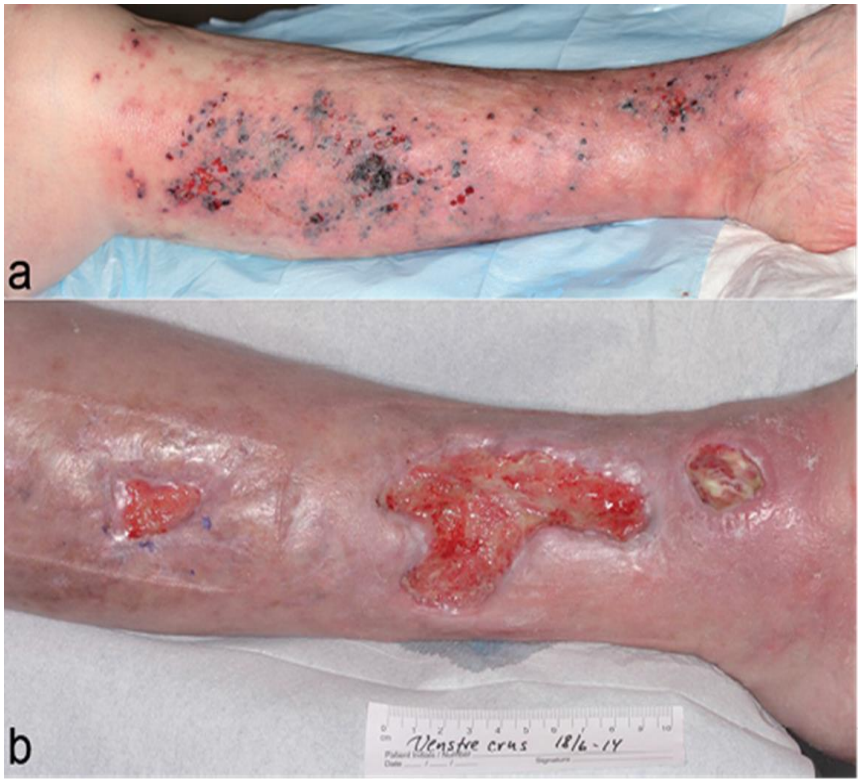
3- Frequently a foreign body such as a wood splinter can be seen.

4-The epidermis commonly shows pseudoepitheliomatous hyperplasia.

5-The inflammatory infiltrate is comprised of histiocytes with multinucleated giant cells, and numerous neutrophils.

6-At high power branching septate pigmented fungal hyphae can be seen





Initial presentation of phaeohyphomycosis of the lower left leg. (b) The same patient 7 months after initiation of itraconazole therapy**.**

Diagnosis of chromoblastomycosis and phaeohyphomycosis

Chromoblastomycosis and phaeohyphomycosis are less common fungal infections caused by dark-pigmented fungi. Virulence factors play an important role in the pathogenesis of these diseases. One of these factors, muriform cells, are the most important element for differential diagnosis of chromoblastomycosis and phaeohyphomycosis using clinical samples and various staining techniques. Accurate identification of pathogens causing chromoblastomycosis and phaeohyphomycosis is very important for correct and early antifungal therapy.

Therefore, species identification of the etiological agent should be confirmed by sequencing of DNA from the culture. Early diagnosis may be crucial, especially in case of invasive forms of these infections. The diagnosis may be guided by some immunohistochemistry methods and DNA detection using polymerase chain reaction directly from clinical samples seems to be useful for identification of pathogens causing these severe and life-threatening infections.

Pathogenesis of fungal diseases (Mycoses):

Fungal infection, also known as **mycosis**, is a disease caused by fungi. Different types are traditionally divided according to the part of the body affected; superficial, subcutaneous, and systemic. Superficial fungal infections include common tinea of the skin, such as tinea of the body, groin, hands, feet and beard, and yeast infections such as pityriasis versicolor.

Subcutaneous types include eumycetoma and chromoblastomycosis, which generally affect tissues in and beneath the skin.Systemic fungal infections are more serious and include cryptococcosis, histoplasmosis, pneumocystis pneumonia, aspergillosis and mucormycosis. Signs and symptoms range widely. There is usually a rash with superficial infection. Fungal infection within the skin or under the skin may present with a lump and skin changes. Pneumonia-like symptoms or meningitis may occur with a deeper or systemic infection.

Fungi are everywhere, but only some cause disease. Fungal infection occurs after spores are either breathed in, come into contact with skin or enter the body through the skin such as via a cut, wound or injection.[3] It is more likely to occur in people with a weak immune system.[14] This includes people with illnesses such as HIV/AIDS, and people taking medicines such as steroids or cancer treatments. Fungi that cause infections in people include yeasts, molds and fungi that are able to exist as both a mold and yeast. The yeast *Candida albicans* can live in people without producing symptoms, and is able to cause both superficial mild candidiasis in healthy people, such as oral thrush or vaginal yeast infection, and severe systemic candidiasis in those who cannot fight infection themselves.

Fungal infections have a world-wide distribution and are common, affecting more than one billion people every year. An estimated 1.7 million deaths from fungal disease were reported in 2020. Several, including sporotrichosis, chromoblastomycosis and mycetoma are neglect ed. A wide range of fungal infections occur in other animals, and some can be transmitted from animals to people.

Most fungi are saprophytic or parasitic to plants and are adapted to their natural environment. Infection in humans is a chance event, occurring only when conditions are favourable. Except for few fungi such as the dimorphic fungi that cause systemic mycoses and dermatophytes, which

are primary pathogens, the rest are only opportunistic pathogens. Human body is a hostile environment and offers great resistance to fungal invasion.

Most fungi are saprophytic and their enzymatic pathways function more efficiently at the redox potential of non-living substrates than at the relatively more reduced state of living metabolizing tissue. Some fungi such as Candida and Malasezzia have adapted to human environment and exist as commensals. The complex interplay between fungal virulence factors and host defence factors will determine if a fungal infection will cause a disease. Infection depends on inoculum size and the general immunity of the host.

Fungal Pathogenicity (virulence factors):

• Ability to adhere to host cells by way of cell wall glycoproteins

• Production capsules allowing them to resist phagocytosis

• Production of a cytokine called GM-CSF by Candida albicans that suppress the production of complement.

• Ability to acquire iron from red blood cells as in Candida albicans

• Ability to damage host by secreting enzymes such as keratinase, elastase, collagenase

• Ability to resist killing by phagocytes as in dimorphic fungi

• Ability to secrete mycotoxins • Having a unique enzymatic capacity • Exhibiting thermal dimorphism

• Ability to block the cell-mediated immune defences of the host.

• Surface hydrophobicity.

A. Virulence Factors that Promote Fungal Colonization:

Virulence factors that promote fungal colonization of the host include:

1. contact and adherence to the host cells with cell wall adhesins and host cell receptors play a basic role in fungal virulence.
2. Invasion of the host cells:

Many factors help the infecting fungi to invade the host e.g.

- Production of conidia that are very small to pass the airway defenses e.g. arthroconodia of *coccidiodes immitis*.

- Production of enzymes that contribute to fungal invasion e.g. C. albicans produces acid proteases and phospholipases that aid in the penetration and damage of host cell membranes.
- Physiologic alteration: Factors such as body temperature, osmotic stress, oxidative stress, and certain human hormones activate a dimorphism-regulating histidine kinase enzyme in dimorphic molds, such as Histoplasma capsulatum, Blastomyces dermatitidis, and Coccidioides immitis, causing them to switch from their avirulent mold form to their virulent yeast form. It also triggers the yeast Candida albicans to switch from its yeast form to its more virulent hyphal form.

3. Competing for nutrients e.g. C. albicans is able to acquire iron from red blood cells.
4. Resistance of innate immune defenses such as phagocytosis and complement e.g.

- Some fungi produce capsules allowing them to resist phagocytic engulfment, such as the yeast Cryptococcus neoformans and the yeast form of Histoplasma capsulatum.
- Candida albicans stimulates the production of a cytokine called GM-CSF and this cytokine can suppress the production of complement by monocytes and macrophages. This may decrease the production of the opsonin C3b as well as the complement proteins that enhance chemotaxis of phagocytes.
- When candida is engulfed by macrophages, it starts producing the tubular germ tubes which penetrate the membrane of the macrophage thus causing its death.
- The yeast Cryptococcus neoformans inhibits the productions of the cytokines TNF-alpha and interleukin-12 (IL-12) while stimulating the production of Interleukin-10 (IL-10). TNF and IL-12 activate macrophages while IL-10 suppresses their activation. As a result, macrophages are not activated.
- Most pathogenic fungi can resist the effect of active oxygen radicals released during the respiratory burst of phagocytosis.

6. Evasion of adaptive immune defenses.

B. Virulence Factors that Damage the Host:

Damage of the host tissues is due to both the invading fungus and immune mediated mechanisms.

1. As fungi grow in the body, they can secrete enzymes to digest cells. These include proteases, phospholipases, and elastases. In response to both the fungus and to cell injury, cytokines are released this leads to an inflammatory response and cellular killing by phagocytes that causes further destruction of host tissues.

2. Some fungi as *coccidiodes immitis* can produce molecules that are structurally and antigenically similar to host molecules leading to autoimmune destruction of host tissues.

3. Many molds secrete mycotoxins, especially when growing on grains, nuts and beans. These toxins may cause a variety of effects in humans and animals if ingested including loss of muscle coordination, weight loss, and tremors. Some mycotoxins are mutagenic and carcinogenic.

NB: Unlike bacteria; no classic exotoxins production by fungi and no fungal cell wall components having endotoxin like activity. However mannan is known to circulate widely in the body.

Host defence factors:

• Physical barriers, such as skin and mucus membranes

• The fatty acid content of the skin

• The pH of the skin, mucosal surfaces and body fluids

• Epithelial cell turnover

• Normal flora •

Chemical barriers, such as secretions, serum factors •

Most fungi are mesophilic and cannot grow at 37o C.

• Natural Effector Cells (polymorphonuclear leucocytes) and the Professional Phagocytes (monocytes and macrophages).

Factors predisposing to fungal infections:

• Prolonged antibiotic therapy

• Underlying disease (HIV infection, cancer, diabetes, etc.)

• Age

• Surgical procedures

• Immunosuppressive drugs • Irradiation therapy

• Indwelling catheters

• Obesity

• Drug addiction

• Transplants

• Occupation

Immunity to fungal infections:

Mechanism of immunity to fungal infections can be innate or acquired. The non-specific immunity includes the physical barriers offered by skin and mucus membranes along with their secretions and normal flora. The pH, body temperature and serum factors along with phagocytic cells play an important part in providing non-specific immunity. Even though body mounts both humoral and cell mediated immunity, it is the latter that is the mainstay of host defence.

Cell mediated immunity:

Immunity is provided non-specifically be effector cells (polymorphonuclear leucocytes) and professional phagocytes (monocytes and macrophages) and specifically by T lymphocytes. The phagocytes are very important in defence against Candia, Aspergillus and Zygomycetes as is evidenced by their severity in granulomatous diseases, myeloperoxidase deficiency and cytotoxic chemotherapy. Expression of T-cell-mediated immunity to fungi includes:

• delayed-type hypersensitivity

• contact allergy

• chronic granulomatous reactions

Humoral immunity:

Even though antibodies are produced against many fungi, their role in protection is not very clear. However, antibodies help in clearing fungal pathogens through opsonisation, which is important against Candida and Cryptococcus. Another component of humoral immunity is the complement, which can act as opsonins and may even cause damage to their cells through complement activation. Antibodies are important to fungal serodiagnosis.

Hypersensitivity:

As a result of dermatophyte infection some fungus-free skin lesions of variable morphology occur elsewhere on the body, which are thought to result from hypersensitivity to the fungus. These reactions are called "id reaction". These reactions are also seen n Candida infections. An inflamed boggy lesion of the scalp called the kerion may result from a strong immune reaction to the dermatophyte. Granulomas due to intracellular fungi represent delayed hypersensivities. Many fungi are

significant allergens to humans, the allergens being spores, conidia, hyphae and other fungal products. On inhalation they may produce allergic pulmonary diseases such as allergic bronchopulmonary aspergillosis, farmer's lung, maple bark stripper's lung, bronchial asthma etc, which may be Type I or III hypersensitivity.

Diagnosis and Identification of Fungi

Diagnosis of fungal infections is based on:

(1) Clinical diagnosis:

Suspension of fungal infection requires awareness of possible exposure or predisposing risk factors. Detailed history and careful patient examination are usually required.

(2) Laboratory diagnosis:

Methods of laboratory diagnosis of fungal infections include:

I- Microscopic examination of patient samples.

II- Detection of fungal antigens in patient samples.

III- Culture and isolation of fungal pathogens.

IV- Indirect methods based on the host immune response.

I- Microscopic examination of patient samples:

Direct microscopic examination of clinical specimens is a crucial first-line procedure in detecting the presence of fungal elements and it is perhaps the most rapid, useful, and cost-effective means of diagnosing fungal infections. It serves to guide the laboratory in selecting the most appropriate means to culture the clinical material, as well as in interpreting the culture results.

Wet mounts and stained smears of patient samples or histopathological examination of tissue sections can be used.

A- Wet mounts: Include

- Potassium hydroxide (KOH) mounts:

KOH 10-20% breaks down the human cells and dissolves keratin of skin scrapings, hairs and nail clippings although the fungus is unaffected.

- India ink mounts of CSF sediment:

It is used to demonstrate the encapsulated yeast; *Cryptococcus neoformans* in C.S.F.

- Calcofluor white mounts:

It binds to the chitin in the fungal cell wall and fluorescence blue-white or green, thus providing a rapid and sensitive means of detecting fungi in clinical material.

- Lactophenol cotton blue mounts:

It is commonly used to detect mycelia and spores specially in slide culture technique.

B- Stained smears:

Different stains can be used e.g.

- Gram stain: most fungi are gram positive.
- Giemsa stain.

C- Histopathological examination:

- Wright's stain of thick blood or bone marrow smears to detect *Histoplasma capsulatmn*.
- Gomori methenamine silver stains fungal cells black in tissue sections.
- Periodic acid Schiff stains fungus bright red on green or blue background.
- Hematoxylin and eosin rarely used as they may not stain some fungal cells.

II- Detection of fungal antigens in patient samples:

Can be performed by many methods e.g.

- Latex agglutination as in Cryptococcus meningitis.
- ELISA.
- RIA.
- Direct immuonoflurescence.

III- Culture and isolation of fungal pathogens:

All methods of direct examination are less sensitive than culture, and negative results of direct examination of a clinical specimen never rule out a fungal infection**.**

Cultures are usually done on Sabouraud's dextrose agar medium, this is a traditional agar that encourages the growth of fungi and

discourages bacterial growth as it has low pH (5.6) and added antibiotics(chloramphenicol and gentamicin). cyclohexamide is added to prevent saprophytic fungi.

Specimens are inoculated in two sets; one is incubated at room temperature (25°c) and the other is incubated at body temperature (37°c) to reveal dimorphism. Fungi grow slowly so cultures are incubated for 1-2 weeks.

Identification of isolated organism is based on:

a- Macroscopic appearance: e.g. appearance of the mycelium, septation, branching, pigmentation, spore or conidia production.
b- Microscopic morphology: of the growing organisms.
c- Biochemical reactions: e.g. sugar assimilation and fermentation, nitrogen assimilation, detection of extra cellular enzyme production as urease, lipase, and catalase….etc.
d- Nucleic acid probes: have been developed for the most common fungi causing systemic mycoses.

Technique:
Ribosomal RNA is extracted from the culture and a labeled single stranded DNA probe is added. If the culture contains the target organism DNA probe hybridize with its complementary RNA and the complex can then be easily detected.

Advantages:

- The test requires minimal fungal growth (can be achieved in less than 5 days).
- It can be applied to yeast or mycelial form of fungi.

IV- Indirect methods based on the host immune response:

a- Skin tests: e.g. candidin test, histoplasmin test and skin tests for aspergillosis. These tests can give false positive and false negative results so they are not reliable for diagnosis. They are used only to evaluate immunity of the patient and to construct an exposure index in epidemiological studies.

b- Serologic tests:

1- Tests to detect specific serum antibodies:
Disadvantages:

Most conventional serologic tests designed to detect specific serum antibodies (as CFT and latex agglutination test) are ineffective because of the following:

1. Many patients who are at risk for fungal disease are not capable of mounting a specific antibody response to infection.

2. Determination of the presence of an acute infection typically requires a comparison of the type and quantity of antibody present in acute-phase and convalescent-phase serum samples that is not helpful during the acute presentation, when therapeutic interventions are being decided.
3. Cross-reactions among different species.
4. Presence of antibodies to common environmental or commensal fungi.
5. Lack of standardization of antigens.

Advantages:

These tests are semi quantitative so when applied serially assess the evolution of the disease.

2- Tests to detect fungal antigens:

Detection of fungal cell wall and cytoplasmic antigens in serum or other body fluids by immunologic or biochemical methods represents the most direct means of providing a serologic diagnosis of invasive fungal infections. E.g.

- Detection of the polysaccharide antigens of *C. neoformans* and *H. capsulatum*.
- galactomannan (GM) immunoassay which is a cell-wall polysaccharide specific to *Aspergillus* species.
- (1→3)-β-D-glucan (BG) assay which is a cell-wall constituent of many pathogenic fungi. This assay is used for diagnosis of invasive disease caused by *Aspergillus* and *Candida* species and other opportunistic fungi.

SPECIAL MYCOLOGY

Fungal Diseases:

Fungal diseases may be in the form of fungal allergy, fungal infections or mycotoxicosis.

I- Fungal Allergies:

1- Allergic reactions due to inhalation of fungal spores:

They are common since moulds grow on any damp organic surface and spores are constantly suspended in the air. It generally occurs in individuals with other allergies. E.g. Fungal allergy reported with *Aspergillus*.

2- Id reaction (dermatophytid reaction):

It is a cutaneous lesion commonly seen in the fingers from which no organism can be recovered and it does not respond to topical therapy it disappears spontaneously when the primary lesion is treated. It occurs as a hypersensitivity reaction to the circulating dermatophyte antigens.

3- Ocular histoplasmosis:

It is not true retinal infection. It occurs as a hypersensitivity reaction to infection with *histoplasma capsulatum*.

II- Fungal Poisonings:

Mycotoxicosis is due to ingestion of mould-contaminated food which is primarily an animal problem except for aflatoxin (produced in moldy peanuts); which is a known carcinogen. Also, Mushroom poisoning varies from mild gastrointestinal disturbances or mild neurological disturbances to very severe poisoning; which may be fatal.

III- Fungal Infections:

They are called mycoses (singular: mycosis). It ranges from superficial to overwhelming infections; rapidly fatal in the immuno-compromised host. The incidence is obviously increasing due to the increased use of antibiotics, corticosteroid and cytotoxic drugs.

Classification of Mycoses:

1- Classification based on the tissue involvement:

Mycoses are classified as superficial, cutaneous, subcutaneous, and systemic (deep) infections depending on the type and degree of tissue involvement and the host response to the pathogen.

2- Classification based on the route of acquisition:

Infecting fungi may be either exogenous or endogenous. Routes of entry for exogenous fungi include airborne, cutaneous and percutaneous. Endogenous infection involves colonization by a member of the normal flora or reactivation of a previous infection.

3- Classification based on the virulence:

Primary pathogens can establish infections in normal hosts. Opportunistic pathogens cause disease in individuals with compromised defense mechanisms.

Fungal Diseases (Mycoses):

Mycoses can be conveniently studied as:

1. Superficial mycoses

I. Superficial phaeohyphomycosis

II. Tinea versicolor

III. Black piedra

IV. White piedra

2. Cutaneous mycoses

I. Dermatophytosis

II. Dermatomycosis

3. Subcutaneous mycoses

I. Chromoblastomycosis

II. Rhinosporidiasis

III. Mycetoma

IV. Sporotrichosis

V. Subcutaneous phaeohyphomycosis

VI. Lobomycosis

4. Systemic (deep) mycoses

I. Blastomycosis

II. Histoplasmosis

III. Coccidioidomycosis

IV. Paracoccidioidomycosis

5. Opportunistic mycoses

I. Candidiasis

II. Cryptococcosis

III. Aspergillosis

6. Other mycoses

I. Otomycosis

II. Occulomycosis

7. Fungal allergies

8. Mycetism and mycotoxicosis

I- Superficial Mycoses

General Characteristics:

- Affect outermost layer of skin and hair.
- Generally cause no cellular response to the infection.
- It has primarily cosmetic symptoms.

It includes pityriasis versicolor, tinea nigra, and white and black piedra.

A- Pityriasis Versicolor (Tinea versicolor):

Etiology:

It is caused by *Malassezia furfur* which is not a member of dermatophytes but only infects the skin.

Clinical manifestations:

It is a fungal infection of the stratum corneum that manifests as hypo-or hyper pigmented skin patches, usually on the trunk of the body. (Color of patches varies with pigmentation of skin i.e. it appears as hypo pigmented in dark skin persons while appears as hyper pigmented in light skin persons, exposure to sun, and severity of disease).

This discoloration is due to inhibition of tyrosinase enzyme which is involved in melanin synthesis by fungal lipids rich in C14 and C19 dicarboxylic acids.

These skin patches may be associated with itching.

Laboratory diagnosis:

It is diagnosed by KOH mount of skin scales that show the fungus as short curved septate hyphae and yeast-like cells (spaghetti and meat balls). Wood's lamp examination will show yellow fluorescence.

Treatment:

It is treated most easily with selenium sulfide or ketoconazole. It can be stripped off with adhesive tape or treated with a keratolyic agent. Recurrence is common.

NB: *Malassezia furfur* is the causative agent of Pityriasis versicolor, Pityriasis folliculitis and it has recently been implicated as a causative agent of seborrhoeic dermatitis and dandruff. It has also been recovered in blood cultures from neonate and adult patients undergoing lipid replacement therapy.

Pityriasis folliculitis:

This is characterized by follicular papules and pustules localized to the back, chest and upper arms, sometimes the neck, and more seldom the face. These are itchy and often appear after sun exposure. Scrapings or biopsy specimens show numerous yeasts occluding the mouths of the infected follicles. Most cases respond well to topical imidazole treatment; however patients with extensive lesions often require oral treatment with ketoconazole or itraconazole.

Seborrhoeic dermatitis and dandruff:

Current evidence suggests M. furfur, combined with multifactorial host factors is also the direct cause of seborrhoeic dermatitis, with dandruff being the mildest manifestation. Clinical manifestations are characterized by erythema and scaling in areas with a rich supply of sebaceous glands i.e. the scalp, face, eyebrows, ears and upper trunk. Lesions are red and covered with greasy scales and itching is common in the scalp. The clinical features are typical and skin scrapings for a laboratory diagnosis are unnecessary. The use of a topical imidazole is recommended, especially ketoconazole which has proved to be the most effective agent.

Fungaemia:

M. furfur has also been reported as causing catheter acquired fungaemia in neonate and adult patients undergoing lipid replacement therapy. Such patients may also develop small embolic lesions in the lungs or other organs. Diagnosis requires special culture media and blood drawn back through the catheter is the preferred specimen. Culture of the catheter tip is also recommended.

B- Tinea nigra:

Etiology:

Hortaea werneckii (syn. *Exophiala werneckii*).

Clinical manifestations:

Skin lesions are characterized by brown to black macules which usually occur on the palmer aspects of hands and occasionally the plantar and other surfaces of the skin. Lesions are non-inflammatory and non-scaling. Familial spread of infection has also been reported.

Laboratory diagnosis:

Direct microscopy of skin scrapings mounted in 10% KOH show pigmented brown to dark dematiaceous septate hyphal elements and budding yeast cells typical of *Hortaea werneckii.*

Treatment:

Usually, topical treatment with Whitfield's ointment (benzoic acid compound) or an imidazole agent twice a day for 3-4 weeks is effective.

C- White piedra:

Etiology:

White piedra is a superficial cosmetic fungal infection of the hair shaft caused by *Trichosporon beigelii*.

Clinical manifestations:

Infections are usually localized to the axilla or scalp but may also be seen on facial hairs and sometimes pubic hair. White piedra is common in young adults. The presence of irregular, soft, white or light brown nodules, 1.0-1.5 mm in length, firmly adhering to the hairs is characteristic of white piedra.

Laboratory diagnosis:

Direct microscopy of hairs using 10% KOH and Parker ink or calcofluor white mounts shows irregular, soft, white or light brown nodules, 1.0-1.5 mm in length, firmly adhering to the hairs.

Treatment:

Shaving the hairs is the simplest method of treatment. Topical application of an imidazole agent may be used to prevent reinfection.

D- Black piedra:

Etiology:

Black piedra is a superficial fungal infection of the hair shaft caused by *Piedra hortae*. It is common in Central and South America and South-East Asia.

Clinical manifestations:

Infections are usually localized to the scalp but may also be seen on hairs of the beard, moustache and pubic hair. Black piedra mostly affects young adults and epidemics in families have been reported following the sharing of combs and hairbrushes. Infected hairs generally have a number of hard black nodules on the shaft.

Laboratory diagnosis:

Direct Microscopy of hairs using 10% KOH and Parker ink or calcofluor white will show darkly pigmented nodules that may partially or completely surround the hair shaft.

Treatment:

The usual treatment is to shave or cut the hairs short, but this is often not considered acceptable, particularly by women. In-vitro susceptibility tests have shown that *Piedra hortae* is sensitive to terbinafine.

II- Cutaneous Mycoses (dermatophytoses)

Involve the skin, hair, or nails.

Etiology:

Caused by any of the dermatophytes; a homogeneous group of filamentous fungi with three genera:

A- *Trichophylon:*(21 species) infect skin, hair and nails and occasionally cause subcutaneous infections in immunocopromised individuals.

B- *Microsporum:*(17 species)infect skin and hair but not nails.

C- *Epidermophyton floccosum:* infect skin and nails but not hair.

Epidemiology:

Dermatophytes are classified according to their habitat to:

- zoophilic dermatophytes that are acquired from animals by close contact.
- geophilic dermatophytes that are acquired from soil.
- anthropophilic dermatophytes that are acquired from humans by close contact or via contaminated objects.

Clinical manifestations:

Dermatophytes affect the keratinized tissues and spread peripherally from initial foci to produce a ring like lesions. Hence the name ringworm or tinea (Tinea is the Latin name for a growing worm).

May give rise to a hypersensitivity state called the dermatophytid or ID reaction as a result of circulating fungal antigens. It is a cutaneous lesion commonly seen in the fingers from which no organism can be recovered and it does not respond to topical therapy it disappears spontaneously when the primary lesion is treated.

Clinical forms of the disease are named according to the site affected:

Skin disease	Location of the lesion	Clinical features	Most frequently responsible fungi
Tinea corporis (ring worm)	Non hairy smooth skin of the body.	Circular itchy patches with advancing red border and central scaling.	*T. rubrum* *E. floccosum*
Tinea pedis (athlete's foot)	Interdigital spaces of feet.	Acute: itchy red vesicular lesions. Chronic: itchy scaling fissures.	*T. rubrum* *E. floccosum* *T.mentagrophyte*
Tinea cruris (jock itch)	Groin, perineum or perianal area.	Erythematous scaly lesions with itching.	*T. rubrum* *E. floccosum* *T.mentagrophyte*
Tinea capitis	Scalp hair. Endothrix:	Circular bald patches with:	

	fungus inside hair shaft. Ectothrix: fungus on the surface of hair.	In ectothrix: short hair stubs. In endothrix: hair breaks at the mouth of the follicle that becomes plugged with sebum (black dot ring worm). In favus: fungal growth around the hair follicle produces a waxy honey comb like crust on the scalp. In kerion: highly inflammatory suppurative raised lesion.	*T.verrucosum* and Microsporum sp. *T.tonsurans, T.violaceum* and *T.mentagrophyte* *T.schoenleinii.* Zoophilic species
Tinea barbae	Beard hair.	Edematous erythematous lesions.	*T.mentagrophyte*
Tinea unguium (onycomycoses)	Nail.	Nails are thickened, lusterless and discolored. Usually associated with tinea pedis.	*T. rubrum* *E. floccosum* *T.mentagrophyte*

Laboratory Diagnosis:

1. Wood's light examination:

The tissues infected with microsporum species fluorescence green when exposed to U.V.

2. Direct microscopic examination:

Few hairs and some of the skin scales are put in a drop of 10-20% potassium hydroxide solution on a slide a cover slip is added and heat gently but not to boil. After ½ to 2 hours, the preparation is examined for the presence of hyphae or spores and for the type of hair invasion; ectothrix or endothrix.

3. Culture:

For the isolation of dermatophytes, the medium universally used is Sabouraud's dexstrose (SDA) agar. To inhibit bacterial contaminants, antibiotics are added as chloramphenicol. Also actidione is added (0.5 gm/L) as an inhibitor for contaminating moulds. Hairs and skin scrapings are inoculated on the surface of the medium and incubated at 30°C for 2-8 weeks.

The growing colonies are described macroscopically and a micro culture is made to study the microscopic structures. A micro culture is done by inoculating one cm^2 agar block on the 4 edges, on a slide and covered by a cover slip. The whole preparation is then incubated in a moist chamber, and examined daily under the microscope. The colonies are examined using lactophenol cotton blue.

Treatment:

- Topical therapy:

tolnaftate, clotrimazole and miconazole are usually successful for eradicating dermatophytoses but *T. rubrum* is usually resistant.

- Oral therapy:

Oral antifungal agents are indicated in extensive infections or infections refractory to topical therapy. For some infections particularly those involving the nails the drug of choice is griseofulvin that must be administrated for several months. Allylamines may offer an alternative to griseofulvin but with less efficiency.

III- Subcutaneous Mycoses

These are caused by fungi that grow in the soil and vegetations and are introduced into the subcutaneous tissue through trauma. It includes:

1- Eumycotic Mycetoma (Madura foot):

Etiology:

It is caused by filamentous fungi living in soil and on vegetations. The most common fungal causes are *Madurella mycetomatis, Exophiala jeanselmei, Pseudallescheria boydii* that enters the body via wounds; usually occurs in rural area in agricultural workers in the tropics.

Actinomycotic mycetoma	Eumycotic Mycetoma
*Bacterial infection caused by actinomyces.	*Fungal infection caused by filamentous fungi e.g. *Madurella mycetomatis*.
*Has good prognosis.	*Has bad prognosis.
*Easily treated with sulphonamides	*Resistant to treatment.

and aminoglycosides.	Amputation of the affected limb is the only treatment.

NB: the term mycetoma only refers to the disease caused by mixed bacterial and fungal infection.

Clinical manifestations:

It is a subcutaneous disease characterized by swelling, abscess formation and drainage through sinus tracts. Granules (0.5 -2 mm in width) and variable species specific colors are found in the exudates.

Laboratory diagnosis:

Exudates from draining sinuses and tissue biopsy are the suitable samples.

A- Microscopic examination:

Causative fungi are difficult to be identified with microscopic examination. Examination of the granules may show filaments 4-10 microns wide with clubbing at the periphery of the granule which is characteristic.

A- Culture:

Culture of the granules is required to isolate the causative fungi with subsequent identification with colony morphology, conidia formation and biochemical reactions.

B- Serology:

It is used for diagnosis in the tropics. Immuno diffusion and counter immuno electrophoresis (CIE) can be used.

Treatment:

Surgical draining and debridement of diseased tissue are used along with antifungals. Ketoconazole and miconazole can be used but with low response and the drug has to be administrated for years. Amputation of the affected limb is the only treatment in the majority of cases.

2- Chromomycoses:

It is chronic fungal infection of subcutaneous tissue that occurs mainly in tropical areas.

Etiology:

The disease is caused by pigment producing filamentous fungi. The most common involved species are *Fonsecaea pedrosoi*, *F. compacta* and *Phialophora verrucosa*. They are dematiaceous fungi as they grow as black colonies. The pigment accumulates in mycelial cell wall in culture

and in tissues. The normal habitat of these fungi is the soil and vegetations from which infection can be transmitted to human commonly through to trauma to the feet.

Clinical manifestations:

It is a long-term disease that progress slowly over a period of several years. The affected area becomes rough, irregular and itchy. Dull red or grayish or dark brown cauliflower-shaped nodules will appear. It commonly affects the feet rarely hands, arms and buttocks.

Laboratory diagnosis:

No serological tests are available to help diagnosis. Tissue biopsy examination, culture and isolation of the causative fungus are the only available methods for diagnosis.

A- Microscopic examination:

In tissues; the fungus forms golden brown sclerotic bodies 4-14 μm in diameter frequently located in the giant cells. These sclerotic bodies are the reproductive forms they divide by fission and produce granulomatous reaction. The species of the infecting fungi cannot be differentiated by examination of these sclerotic bodies.

B- Culture:

In culture; the fungus shows black, long, septate and branching hyphae with terminal conidia.

Treatment:

Surgical excision of the lesion and amphotrecin B or itraconazole. Results of treatment are not encouraging.

3- Sporotricoses:

Etiology:

It is caused by the dimorphic fungus *Sporothrix schenckii* which is present in soil, vegetations, hay, or decaying material.

Mode of transmission:

- Trauma to the skin commonly thorn prick in the hands leads to direct inoculation of the organism (so t is known as rose grower's disease).
- Zoonotic sporotrichosis occurs with exposure to infected animals, most often cats with ulcerated lesions that contain large numbers of organisms.
- Less commonly, inhalation of *S. schenckii* conidia from soil can lead to pulmonary infection.

Pathogenesis:

Sporotrichosis develops when *S. schenckii* conidia from the mold phase are inoculated into the skin or subcutaneous tissues. The organism

converts to the yeast form in the body. The clinical picture evolves as the organisms spread along lymphatics draining the primary inoculation site.

Some *S. schenckii* strains grow poorly at temperatures higher than 35°C and generally are associated with fixed cutaneous lesions that do not extend along lymphatics. In immunocomprimised patients dissemination of infection to osteoarticular structures, lungs, meninges, and other organs can occur.

Clinical manifestations:

Sporotrichosis is chronic subcutaneous disease. After inoculation, a papule develops at the site within days to weeks. The primary lesion generally ulcerates, but remains only mildly tender. Nodules develop proximal to the primary lesion following the lymphatic distribution and often ulcerate, mimicking the primary lesion.

Other rare forms of sporotrichosis include:

- pulmonary sporotrichosis that may be primary due to inhalation of *S. schenckii* conidia or secondary due to dissemination of infection in immunocomprimised patients.
- Osteoarticular, meningeal…etc. especially in AIDs patients.

Laboratory diagnosis:

Specimens vary according to the lesion but commonly pus aspirated from a lesion or a tissue biopsy.

1- Direct examination:

The organisms may be difficult to find because they are often present in small numbers. So KOH mounts are not diagnostically useful.

2- Histopathologic examination:

Typically, a mixed granulomatous and pyogenic process is noted, but the organisms are present in small numbers.

In tissues, the yeasts are 3 to 5 mm in diameter, oval to cigar-shaped, showing multiple buds and surrounded with eosinophilic rays forming an asteroid body (splendori reaction).

3- culture:

It is the only definitive diagnostic method to confirm sporotrichosis. At room temperature colonies grow as white and membranous in 3-5 days and become black and leathery after 2-3 weeks.

Microscopically *S. schenckii* forms delicate thin conidiophore with pyriform conidia arranged in cluster around its tip.

4- Serology:

Serology has not been useful for diagnosing sporotrichosis, and antigen based tests are not available.

Treatment:

Saturated solution of potassium iodide is used for treatment of lymphocutaneous sporotrichosis but it is associated with many side

effects, so itraconazole or amphotrecin B are used they are also used for systemic form of the disease.

IV- Systemic Mycoses (Deep Mycoses)

They are mycoses that affect internal organs and may disseminate to multiple sites of the body. It is subdivided into:

A- Primary systemic mycoses (endemic mycoses).

B- Opportunistic mycoses.

A- Primary systemic mycoses (endemic mycoses):

They are caused by true pathogenic dimorphic fungi that are found in the human body at 37°C as the yeast form and grow in lab cultures at 25°C or lower as filamentous forms. They are found in sand, soil, decaying organic material, bird or bat feces and all produce airborne spores.

1- Blastomycosis:

Etiology:

It is caused by *Blastomyces dermatitidis* which is commonly found in soil and decaying wood. The disease is endemic in eastern half of North America and sporadically occurs in other parts of the world.

Mode of transmission:

Blastomycosis is acquired through inhalation of the conidia of the mold form of *B dermatitidis* into the alveoli, and extremely rarely through direct cutaneous inoculation.

Pathogenesis:

The organisms change to the yeast form in the lungs and then multiply through budding. Many patients infected with *B dermatitidis* probably experience hematogenous dissemination of the organism before immunity develops.

Immunosuppressed patients do not seem to be at greater risk for developing blastomycosis, but more severe disease is likely to occur and the mortality rate is higher in these patients

Clinical manifestations:

The disease is mainly presented as pulmonary or cutaneous form. Hematogenous dissemination occurs without clinical manifestations, and only few patients may present with other organ involvement.

- Cutaneous lesions:

The lesions are typically well-circumscribed non painful papules, nodules, or plaques that often become verrucous and develop punctate

microabscesses in the center. These lesions may occur as primary infection of the skin or secondary to systemic disease.

- Pulmonary disease: may be presented as

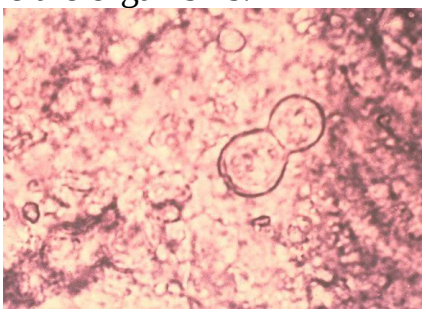
*Acute pneumonia (less common).
*Sub acute to chronic pneumonia with symptoms of fever, night sweats, fatigue, productive cough, and dyspnea. Chest radiography often shows a mass-like lesion, but multiple nodular lesions, lobar infiltrates, and cavitary lesions are also seen. The differential diagnosis of chronic pulmonary blastomycosis includes lung cancer, tuberculosis, histoplasmosis, and sarcoidosis.

Laboratory diagnosis:

Samples include pus or scraping from skin lesions, sputum for pulmonary infection, tissue biopsy from obvious lesions and occasionally urine samples if the infection has disseminated to the prostate.

Microscopic examination:

It allows early diagnosis of blastomycosis based on the distinctive morphology of the yeast form of *B dermatitidis* which is large and double-walled. The buds are single and broad based.
Microscopic examination is performed on:
Wet mounts using KOH or calcofluor white.
Histopathologic sections using methenamine silver or periodic acid–Schiff stains to visualize the organisms.



Culture:

It is the definitive diagnostic method for blastomycosis. Growth of the organism in mold phase occurs at room temperature (25°c) in about 2-4 weeks. Conversion of the mold phase to the yeast phase occurs at body temperature (37°c) in 7-10 days. Identification of the isolated organism can be accomplished by:

<u>Microscopic examination:</u>

The appearance of the mycelia and its micro conidia is indistinguishable from any other fungi so it is only the examination of yeast phase is diagnostic for blastomycosis.

<u>Exoantigen test:</u>

It is a rapid method for identifying the mold phase. It is a double immuonodiffusion reaction; an aqueous extract of 7-10 days old mycelial culture is precipitated against a known standardized antiserum. Precipitation band is formed when the antigen meets its specific antiserum.

Nucleic acid probes:

They are highly specific and sensitive DNA probe for *B dermatitidis* that can rapidly confirm the identity of the organism.

Serology:

It is used to detect antibody response to *B dermatitidis* infection. Two tests can be used:

Immunodiffusion precipitation test:

It is positive 2-3 weeks after the onset of infection. Positive test indicates recent or active disease.

CFT:

It takes 2-3 months to become positive. It has poor sensitivity and specificity. However; its quantitative results can be used to monitor patient response to therapy.

Treatment:

Patients who experience any manifestations of dissemination, even if only one skin lesion, require systemic antifungal therapy to prevent progression of the disease.

Patients who have mild to moderate illness should be treated with an azole; itraconazole is the preferred azole agent for treating mild to moderate blastomycosis.

Patients with severe disease and immunosuppressed patients should be treated with amphotericin B initially followed by an azole.

2- Histoplasmosis:

Etiology:

It is a granulomatous fungal infection caused by *Histoplasma capsulatum*; a dimorphic fungus found in soil enriched with bat or bird (particularly chicken or starling) guano.

Histoplasma capsulatum can be isolated from most areas around the world; the major endemic region lies in the drainage areas of Ohio, Missouri, and Mississippi rivers.

Mode of transmission:

Inhalation of the aerosolized particles contaminated with the organism is the most common mode of transmission.

Pathogenesis:

After inhalation *Histoplasma capsulatum* is taken by alveolar macrophages and behave as a facultative intracellular parasite circulating throughout the reticuloendothelial system (RES) such as bone marrow, liver and spleen. Cell mediated immunity develops against this fungus which is evident by positive skin testing.

Clinical manifestations:

Histoplasmosis may remain mild or asymptomatic. Manifest disease is presented as pulmonary, fulminant or ocular histoplasmosis.

Pulmonary histoplasmosis:

It is the most common form in adults. The severity of the disease depends largely on the general health state, lung structure, and immune system of the host and the dose of the inoculum.

It can be presented as acute pneumonia but more commonly as chronic pulmonary disease. There is cough which is initially dry the productive or bloody, anorexia, weight loss and night sweats; a picture similar tuberculosis but the chest x-ray shows bilateral interstitial infiltrates that is not seen with tuberculosis.

Disseminated histoplasmosis:

This form is common in children and commonly presented as hepatosplenomegally. The disease is fatal.

Ocular histoplasmosis:

It is not true retinal infection. It occurs as a hypersensitivity reaction to undetected infection with *histoplasma capsulatum* elswhere.

Laboratory diagnosis:

Type of the samples depends on the presentation of the patient. Commonly sputum samples. Sometimes blood, bone marrow smear, or liver biopsy can be used.

Microscopic examination:

The organism can be detected by histopathological examination as intracellular yeast cells 5-6µm in diameter in tissue phagocytes or circulating polymophonuclear leucocytes or monocytes in the peripheral blood.

Thick blood, bone marrow smear, or liver biopsy can be stained with Wright's or Giemsa stain. In tissue sections stained with Giemsa stain or H&E the inflammatory reaction is generally granulomatous with giant cells. Necrotic centers and calcifications may be detected.

Culture:

Cultures of *Histoplasma capsulatum* is the definitive method for diagnosis. At 25°C; it produces filamentous, white to brown colonies, and hyphae with small, tear-shaped microconidia and large round tuberculate macroconidia.

At 37°C; it produces creamy white yeast colonies of non-descript small cells with a narrow neck between buds and mother cells. Definitive identification of cultures is based on:

Microscopic examination:

It is done by conversion from yeast form to the filamentous form with microscopic demonstration of typical sporulation.

Exoantigen test: (see before)

It is an alternative method using soluble antigens from the lab culture in an immunodiffusion test with known antibodies.

Nucleic acid probes:

It is highly specific and sensitive method to confirm the diagnosis.

Serology:

1- Latex agglutination test:

Latex particles coated with fungal antigen extract are used to detect IgM antibodies that appear early in the disease (in the first 2 weeks) and gradually fades in about 3 months.

2- Complement fixation test:

It is performed separately with antigens prepared from the yeast form and from the mycelial form of the fungus. For unknown reason some patients react with one form and do not react with the other and some do not react with both.

Disadvantages: cross reactivity with other fungal pathogens and time delay till the appearance of detectable antibodies are the main limitations.

Advantages: the qualitative results allow evaluation of patient response to therapy.

3- Immunodiffusion test:

This test produces two precipitation ands; H and M. An H band or H and M bands together indicate active disease while an M band alone may indicate active disease, past infection or recent skin testing.

4- Skin test (histoplasmin test):

It can not be used to diagnose active disease. It can be used to demonstrate previous exposure to the antigen.

A negative test is a poor prognostic sign in a patient with known active histoplasmosis

If done before serology it can boost the antibody levels (e.g. gives positive CFT or M band in immuonodiffusion test).

Treatment:

The drug of choice is amphotrecin B. azoles can be used for mild cases.

3- Coccidioidomycosis:

(Also known as California disease, Desert rheumatism, San Joaquin valley fever, Valley fever)

Etiology:

It is caused by *Coccidioides immitis*; a dimorphic fungus that grows as a mycelium in the soil and produces a spherule form in the host. It is present in the soil in certain parts of the southwestern United States, northern Mexico, and parts of Central and South America.

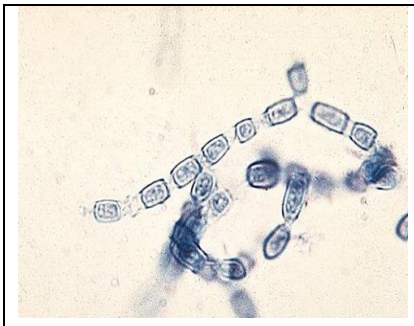
Mode of transmission:

Infection is caused by inhalation of the air borne spores. Spread of the spores is favored by disruption of soil, such as during construction, farming, or an earthquake. The disease is not transmitted from person to person.

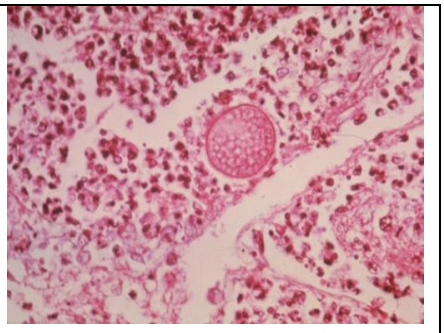
Pathogenesis:

C.immitis is present in the soil as saprophytic mycelial form producing arthroconidia which are chains of barrel shaped spores (arthrospores) that when inhaled are trapped in the alveolar spaces where they become round and enlarge into multinucleated spherule (parasitic form).

The spherules segment into uninucleated endospores. When the spherule is mature the wall ruptures releasing the endospores, each endospore develops into spherule and the cycle is repeated.



Arthroconidia of *C.immitis*



Spherule of *C.immitis*

Clinical manifestations:

The disease may be presented as:

1- Primary coccidioidomycosis:

The respiratory tract is the primary target of *c.immitis*. Infection may be acute or progressive.

a- Acute coccidioidomycosis: infection is usually mild with flu-like symptoms, disappears without treatment and it accounts for about half of cases. Some people develop desert rheumatism as allergic reactions to invading fungus (arthritis, skin nodules and conjunctivitis).

b- Progressive coccidioidomycosis: uncommon and may develop weeks, months, or even years after the initial infection. Symptoms include mild fever and loss of appetite, weight, and strength. The lung infection may worsen, causing increased shortness of breath; a picture similar to TB.

2- Disseminated coccidioidomycosis:

The infection spreads throughout the body and is often fatal. For unknown reason it is more common among men and among blacks, Filipinos, and Native Americans. This form is more likely to occur when the immune system is weakened.

The infection may spread from the lungs to the bones, joints, liver, spleen, and kidneys. The fungi can also infect the brain and meninges, causing meningitis. This infection is often chronic, causing headaches, confusion, loss of balance, double vision, and other problems. Infection can spread also to the eyes. Unlike ocular histoplasmosis; ocular coccidioidomycosis is a true infection.

Laboratory diagnosis:

Microscopic examination:

KOH mounts of the sputum samples or histopathological examination of tissue smears reveals spherules 30-60 µm in diameter filled with endospores 3-5 µm in diameter which is diagnostic.

Culture:

At room temperature; mycelia take 2-3 weeks to grow and develop arthroconidia. At 37°c; spherules develop under special conditions. Definitive identification of cultures is based on microscopic examination, exoantigen test and nucleic acid probes.

Serology:

1- Latex agglutination test:

Latex agglutinating antibodies develop within2 weeks. It is reliable easy test for diagnosis.

2- CFT:

It becomes positive within 1 month. Titer higher than 1:128 usually indicates extensive dissemination.

3- Immuonodiffusion test:

It is 100 % specific and 85 % sensitive for *C.immitis*.

4- Enzyme immunoassay (EIA): screens for both IgG & IgM antibodies.

Treatment:

Amphotrecin B is the drug of choice. Azoles can be used as alternatives.

4- Paracoccidioidomycosis:

Etiology:

It is caused by *Paracoccidioides brasiliensis*; a dimorphic fungus distributed in Brazil and South America. The habitat of the infectious agent is unknown but appears to be the soil. It rarely affects the fertile-age women, probably due to a protective effect of estradiol.

Mode of transmission:

Most probably by air borne infection.

Pathogenesis:

Invading organism disseminate in the body via the blood and lymphatic system. It has a long incubation period up to 20 years.

Clinical manifestations:

Paracoccidioidomycosis is a chronic granulomatous disease of the mucous membranes, skin, respiratory system and lymphoid tissues.

Triad of symptoms is commonly seen in endemic areas:

- Pulmonary lesions:

It has the same clinical picture of other fungal infections of the lung. It is misdiagnosed as pulmonary TB.

- Edentulous mouth:

P.brasiliensis invades the mucous membrane of the gums causing chronic inflammation and falling of the teeth.

- Cervical lymphadenopathy.

Laboratory diagnosis:

Microscopic examination:

KOH mounts of sputum or crust from one of the lesions or histopathological examination of tissue sections reveal yeast cells with multiple narrow based buds; a picture commonly described as (captain's wheel) which is diagnostic of Paracoccidioidomycosis.

Culture:

At room temperature, dense white mycelial colonies develop within 2-3 weeks. The conidia are not diagnostic so conversion to yeast form at 37°c is essential for diagnosis.

Identification of the isolated organism is carried out by microscopic examination, exoantigen test and nucleic acid probes.

Serology:

The best serologic test for detection of antibodies to *P.brasiliensis* is immuonodiffusion test.

Treatment:

Amphotrecin B is the drug of choice. Some azole derivatives can be used as alternatives.

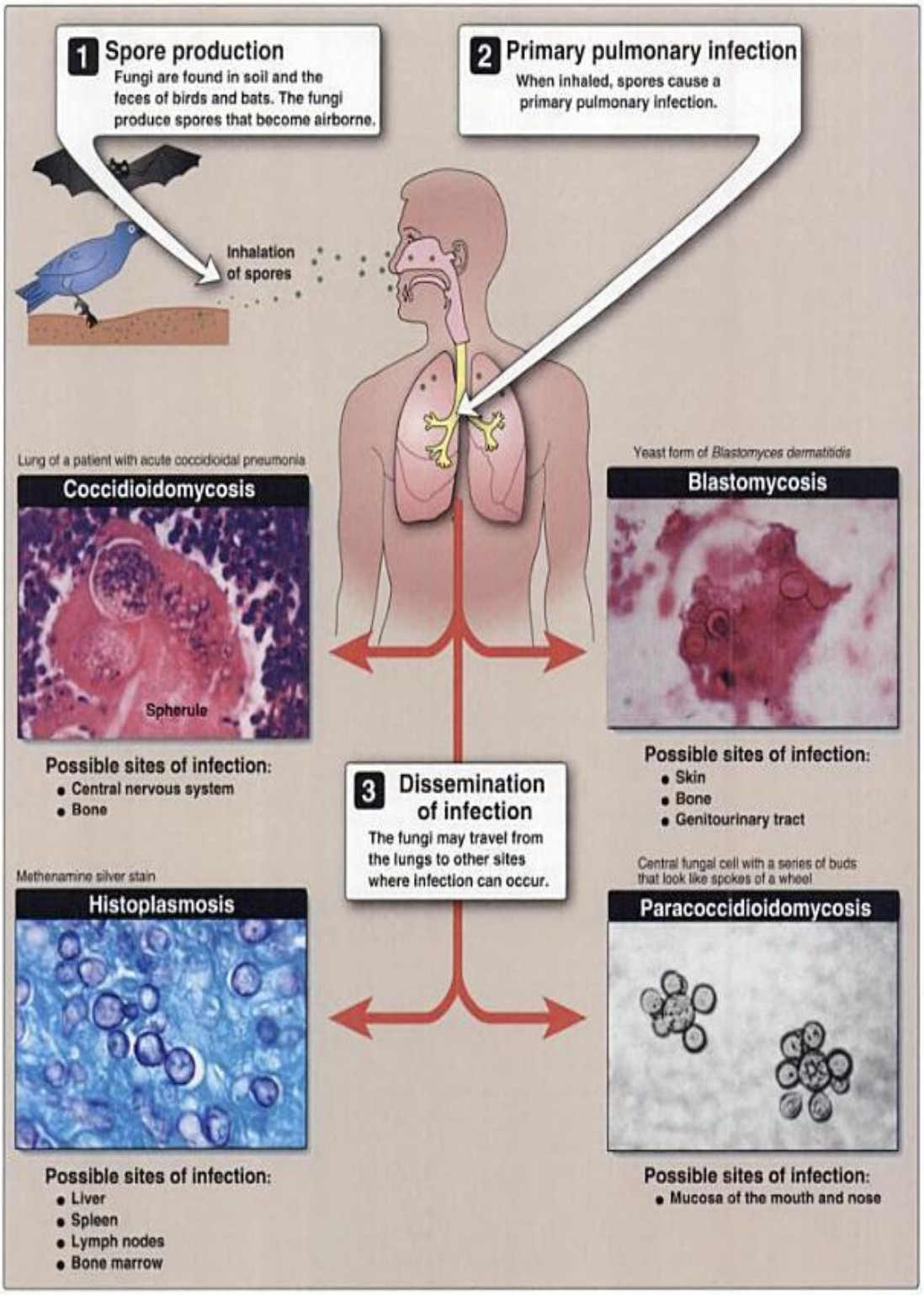


Figure 20.8
Systemic mycoses.

B- Opportunistic Systemic Mycoses:

Opportunistic pathogens have low virulence and can invade and cause disease only in immunocompromised patients. Opportunistic mycoses are caused by saprophytic (i.e. from the environment) or endogenous (i.e. commensal) fungi. Commonly isolated organisms from these patients include *Candida* species, *Cryptococcus neoformans, Aspergillus* species and *Mucor* species.

Risk factors of opportunistic mycoses:

Any factor that suppresses the patient immunity predisposes to opportunistic mycoses e.g.

- Drug therapy:

Anti-neoplastic drugs, steroids, and immunosuppressive drugs. Over-use or inappropriate use of antibiotics can also contribute to the development of fungal infections by altering the normal flora of the host and facilitating fungal overgrowth or by selecting for resistant organisms.

- Severe illness or chronic debilitating diseases:

Diabetes, tuberculosis, malignancies, AIDs and severe burns.

- Invasive procedures:

Indwelling catheters, prosthetic valves…etc.

Clinical presentation of opportunistic mycoses: is variable due to:

- Patients present with atypical signs and symptoms.
- Unusual histopathology.
- The fungus may have an unusual organ affinity.
- The etiological agent may be a saprophyte or commensal.
- The systemic mycoses may occur outside the known endemic area.
- The serologic response may be suppressed.

For these reasons also diagnosis of opportunistic mycoses represents a challenge.

Treatment of opportunistic mycoses:

Treatment is difficult and opportunistic mycoses have a high mortality rate so it s recommended for patients who are at risk of infection to have a life long chemoprophylaxis.

A course of induction therapy (usually with amphotrecin B) is followed by maintenance oral therapy.

Opportunistic mycoses include:

1- Candidiases (Moniliases)

This term refers to infections caused by different Candida species the commonest of them is *Candida albicans* which is a part of normal flora of the skin, mucous membranes, and gastrointestinal tract.

Predisposing factors to Candida infections are:

- Extremes of age.
- Chronic debilitating diseases e.g. diabetes mellitus.
- Nutritional disorders.
- Excessive moisture.
- Pregnancy.
- Long-term antibiotic and steroid usage.
- Invasive procedures e.g. indwelling catheters.

NB: In the body *C. albicans* switch from its yeast form to its more virulent hyphal form however it is not a dimorphic fungus as it is not a thermal dimorphism and this occurs only in vivo.

Common forms of Candidiases:

I- Superficial candidiases: include the following forms

1. Oral thrush:

It is infection of the oral mucous membranes manifested as white curd like patches. It commonly occurs in children with prolonged antibiotic therapy, immunosuppressed patients e.g.AIDS patients.

2. Vulvovaginitis or vaginal thrush:

It is infection of the vagina manifested as a thick yellow-white discharge, burning sensation, curd-like patches on the vaginal mucosa and inflammation of the perineum. It is commonly seen in diabetic patients and during pregnancy.

3. Cutaneous Candidiasis:

It involves nails, skin folds, or groin region.

4. Alimentary tract disease, including esophagitis:

It is usually an extension of oral thrush found in AIDS patients and other immunosuppressed patients, particularly those on long-term antibiotics.

Its incidence is reduced in highly susceptible populations by antifungal
prophylaxis.

II- Systemic candidiasis: may occur almost anywhere in the body

- Candidemias or blood-borne infections occur most commonly in patients with indwelling intravenous catheters.
- Endocarditis occurs in patients who have manipulated or damaged valves or in intravenous drug abusers.
- Bronchopulmonary disease (usually manifested by persistent cough) occurs in patients with chronic lung disease.

Diagnosis:

I- Superficial candidiases:

Diagnosis is mainly clinical and confirmed by detection of yeast cells in Gram stained film or KOH mount of the lesion.

II- Systemic candidiasis:

Samples differ according to the site of infection and include urine, sputum, bronchial washings, cerebrospinal fluid, pleural fluid, blood and tissue biopsies from various visceral organs.

Direct microscopy:

Demonstration of the presence of pseudohyphae and yeast cells is diagnostic when samples are obtained from normally sterile site e.g. blood or when it is obtained from a site where candida is normally present as a part of body flora and the clinical presentation is consistent with candidiases.

Culture:

Colonies are typically white to cream colored with a smooth, glabrous to waxy surface. The organism is identified by:

- The formation of pseudohyphae and chlamydoconidia**.**
- Carbohydrate assimilation tests.
- Germ tube test:

When yeast isolates are incubated in serum at 37°C germ tubes (drum stick non septate elongation of yeast cells) are formed within 2-3 hours. This test is positive only with *c.albicans*.

NB: germ tubes are non septate and show no constriction at the point of attachment while pseudohyphae may be septate and show constriction at the point of attachment.

Serology:

Serological tests for detection of antibodies against candida antigens are usually unuseful because they can not discriminate infection and normal colonization also immunocomprimised patients who are at risk of infection have weak antibody response.

A skin test; candidin test can be also used but of limited value.

Treatment:

I- Superficial candidiases:

Cutaneous and oropharyngeal candidiasis: topical application of nystatin or ketoconazole.

Esophageal candidiasis: oral administration of clotrimazole, ketoconazole or fluconazole.

Vaginal candidiasis: oral ketoconazole or fluconazole in addition to topical vaginal treatment to prevent repeated reinfection from intestinal source.

II- Systemic candidiasis:

Amphotrecin B is the drug of choice in addition to removal of the predisposing factor e.g. indwelling catheter.

2- Cryptococcosis

Etiology:

It is caused by *Creptococcus neoformans* which are yeast cells possessing an antigenic polysaccharide capsule. It is present in vegetations, soil and associated with pigeon excreta; an occupational hazard to pigeon handlers.

Mode of transmission:

Infections occur commonly in immunocomprimised patients by inhalation where it causes subclinical lung infection or pneumonia. Infection spreads systemically to the meninges causing meningitis.

Pathogenesis:

- The antiphagocytic polysaccharide capsule is the major virulence factor.

- Melanin production is another virulence factor. It is deposited in the cell wall protecting the organism from oxidants released by phagocytic cells.

Clinical manifestations:

1. creptococcal meningitis:

It is the most common clinical presentation of cryptococcosis. It presents as headache of increasing severity (over a period of several months), usually with fever followed by typical meningitis signs.

2. Pulmonary cryptococcosis:

It is usually asymptomatic and self-resolving. Fulminant forms are highly variable but may resemble pneumococcal pneumonia.

Laboratory diagnosis:

1- Examination of CSF:

Physical examination:

CSF is turbid and under tension.

Chemical examination:

Protein level is increased, glucose level is decreased and the number of leukocytes is increased (mainly mononuclear cells).

Microbiological examination:

India ink wet mount of CSF sediment for demonstration of encapsulated yeast cells. This has been greatly replaced by latex agglutination test for detection of the capsular antigen in CSF (can be also performed on serum samples).

Diagnosis is confirmed by isolation of *C. neoformans* by culture of CSF.

2- Serology:

Indirect immunoflourescence for antibody detection but it does not discriminate between active infection and past exposure.

3- culture:

Performed on cyclohexamide free media. Colonies are creamy mucoid (because of the capsule). Organism is identified by urease production, carbohydrate assimilation or direct immunoflourescence

Treatment:

By amphotrecin B usually in combination with 5-flourocytosine.

Oral fluconazole is used to prevent the relapse.

3- Aspergillosis

Etiology:

Aspergillosis is the name given to a wide variety of diseases caused by fungi of the genus Aspergillus. The most common are *A. fumigatus*, *A.niger* and *A.flavus*.

Aspergillosis develops mainly in immunocompromised individuals.

Clinical manifestations:

Asprigillus species can invade any part of the body but commonly cause disease in the respiratory system. There are 3 form of pulmonary aspergillosis:

- Allergic bronchopulmonary aspergillosis: due to allergy to inhaled fungal spores.
- Pulmonary aspergilloma: A fungus ball in the lungs (commonly in the cavities of previous TB infection) may cause no symptoms and may be discovered only with chest X-ray (manifests as air crescent sign), or it may cause repeated coughing of blood.
- Invasive aspergillosis: propagation of the fungus through the lung parenchyma. It is seen in immunocompromised individuals particularly children.

Laboratory diagnosis:

Microscopic examination:

Aspergillus species are reliably demonstrated by silver stains as Gomori methenamine-silver. Aspergillus hyphae tend to have dichotomous branching that is progressive and primarily at acute angles of about 45°.

Culture:

At 25°c colonies appear after 2-3 days with yellow or greenish coloration. Wet mount of the isolated organism shows that colonies are arranged in radiating columns.

Serology:

- Detection of rising specific IgG in patients with aspergilloma.
- Detection of IgE in patients with allergic bronchopulmonary aspergillosis.
- Skin test; aspergillin test.

Treatment: depends on the type of disease

- Allergic bronchopulmonary aspergillosis: avoiding the exposure, desensitization and steroid therapy.
- Aspergilloma: is treated by surgical excisison.
- Invasive aspergillosis: amphotrecin B, itraconazole canbe used as an alternative.

4- zygomycosis (mucormycosis, phycomycosis)

Etiology:

It is an opportunistic infection caused by Zygomycetes. Mainly three genera are inolved *Rhizopus*, *Absidia* and *Mucor*. Thes fungi have a world wide distribution and commonly isolated from soil, food, organic debris, decaying vegetables and moldy bread.

Clinical manifestations:

Infection is commonly seen in patients with uncontrolled diabetes mellitus and usually begins in the paranasal sinuses following the inhalation of sporangiospores.

The infecting fungi have a predilection for invading vessels of the arterial system, causing embolization and subsequent necrosis of surrounding tissue. Spread of infection to the brain can occur through the cribriform plate. Once infection reaches the brain it is rapidly fatal.

Diagnosis:

It is mainly clinical to allow immediate start of treatment. Typically there is cotton like growth on the roof of the mouth and nares in uncontrolled diabetic patient. Confirmation of diagnosis can be done by:

- KOH mount of the lesion: shows mold with non septate ribbon like hyphae.
- Culture: the organism is rapidly growing (24-48 hours) and it is identified by its morphology in the culture.
- Immunodiffusion test.

Treatment:

Control of diabetes and administration of amphotrecin B.

NB: other forms of zygomycosis can also present e.g. pulmonary, intestinal, cutaneous and disseminated zygomycosis.

5- pneumocystis carinii pneumonia (PCP)

Etiology:

It is caused by a yeast-like fungus *Pneumocystis jirovecii* (previously known as *Pneumocystis carinii*) commonly found in the lungs of healthy people, but being a source of opportunistic infection in immuncompromised patients.

Clinical manifestations:

Symptoms of PCP include fever, non-productive cough (because sputum is too viscous to become productive unless the patient has an additional bacterial infection), shortness of breath (especially on exertion), weight loss and night sweats.

The fungus can invade other visceral organs, such as the liver, spleen and kidney, but only in a minority of cases. Pneumothorax is a well-known complication of PCP.

Laboratory diagnosis:

P.carinii can not be cultivated on artificial media so diagnosis is carried out by identification of the causative organism in sputum, broncho-alveolar lavage or lung biopsy which will show characteristic

cysts that resemble crushed ping-pong balls and are present in aggregates of 2 to 8.

Treatment:

P.carinii lack ergosterol in thier membranes so insensitive to antifungal agents. The most effective treatment is a combination of trimethoprim and sulfamethoxazole.