

A Review on: Mucormycosis

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Abstract - The diagnosis and treatment of mucormycosis are challenging. The incidence of the disease seems to be increasing. Mucormycosis is an angio invasive fungal infection, due to fungi of the order Mucorales. Its incidence cannot be measured exactly, since there are few population-based studies, but multiple studies have shown that it is increasing. The prevalence of mucormycosis in India is about 80 times the prevalence in developed countries, being approximately 0.14 cases per 1000 population. Diabetes mellitus is the main underlying disease globally, especially in low and middle-income countries. In developed countries the most common underlying diseases are hematological malignancies and transplantation. The main aim and purpose of this review related to overview and Etiopathogenesis of Mucormycosis, fatality of rhinocerebral Mucormycosis, recent advances in diagnostic and treatment methods.

Index Terms - Mucormycosis, Zygomycosis, Mucor, Fungal infection.

1. INTRODUCTION

Mucormycosis, informally referred to as black fungus, is a fungal infection caused by fungi. This disease can be potentially life-threatening in diabetic or severely immunocompromised individuals. It has been detected that many patients who are recovering or are recovered from Covid-19 are being infected with Mucormycosis or black fungus. People catch mucormycosis by coming in contact with the fungal spores in the environment. It can also develop on the skin after the fungus enters the skin through a cut, scrape, burn, or other type of skin trauma.

Mucormycosis frequently infects the sinuses, brain, or lungs. It begins to manifest as skin infection in the air pockets located behind our forehead, nose, cheekbones, and in between the eyes and teeth. It then spreads to eyes, lungs and can even spread to the brain. It leads to blackening or discoloration over the nose,

blurred or double vision, chest pain, breathing difficulties and coughing of blood.

1.1. MUCOR

Mucor is a mould or a type of fungi that is found everywhere. There are many species of Mucor (around 50) that are distributed worldwide. It can cause diseases particularly called mucormycosis that might affect the mucous membrane, lungs, eyes, skin etc. Mucor species are fast-growing fungi, which have a highly developed mycelium and branched hyphae. The hyphae in Mucor are generally coenocytic, but septa may appear in the mature hyphae. The cytoplasm of the hypha appears granular.

1.1.1. Classification:

- Kingdom: Mycota
- Division: Zygomycota
- Sub-division: Zygomycotina
- Class: Zygomycetes
- Order: Mucorales
- Family: Mucoraceae
- Genus: Mucor

1.1.2. Habitat:

Mucor lives in a habitat like organic soil, a dead decaying matter of fruits, vegetables and plants.

1.1.3. Distribution: Cosmopolitan.

1. Characteristics of Mucor
2. Structure of Mucor
3. Life Cycle of Mucor

Vegetative Reproduction, Asexual Reproduction, Sexual Reproduction

1.1.4. Characteristics of Mucor:

Some common characteristics of Mucor include:

1. Mucor is also called "Black or Bread mould".
2. It belongs to the class of Zygomycetes.
3. For most of the Mucor, the mode of nutrition is "Saprophytic" (grows in the dead decaying

matter), and for others, it is “Coprophilous” (grows in cow dung or the dung of other herbivorous animals).

4. Mucor grows on a variety of substrates like bread, jam, jellies, vegetables etc. The absorption of nutrition is through the mycelial surface or hyphae.
5. The vegetative body of Mucor is “Eucarpic” because in this the only thallus differentiates into the reproductive structure.
6. The major reserve food material is in the form of glycogen and oil droplets.
7. The cell of Mucor is composed of mainly cellulose and chitin.

1.1.5. Structure of Mucor:

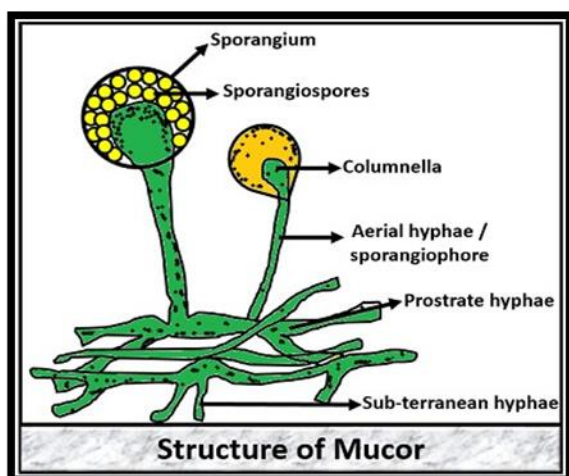


Fig1: Structure of Mucor

1.1.6. Morphological Features:

- Mycelium: The mycelium of Mucor is highly branched, and it forms a fine network of hyphae. A mycelium is simply a cluster of hyphae.
- Hyphae: These are the thread-like and very thin structures that form a “Mycelial network”. Hyphae of Mucor is filamentous, aseptate or coenocytic. In Mucor, the hyphae are of three types:
 1. Sub-terranean hyphae are the type which is highly branched, more penetrating and is present horizontally to the substratum.
 2. Prostrate hyphae are the type which is also present horizontally between or under the substratum. These two hyphae, i.e. sub-

terranean and prostrate hyphae, help in absorption of water and nutrition.

3. Aerial hyphae are the type, which originates vertically out from the prostrate hyphae.
 - Sporangiphore: It is elongated, slightly narrow in shape.
 - Columella: Sporangiphore swells up to form a dome-like structure called “Columella” which can vary in both shape and size.
 - Sporangium: It is the round and thick outer covering which carries numerous spores inside it. It can be globose to spherical.
 - Spores: These are the reproductive structures forms within the sporangium which are simple, flattened and variable in shape and size.
 - Nucleus: Multinucleate nuclei present in Mucor.

Macroscopic Features

- The colony of Mucor shows rapid growth.
- The colour of the colony is usually white to grey and turns to brown when the culture becomes old.

Microscopic Features

- Hypha: Coenocytic and branched
- Spores: Generally black in colour but can vary with different species. The spores can be motile or non-motile and can exist in variable shapes.

1.1.7. Life Cycle of Mucor:

It has three modes of reproduction in its lifecycle:

Vegetative Reproduction

It occurs by the fragmentation method, where a vegetative cell breaks into several fragments during some unfavourable conditions. After which, each fragment then develops into a new vegetative body.

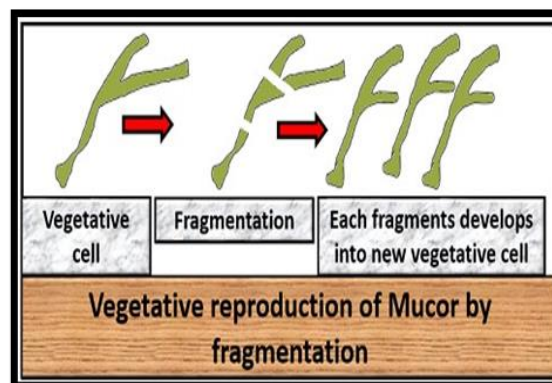


Fig2: Vegetative reproduction of mucor by fragmentation

Asexual Reproduction

It occurs through the asexual and non-motile spores like:

Sporangiospores

These are the spores that form within the cell or sporangium and are non-motile. There are following steps involved in the asexual reproduction of Mucor through sporangiospores:

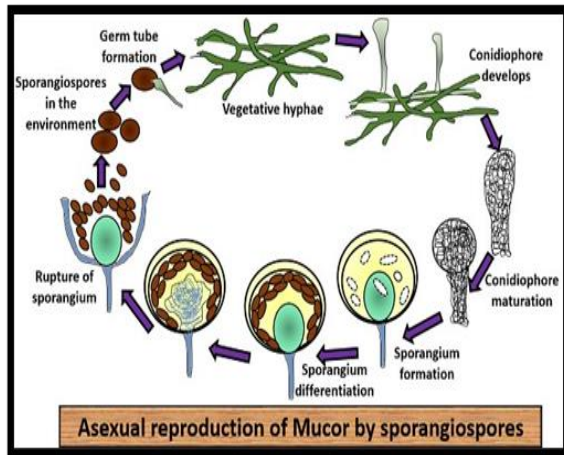


Fig3: Asexual reproduction of Mucor by Sporangiospores

1. From the hyphae, first sporangiophores arise singly that are erect in position and unbranched.
2. Then, maturation of sporangiophore occurs where the cytoplasm and nuclei push upwards by making the aerial hyphae swollen from the apical end.
3. After that, it develops a large round sporangium.
4. During the maturation phase, sporangium differentiates into:
 - Sporoplasm: It is thick, dense, multinucleate and present inside the sporangial wall.
 - Columellaplasm: It is vacuolated and nucleated towards the centre.
5. After this, several small vacuoles appear between these differentiated portions. The space between the vacuoles forms cleavage furrows (cavity for cleavage).
6. Then, a septum forms to the inner side of the cavity, which further divides into the inner columella and upper sporoplasm. This septum then grows to form a dome shape and later it pushes itself into the sporangium.

7. Cleavage occurs in the sporoplasm between the nucleus and the cytoplasm. This division forms a wall around many thin-walled, multinucleate spores called “Sporangiospores”.
8. The sporangiospores then releases out of the sporangia after the columella swells up due to the pressure exerted on the sporangial wall. As a result, cell lysis occurs.
9. The spores remain dormant for some time, and when they obtain suitable substratum, they germinate to a new vegetative body through the germ tube.

Chlamyospores

A hard wall covers these spores, and it develops inside the vegetative cell during unfavourable conditions. In unfavourable conditions, mycelium becomes septate by the accumulation of nuclei and cytoplasm in a certain portion and becomes surrounded by a thick wall called chlamyospores. This spore then detaches from the mycelium and remains dormant. On favourable conditions, they form a germ tube.

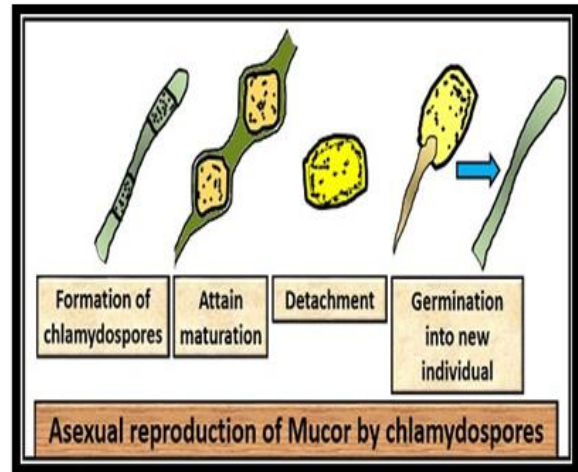


Fig4: Asexual reproduction of Mucor by Chlamyospores

Oidiospores

When a mycelium grows in a substrate (rich in sugar), some small, thin-walled and pearl-like reproductive structures form that detaches out of the vegetative cell as in budding of yeast. Then oidospores remain dormant for some time and on favourable conditions, it forms a germination tube to form a new vegetative body.

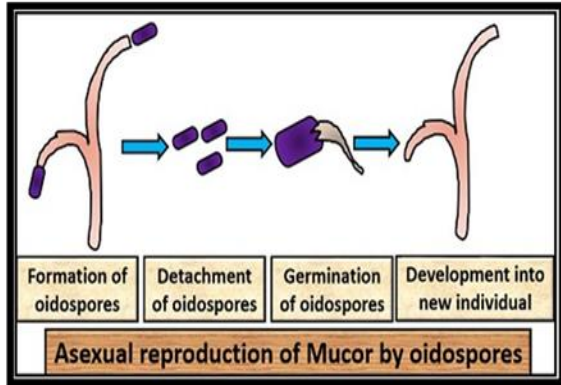


Fig5: Asexual reproduction of Mucor by Oidospores
Sexual Reproduction

In Mucor, the sexual reproduction occurs by the method that is called as Gametangial conjugation, which involves the following steps:

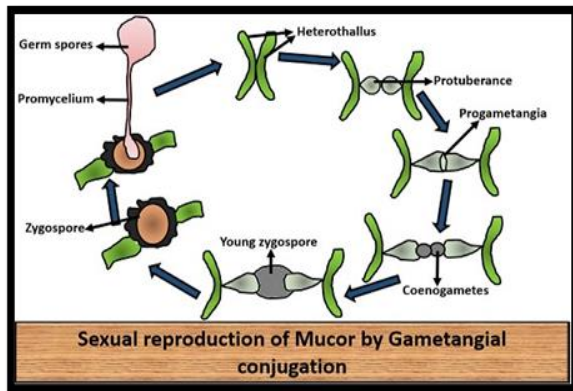


Fig 6: sexual reproduction of Mucor by Gametangial conjugation

1. First, the thallus of two opposite strains, i.e. one is (+), and other is (-), comes in contact with each other.
2. When they come in contact, there develops a small outgrowth or protuberance from both of the thalli.
3. After that, the outgrowth swells to form “Progametangium”.
4. Then septum develops between the progametangium, and the fusion of progametangia occurs that results in the formation of gametes called “Coenogametes”.
5. Then gametes of both the strains fuse to form a “Zygote”.
6. The zygote then enlarges in size and get surrounded by a thick-walled structure called “Zygospore”.

7. Zygospore is dark black in colour, which gets covered by the two layers, namely:
 - Outer layer: Also called Exosporium.
 - Inner layer: Also called Endosporium.
8. The zygospore remains dormant for some time and on favourable conditions, promycelium develops out from the zygospore, forming a new vegetative body.

2. WHAT IS 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, particularly 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, the lung or sinus forms of the infection 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. 3-6 Mucormycosis can also develop on the skin after the fungus enters the skin through a cut, scrape, burn, or other type of skin trauma.

2.1. TYPES OF MUCORMYCOSIS

- Rhinocerebral (sinus and brain) mucormycosis is an infection in the sinuses that can spread to the brain. This form of mucormycosis is most common in people with uncontrolled diabetes and in people who have had a kidney transplant. 7-8
- 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, especially premature and low birth weight infants less than 1 month of age, who have had antibiotics, surgery, or medications that lower the body’s ability to fight germs and sickness. 9-10
- Cutaneous (skin) mucormycosis: occurs after the fungi enter the body through a break in the skin (for example, after surgery, a burn, or other type 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.

2.2. TYPES OF FUNGI THAT MOST COMMONLY CAUSE MUCORMYCOSIS

Examples: Rhizopus species, Mucor species, Rhizomucor species, Syncephalastrum species, Cunninghamellabertholletiae, Apophysomyces species, and Lichtheimia (formerly Absidia) species.

2.3. SYMPTOMS OF MUCORMYCOSIS

The symptoms of mucormycosis depend on where in the body the fungus is growing. 11, 14 Contact your healthcare provider if you have symptoms that you think are related to mucormycosis.

Symptoms of rhinocerebral (sinus and brain) mucormycosis include:

- One-sided facial swelling, Headache, Nasal or sinus congestion, Black lesions on nasal bridge or upper inside of mouth that quickly become more severe, Fever.
- Symptoms of pulmonary (lung) mucormycosis include:
 - Fever, Cough, Chest pain, Shortness of breath.
- Cutaneous (skin) mucormycosis can look like blisters or ulcers, and the infected area may turn black. Other symptoms include pain, warmth, excessive redness, or swelling around a wound.
- Symptoms of gastrointestinal mucormycosis include:
 - Abdominal pain, Nausea and vomiting, Gastrointestinal bleeding
- Disseminated mucormycosis typically occurs in people who are already sick from other medical conditions, so it can be difficult to know which symptoms are related to mucormycosis. Patients with disseminated infection in the brain can develop mental status changes or coma.

3. PEOPLE AT RISK & PREVENTION

3.1. WHO GETS MUCORMYCOSIS?

Mucormycosis is rare, but it is more common among people who have health problems or take medicines that lower the body's ability to fight germs and sickness. Certain groups of people are more likely to get mucormycosis, 15–17 including people with:

Diabetes, especially with diabetic ketoacidosis, Cancer, Organ transplant, Stem cell transplant, Neutropenia (low number of white blood cells), Long-term corticosteroid use, Injection drug use, too much iron in the body (iron overload or hemochromatosis), Skin injury due to surgery, burns, or wounds, Prematurity and low birthweight (for neonatal gastrointestinal mucormycosis)

3.1.1. How does someone get mucormycosis?

People get mucormycosis through contact with fungal spores in the environment. For example, the lung or sinus forms of the infection can occur after someone inhales the spores from the air. A skin infection can occur after the fungus enters the skin through a scrape, burn, or other type of skin injury.

3.1.2. Is mucormycosis contagious?

No. Mucormycosis cannot spread between people or between people and animals.

3.1.3. How can I lower the risk of mucormycosis?

It's difficult to avoid breathing in fungal spores because the fungi that cause mucormycosis are common in the environment. There is no vaccine to prevent mucormycosis. For people who have weakened immune systems, there may be some ways to lower the chances of developing mucormycosis.

1. Protect yourself from the environment. 18, 19 it is important to note that although these actions are recommended, they have not been proven to prevent mucormycosis.

- Try to avoid areas with a lot of dust like construction or excavation sites. If you cannot avoid these areas, wear an N95 respirator (a type of face mask) while you are there.
- Avoid direct contact with water-damaged buildings and flood water after hurricanes and natural disasters. 20
- Avoid activities that involve close contact to soil or dust, such as yard work or gardening. If this is not possible,

- Wear shoes, long pants, and a long-sleeved shirt when doing outdoor activities such as gardening, yard work, or visiting wooded areas.
- Wear gloves when handling materials such as soil, moss, or manure.
- To reduce the chances of developing a skin infection, clean skin injuries well with soap and water, especially if they have been exposed to soil or dust.

2. Antifungal medication. If you are at high risk for developing mucormycosis (for example, if you have had an organ transplant or a stem cell transplant), your healthcare provider may prescribe medication to prevent mucormycosis and other mold infections. 21, 22 Doctors and scientists are still learning about which transplant patients are at highest risk and how to best prevent fungal infections.

4. WHERE MUCORMYCOSIS COMES FROM

The fungi that cause mucormycosis live in the environment. Mucormycetes, the group of fungi that cause mucormycosis, are present throughout the environment, particularly in soil and in association with decaying organic matter, such as leaves, compost piles, and animal dung. 23 They are more common in soil than in air, and in summer and fall than in winter or spring. 24-26 most people come in contact with microscopic fungal spores every day, so it's probably impossible to completely avoid coming in contact with mucormycetes. These fungi aren't harmful to most people. However, for people who have weakened immune systems, breathing in mucormycete spores can cause an infection in the lungs or sinuses which can spread to other parts of the body.

4.1. Types of fungi that cause mucormycosis

Several different types of fungi can cause mucormycosis. These fungi are called mucormycetes and belong to the scientific order Mucorales. The most common types that cause mucormycosis are Rhizopus species and Mucor species. 27 Other examples include Rhizomucor species, Syncephalastrum species, Cunninghamella bertholletiae, Apophysomyces, Lichtheimia (formerly Absidia), Saksenaia, and Rhizomucor.24

5. DIAGNOSIS AND TESTING FOR MUCORMYCOSIS

5.1. How is mucormycosis diagnosed?

Healthcare providers consider your medical history, symptoms, physical examinations, and laboratory tests when diagnosing mucormycosis. Healthcare providers who suspect that you have mucormycosis in your lungs or sinuses might collect a sample of fluid from your respiratory system to send to a laboratory. Your healthcare provider may perform a tissue biopsy, in which a small sample of affected tissue is analyzed in a laboratory for evidence of mucormycosis under a microscope or in a fungal culture. You may also need imaging tests such as a CT scan of your lungs, sinuses, or other parts of your body, depending on the location of the suspected infection.

6. TREATMENT FOR MUCORMYCOSIS

6.1. How is mucormycosis treated?

Mucormycosis is a serious infection and needs to be treated with prescription antifungal medicine, usually amphotericin B, posaconazole, or isavuconazole. These medicines are given through a vein (amphotericin B, posaconazole, isavuconazole) or by mouth (posaconazole, isavuconazole). Other medicines, including fluconazole, voriconazole, and echinocandins, do not work against fungi that cause mucormycosis. Often, mucormycosis requires surgery to cut away the infected tissue.

7. ACKNOWLEDGMENT

The authors thankful to Mr. Nasir Shaikh and Mr. Johed N. Shaikh, AAEMF'S Koregaon Bhima, Pune for his kind co-operation and also thankful to Dr. S. D. Navale & Dr. A.M. Shaikh, Principals, AAEMF'S Delight Institute and Delight College of Pharmacy for providing necessary information to carry out the review work.

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