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Evidence Based Advisory Study in the time of post COVID 19 – Mucormycosis

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ABSTRACT

Mucormycosis or black fungus is a complication caused by a fungal infection. 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 types of skin trauma.

Black fungus also called **COVID-associated mucormycosis**, is a fungus infection in the nose which results from COVID-19. The condition is a type of mucormycosis, which is a fungus infection causing a nasal infection.

The condition is rare. A systematic review of research in May 2021 identified 8 cases. The most common risk factor among patients was diabetes. Patients developed the condition after hospitalization. 7 of the 8 patients died from the condition. Early aggressive treatment may be more effective than waiting. In general any mucormycosis has a mortality rate of 54%.

KEYWORDS – Mucormycosis, Black fungus, COVID-19, Fungal infection, Infectious Diseases, Amphotericin B, Liposomal.

INTRODUCTION

Two cases of mucormycosis, a usually fatal infection reported with increasing frequency, are presented. In one, a young woman with post-abortal necrosis of the spleen, kidneys and adrenals, and severe uremia, mucormycosis was thought to contribute to the fatal outcome. The second case was a young man with hepatic disease, possibly toxic in origin, and ischemic tubular necrosis. In both cases mucormycosis was disseminated, involving the respiratory and gastrointestinal tracts.

Rhizopus arrhizus was identified in the second case. This is the sixth case of visceral mucormycosis in which the organism has been identified by culture. Clinical and pathologic

features of fifty-five cases of mucormycosis reported in the English literature are summarized. In twenty-one of these cases diabetes was present and in thirteen, leukemia or lymphoma. The role of these conditions, as well as that of cortisone and antibiotics in the pathogenesis of mucormycosis, is discussed.

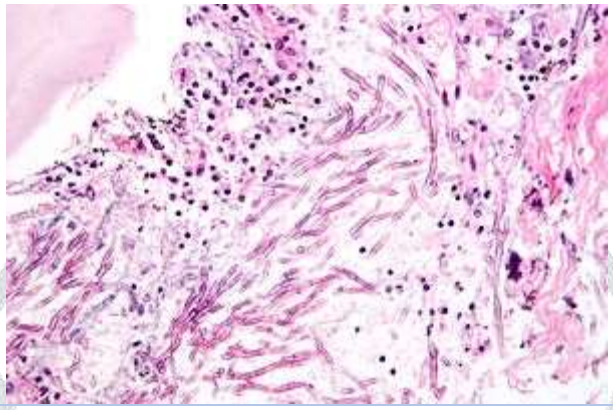
The experimental data are summarized. Alterations resulting from acute alloxan diabetes, acid osis in the form of ketosis, leukopenia, hyperglycemia and cortisone administration have been found to decrease host resistance to mucormycosis.

Mucormycosis (MCM) is a devastating infection with high mortality rates despite recent advances in its diagnosis and treatment. It is caused by the filamentous fungi of the Mucorales order of the class of Zygomycetes. Although it is classically defined as an opportunistic infection, preferentially affecting patients with diabetes mellitus (DM), neutropenia, malignancy, chronic renal failure, and acquired immunodeficiency syndrome and those who have received organ or hematopoietic stem cell transplants, it can affect immunocompetent hosts as well (such as trauma patients). The incidence of MCM worldwide appears to be increasing, particularly in oncological patients and those with DM. Along with aspergillus, it is one of the most common invasive fungal infections affecting immunosuppressed individuals.

Despite aggressive surgical and polyene antifungal therapy, overall mortality for MCM infection remains high, with figures ranging from 20 to 50%. Depending on patient characteristics (such as critically ill or immunocompromised patients) and site of infection, mortality rises markedly, nearing 70–90% for cases of disseminated mucormycosis. Inhalation of sporangiospores is the most common route of transmission, although ingestion of spores, direct implantation into injured skin (burns), trauma with contaminated soil, or intravenous (drug users) transmission have also been described. After nasal inoculation it takes a rapidly progressive course extending to neighboring tissues, including the orbit, and sometimes to the brain. Lipid formulations of amphotericin B are the mainstay of treatment, along with aggressive surgical therapy. However, such drug formulations are not available worldwide due to their elevated costs.

Mycosis is an infectious disease caused by pathogenic fungus in humans and animals. Mycoses are common and a variety of environmental and physiological conditions can contribute to the development of fungal diseases. Inhalation of fungal spores or localized colonization of the skin may initiate persistent infections; therefore, mycoses often start in the lungs or on the skin. Fungal infections of the skin was the 4th most common skin disease in 2010 affecting 984 million people. An estimated 1.6 million people die each year of fungal infections.

Mycosis

Mycosis	
Other names	mycoses, fungal disease, fungal infection ICD-10CM codes: Mycoses B35-B49
	
Micrograph showing a mycosis (aspergillosis). The Aspergillus (which is spaghetti-like) is seen in the center and surrounded by inflammatory cells and necrotic debris. H&E stain.	
Specialty	Infectious Diseases
Causes	Pathogenic fungus
Risk factors	Tuberculosis, COVID-19, Immunodeficiency

CAUSES

Individuals being treated with antibiotics are at higher risk of fungal infections.

People with weakened immune systems are also at risk of developing fungal infections. This is the case of people with HIV/AIDS, people under steroid treatments, and people taking chemotherapy. People with diabetes also tend to develop fungal infections. Very young and very old people, also, are groups at risk. Although all are at risk of developing fungal infections, the likelihood is higher in these groups.

Children whose immune systems are not functioning properly (such as children with cancer) are at risk of invasive fungal infections. Antifungal medications can be given at the development of a fever or when an infection has been formally identified. These agents appear equally efficacious. Research suggests kidney damage was less likely with a lipid preparation of amphotericin C compared with conventional amphotericin B. No significant differences were observed in children when comparing other antifungal agents.

Major Routes of Infection

1. Inhalation
2. Ingestion
3. Traumatic Inoculation

Pathophysiology

1. Angioinvasion
2. Vessel Thrombosis
3. Tissue Necrosis

Relationship between Predisposing factors and Site of Infection

1. Diabetic Ketoacidosis – Rhinocerebral
2. Neutropenia – Pulmonary & Disseminated
3. Steroids
4. Malnutrition – GI Tract

Clinical Features

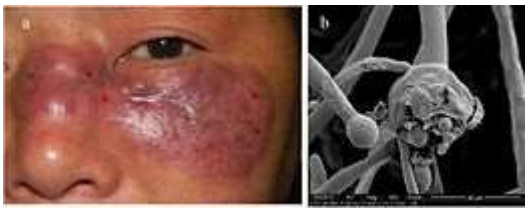
- ➢ Onset with Nasal stuffiness and facial pain.
- ➢ Later, Proptosis, Chemises, Opthalmoplegia.
- ➢ Fever and mental confusion
- ➢ Black necrotic escher on the nasal turbinates or palates.

Complications

- ✓ Cavernous sinus thrombosis
- ✓ Multiple cranial nerve palsies.
- ✓ Visual loss
- ✓ Frontal lobe abscess
- ✓ Carotid artery or jugular vein thrombosis causing hemiparesis.

SYMPTOMS OF MUCORMYCOSIS

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



A 47-year-old man with mucormycosis and electron micrograph of his skin showing sporangia of Mucorales fungi.

Symptoms of rhinocerebral (sinus and brain) mucormycosis **include:**

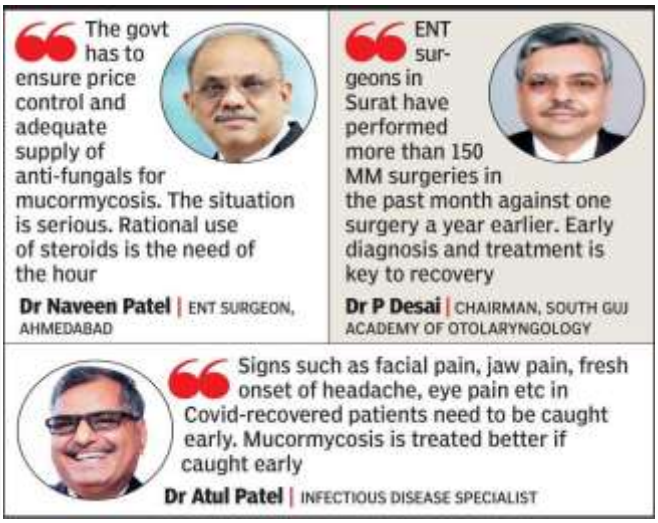
- One-sided facial swelling
- Headache
- Nasal or sinus congestion
- Black lesions on nasal bridge or upper inside of mouth that quickly become more severe
- Fever

Symptoms of pulmonary (lung) mucormycosis **include:**

- Fever
- Cough
- Chest pain
- Shortness of breath

Symptoms of **gastrointestinal mucormycosis** include:

- Abdominal pain
- Nausea and vomiting
- Gastrointestinal bleeding



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.
- 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.

MOLECULAR MECHANISM OF MUCORMYCOSIS

Mucormycosis angioinvasion is reliant on unique interaction between Mucorales CotH and endothelium GRP78, which triggers host cell injury and subsequent hematogenous dissemination of the fungus.

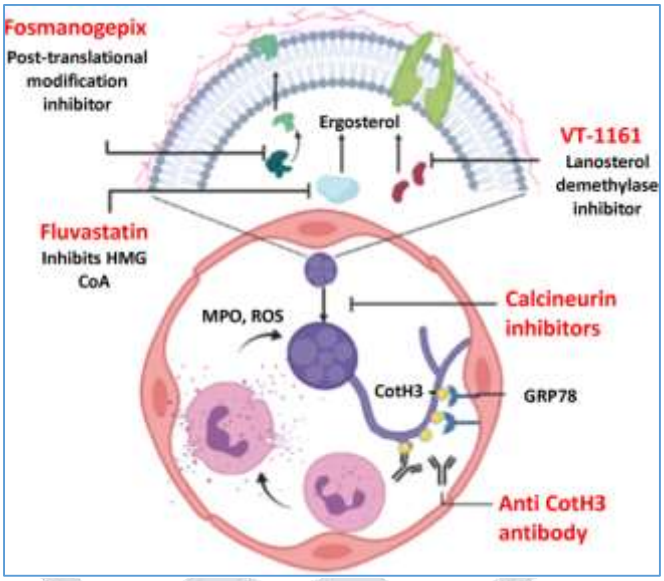


Fig. Management of Mucormycosis

There are several key signs which point towards mucormycosis. One such sign is fungal invasion into the blood vessels which results in the formation of blood clots and surrounding tissue death due to a loss of blood supply. If the disease involves the brain, then symptoms may include a one-sided headache behind the eyes, facial pain, fevers, nasal congestion that progresses to black discharge, and acute sinusitis along with eye swelling. Affected skin may appear relatively normal during the earliest stages of infection. This skin quickly becomes reddened and may be swollen before eventually turning black due to tissue death. Other forms of mucormycosis may involve the lungs, skin, or be widespread throughout the body; symptoms may also include difficulty breathing, and persistent cough.

HOW DOES SOMEONE GETS 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.

IS MUCORMYCOSIS CONTAGIOUS?

No. Mucormycosis can't spread between people or between people and animals.

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.

- **Protect yourself from the environment**. It's important to note that although these actions are recommended, they haven't been proven to prevent mucormycosis.
  - Try to avoid areas with a lot of dust like construction or excavation sites. If you can't avoid these areas, wear an N95 respirator (a type of face mask) while you're there.
  - Avoid direct contact with water-damaged buildings and flood water after hurricanes and natural disasters.
  - Avoid activities that involve close contact to soil or dust, such as yard work or gardening.
  - If this isn't 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.
- **Antifungal medication**. If you are at high risk for developing mucormycosis (for example, if you've had an organ transplant or a stem cell transplant), your healthcare provider may prescribe medication to prevent mucormycosis and other mold infections. Doctors and scientists are still learning about which transplant patients are at highest risk and how to best prevent fungal infections.

Medical illustration of mucormycetes.

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. They are more common in soil than in air, and in summer and fall than in winter or spring. 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.

Etiologic agent

Molds belonging to the order Mucorales, most commonly *Rhizopus* species. Others include *Mucor* species, *Cunninghamella bertholletiae*, *Apophysomyces* species, and *Lichtheimia* (formerly *Absidia*) species.

Reservoir

Mucormycetes are thermotolerant molds that are found in the environment. Environmental sampling studies indicate that Mucormycetes are commonly found in soil, but are rarely found in air samples targeting fungal spores. Specific environmental niches vary among genera and species.

Information for Healthcare Professionals about Mucormycosis

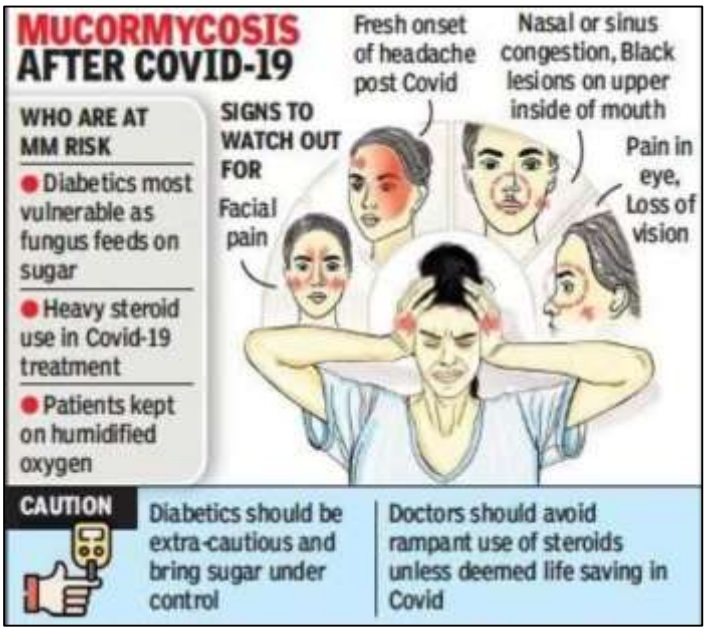
Clinical features

There are five major clinical forms of mucormycosis; of these, rhinocerebral and pulmonary infections are the most common. A classic clinical sign of mucormycosis is the rapid onset of tissue necrosis with or without fever. Necrosis is the result of invasion of blood vessels and subsequent thrombosis.

- **Rhinocerebral mucormycosis** is the most common form in patients with diabetes and with renal transplants. It also occurs in neutropenic cancer patients and hematopoietic stem cell transplant or solid organ transplant recipients. Symptoms may include unilateral facial swelling, headaches, nasal or sinus congestion or pain, serosanguinous nasal discharge, and fever. As the infection spreads, ptosis, proptosis, loss of extraocular muscle function, and vision disturbance may occur. Necrotic black lesions on the hard palate or nasal turbinate and drainage of black pus from eyes are useful diagnostic signs.
- **Pulmonary mucormycosis** generally occurs in patients with hematologic malignancy or profound neutropenia. The symptoms are non-specific and include fever, cough, chest pain, and dyspnea. Angioinvasion results in tissue necrosis, which may ultimately lead to cavitation and/or hemoptysis.
- **Cutaneous mucormycosis** may be primary or secondary. Primary infection is usually caused by direct inoculation of the fungus into disrupted skin and is most often seen in patients with burns or other forms of local skin trauma, and can occur in patients who are not immunosuppressed. Primary infection produces an acute inflammatory response with pus, abscess formation, tissue swelling, and necrosis. The lesions may appear red and indurated and often progress to black eschars. Secondary cutaneous infection is generally seen when the pathogen spreads hematogenously; lesions typically begin as an erythematous, indurated, and painful cellulitis and then progress to an ulcer covered with a black eschar.
- **Gastrointestinal mucormycosis** is less common than the other clinical forms and is believed to result from ingestion of the organism. It typically occurs in malnourished patients or premature infants. The stomach, colon, and ileum are most commonly affected. Non-specific abdominal pain and distension, nausea, and vomiting are the most common symptoms, and gastrointestinal bleeding can occur. It is the most common form of mucormycosis among neonates and is challenging to diagnose partly because of its clinical resemblance to necrotizing enterocolitis, a far more common disease.
- **Disseminated mucormycosis** may follow any of the forms of mucormycosis described above but is usually seen in neutropenic patients with a pulmonary infection. The most common site of spread is the brain, but the spleen, heart, skin, and other organs can also be affected.

Risk Factor

Predisposing factors for mucormycosis include AIDS, uncontrolled diabetes mellitus, cancers such as lymphomas, kidney failure, organ transplant, long term corticosteroid and immunosuppressive therapy, cirrhosis, energy malnutrition, and deferoxamine therapy. Despite this, however, there have been cases of mucormycosis reported with no apparent predisposing factors present



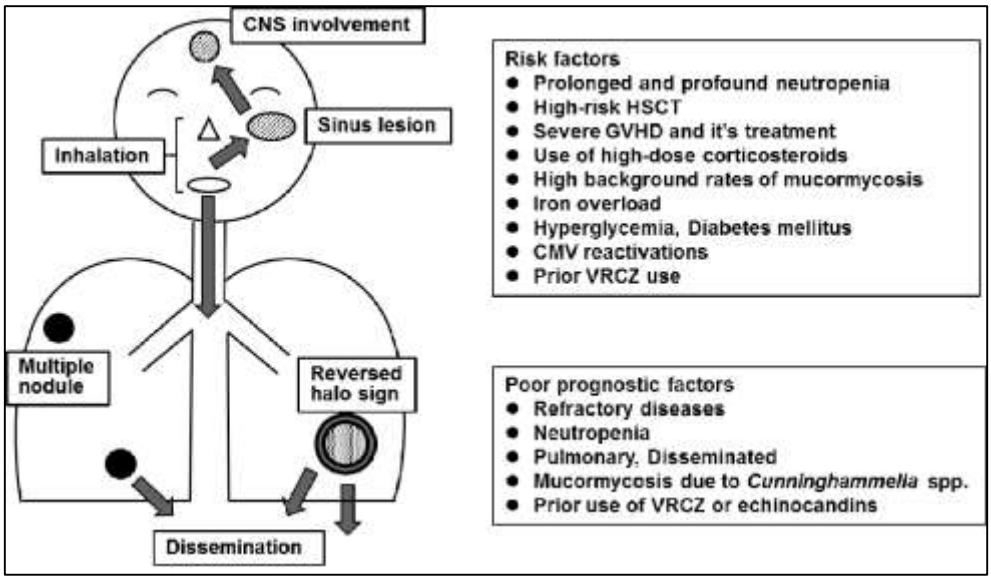
Corticosteroids are commonly used in the treatment of COVID-19 and reduce damage caused by the body's own immune system during a coronavirus infection. They are immunosuppressant and increase blood sugar levels in both diabetics and non-diabetic patients. It is thought that both these effects may contribute to cases of mucormycosis.

Risk groups for mucormycosis include persons with uncontrolled diabetes; malignancy; hematopoietic stem cell transplant or solid organ transplant; persistent neutropenia; prolonged corticosteroid therapy; skin trauma, burns, or surgical wounds; iron overload; intravenous drug use; malnourishment; and premature infants.

Mucormycosis Statistics

How common is mucormycosis?

Mucormycosis is rare, but the exact number of cases is difficult to determine because no national surveillance exists in the United States. Population-based incidence estimates for mucormycosis were obtained from laboratory surveillance in the San Francisco Bay Area during 1992–1993 and suggested a yearly rate of 1.7 cases per 1 million population. Prospective surveillance among 16,808 transplant recipients performed in 23 institutions during 2001–2006 found that mucormycosis was the third most common type of invasive fungal infection in stem cell transplant recipients and accounted for 8% of all invasive fungal infections (77 mucormycete cases occurred among 983 stem cell transplant recipients who developed any fungal infection). Among solid organ transplant recipients, mucormycosis accounted for 2% of all invasive fungal infections (28 mucormycete cases occurred among 1,208 solid organ transplant recipients who developed any fungal infection). The number of cases varied widely across participating institutions.

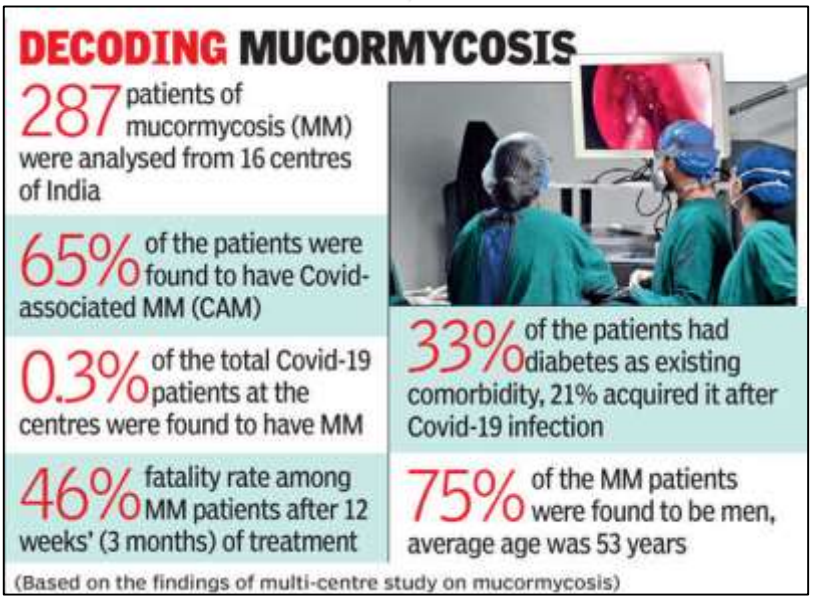


Mucormycosis outbreaks

Healthcare providers who are concerned about an unusual number of new cases should contact their state or local public health agency. Although most cases of mucormycosis are sporadic (not part of an outbreak), outbreaks of mucormycosis have occured. In healthcare settings, it can be difficult to determine whether mucormycosis is healthcare-associated or whether the infections were acquired somewhere else. Some examples of sources implicated in healthcare-associated mucormycosis outbreaks include adhesive bandages, wooden tongue depressors, hospital linens, negative pressure rooms, water leaks, poor air filtration, non-sterile medical devices, and building construction. Community-onset outbreaks have been associated with trauma sustained during natural disasters.

Deaths due to mucormycosis

Mucormycosis is frequently a life-threatening infection. A review of published mucormycosis cases found an overall all-cause mortality rate of 54%. The mortality rate varied depending on underlying patient condition, type of fungus, and body site affected (for example, the mortality rate was 46% among people with sinus infections, 76% for pulmonary infections, and 96% for disseminated mucormycosis).



CASES FOUND IN INDAN AND OTHER STATES

- According to government, of the total 40,845 cases, 31,344 cases are rhinocerebral in nature.
- Rhinocerebral mucormycosis is a rare opportunistic infection of the sinuses, nasal passages, oral cavity, and brain caused by saprophytic fungi.

India has so far reported over 40,845 cases of mucormycosis or black fungus so far, a majority of which infected the brain and sinuses of covid-19 patients. According to the government data released at the 29th meeting of the high-level group of ministers on covid-19 held virtually on Monday, of the total 40,845 cases, 31,344 cases are rhinocerebral in nature. Rhinocerebral mucormycosis is a rare opportunistic infection of the sinuses, nasal passages, oral cavity, and brain caused by saprophytic fungi.

“Fatality from the infections stands at 3,129. Of the total numbers, 34,940 patients had covid-19 (85.5%), 26,187 (about 64.11%) were co-morbid for diabetes while 21,523 (52.69%) of those infected were on steroids," said Harsh Vardhan, Union minister of health and family welfare who chaired the GoM. “13,083 patients were in the age group 18-45 (32%), 17,464 were in the age group 45-60 (42%) while 10,082 (24%) patients were 60+ years of age," he said.

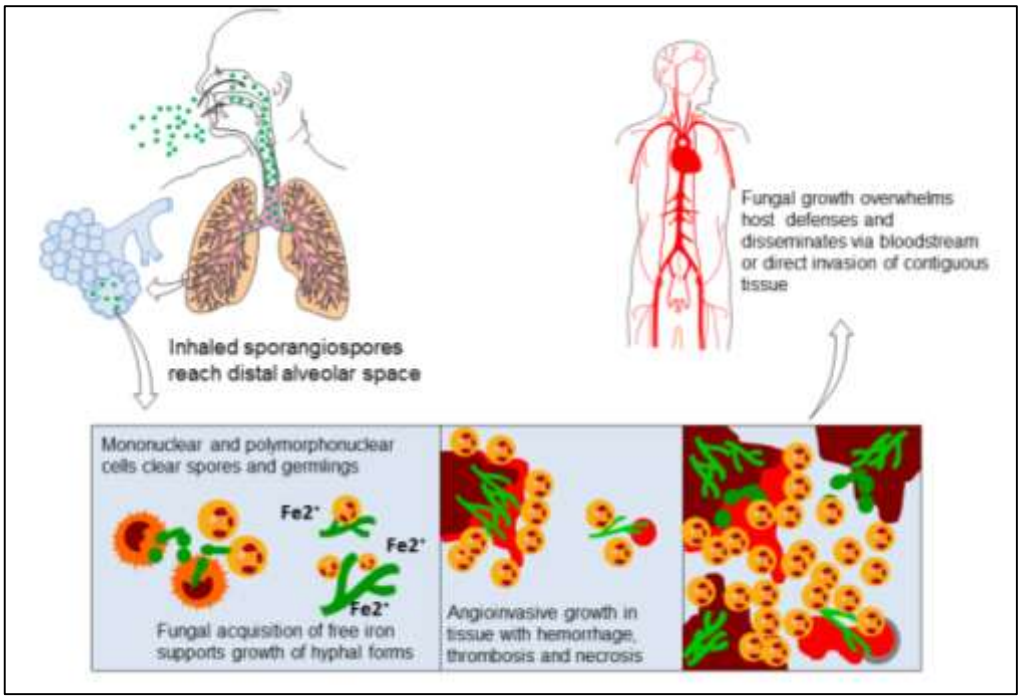
Active cases continue to be concentrated mainly in Maharashtra, Kerala, Tamil Nadu, West Bengal and Odisha which are reporting growth rates more than the national covid-19 growth rate. While 19 states are reporting fatality figures in single-digit (less than 10), four states of Kerala, Karnataka, Maharashtra and Tamil Nadu are reporting more than a hundred deaths daily, the government data showed.

In the last 24 hours, India recorded 46,148 cases, causing the active caseload to decline significantly to 5, 72, 994 in the country. “The recovery rate has been steadily increasing and stands at 96.80% today. 58,578 recoveries were registered in the last 24 hours. Today is the 46th day in succession where our daily recoveries outnumbered new cases. Our case fatality rate has been 1.30%, daily positivity rate at 2.94% and weekly positivity rate also stands at 2.94% which has been consistently below 5% for 21 days now," said Harsh Vardhan.

The Union health minister said that India has overtaken the US in the total number of covid vaccine doses administered so far. The US started vaccinating against covid-19 on 14 December 2020 whereas the drive was launched in India on 16 January 2021. Under the new vaccination policy, the Centre is procuring and supplying free of cost 75% of the vaccines being produced by the vaccine manufacturers in the country to states and union territories.

Diagnosis and testing for Mucormycosis

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.



As swabs of tissue or discharge are generally unreliable, the diagnosis of mucormycosis tends to be established with a biopsy specimen of the involved tissue.

Few additional points on Mucor and COVID19

- Increase in ferritin level is commonly seen in COVID–19 patients. Iron overload can lead to increased susceptibility to Mucormycosis.
- Prolonged use of higher end antibiotics can kill the bacterial commensals, leading to proliferation of fungal commensal such as Rhizopus or Mucor and generating a susceptible environment to cause Mucormycosis.
- Excessive use of steroids can aggravate hyperglycaemia and in turn create a conducive environment for proliferation of fungi.
- Intubation, Mechanical ventilation, Chronic respiratory disease can lead to damaged epithelial and endothelial tissues – site for fungal angioinvasion.
- Besides, the diffuse alveolar damage with severe inflammatory exudation, COVID-19 patients always have immunosuppression with a decrease in CD4 + T and CD8 + T cells. Severe form of COVID-19 illness is also found to reduce the level of lymphocytes as well as neutrophils. Both of which increase the chances of getting Mucormycosis infection.
- Information dissemination, Risk communication and Health education to public on early warning signs and symptoms.

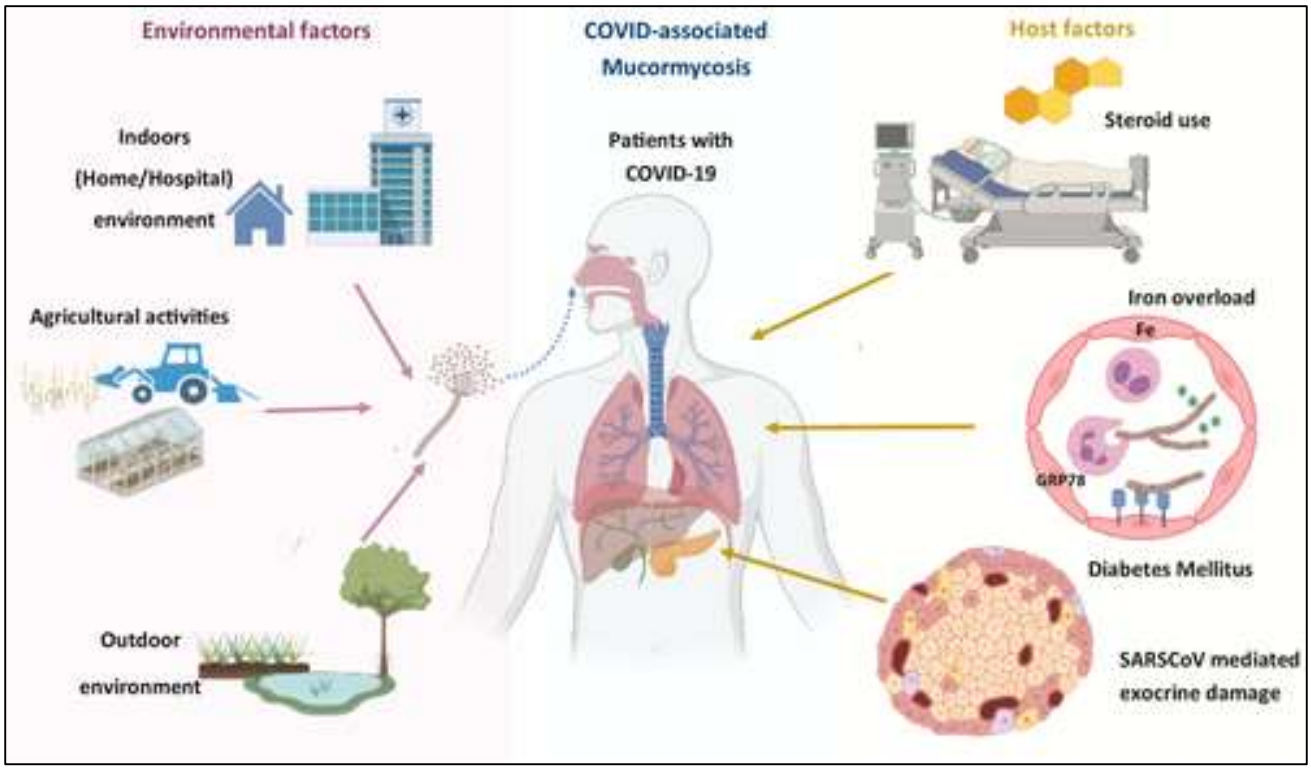


Figure. Recommendations on Treatment of Covid-19 associated mucormycosis

Treatment

If mucormycosis is suspected, amphotericin B therapy should be immediately administered due to the rapid spread and high mortality rate of the disease. Amphotericin B is usually administered for an additional 4–6 weeks after initial therapy begins to ensure eradication of the infection. Isavuconazole was recently FDA approved to treat invasive aspergillosis and invasive mucormycosis.

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.

After administration of either amphotericin B or posaconazole, surgical removal of the "fungus ball" is indicated. The disease must be monitored carefully for any signs of reemergence.

Surgical therapy can be very drastic, and in some cases of disease involving the nasal cavity and the brain, removal of infected brain tissue may be required. In some cases surgery may be disfiguring because it may involve removal of the palate, nasal cavity, or eye structures. Surgery may be extended to more than one operation. It has been hypothesized that hyperbaric oxygen may be beneficial as an adjunctive therapy because higher oxygen pressure increases the ability of neutrophils to kill the fungus.

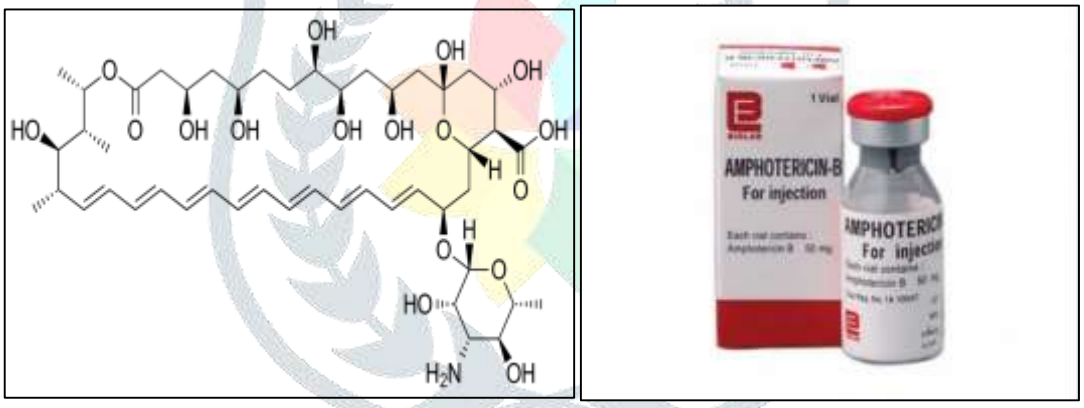
The overall management of mucormycosis should be started as early as possible. Management can involve consultation with various experts like infectious disease specialist, microbiologist, histopathologist, intensivist, pulmonologist, neurologist, ENT specialist, ophthalmologist, dentist, surgeons, and radiologists. People who are suspected of having

mucormycosis should contact their nearest healthcare provider at the earliest and then seek care from the above listed specialists as per the involvement of the organ.

Treatment algorithm

- The following recommendation for the treatment of CAMs is considering the evidence available.
- The following algorithm is generic and should be used as a guiding tool but used judiciously by treating physicians as per the case at hand.
- Special considerations must be made by the multidisciplinary treatment teams while considering extensive surgical debridement regarding future disability and quality of life of the patients.
- This has been recommended by FISF in their recent guidelines specifically for treatment of Covid-19 associated mucormycosis.
- ICMR Advisory for screening, diagnosis and management of covid-19 associated mucormycosis.
- The guide box on manageing covid-19 associated mucormycosis by DGHS.
- The clinical guidelines from All India Institute of Medical Sciences (AIIMS), New Delhi.

Amphotericin B



Amphotericin B is an antifungal medication used for serious fungal infections and leishmaniasis. The fungal infections it is used to treat include aspergillosis, blastomycosis, candidiasis, coccidioidomycosis, and cryptococcosis. For certain infections it is given with flucytosine. It is typically given by injection into a vein.

Common side effects include a reaction with fever, chills, and headaches soon after the medication is given, as well as kidney problems. Allergic symptoms including anaphylaxis may occur. Other serious side effects include low blood potassium and inflammation of the heart. It appears to be relatively safe in pregnancy. There is a lipid formulation that has a lower risk of side effects. It is in the polyene class of medications and works in part by interfering with the cell membrane of the fungus.

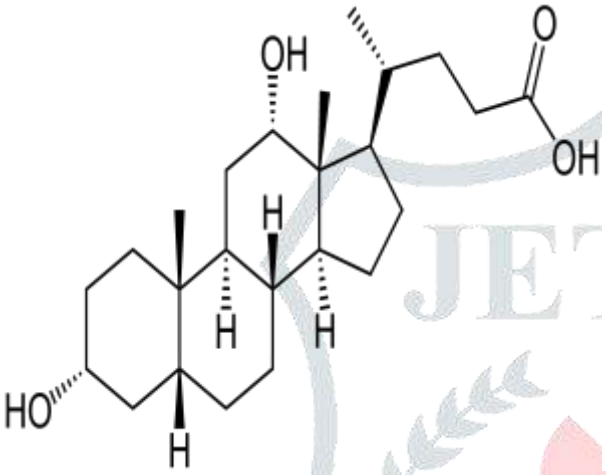
Amphotericin B was isolated from Streptomyces nodosus in 1955 and came into medical use in 1958. It is on the World Health Organization's List of Essential Medicines, the safest and most effective medicines needed in a health system. It is available as a generic medication. The cost in the developing world of a course of treatment as of 2010 is between US$162 and 229.

Available Formulations

Intravenous

Amphotericin B alone is insoluble in normal saline at a pH of 7. Therefore, several formulations have been devised to improve its intravenous bioavailability. Lipid-based formulations of amphotericin B are no more effective than conventional formulations, although there is some evidence that lipid-based formulations may be better tolerated by patients and may have fewer adverse effects.

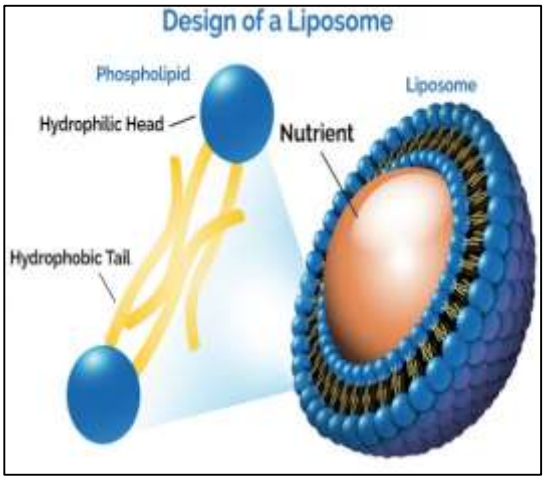
Deoxycholate



The original formulation uses sodium deoxycholate to improve solubility. Amphotericin B deoxycholate (ABD) is administered intravenously. As the original formulation of amphotericin, it is often referred to as "conventional" amphotericin.

Liposomal

In order to improve the tolerability of amphotericin and reduce toxicity, several lipid formulations have been developed. Liposomal formulations have been found to have less renal toxicity than deoxycholate, and fewer infusion-related reactions. They are more expensive than amphotericin B deoxycholate.



AmBisome (LAMB) is a liposomal formulation of amphotericin B for injection and consists of a mixture of phosphatidylcholine, cholesterol and distearoyl phosphatidylglycerol that in aqueous media spontaneously arrange into unilamellar vesicles that contain amphotericin B.

It was developed by NeXstar Pharmaceuticals (acquired by Gilead Sciences in 1999). It was approved by the FDA in 1997. It is marketed by Gilead in Europe and licensed to Astellas Pharma (formerly Fujisawa Pharmaceuticals) for marketing in the US, and Sumitomo Pharmaceuticals in Japan. Fungi some is a generic liposomal complex of amphotericin B marketed by Lifecare Innovations of India. Amphotericin is available in by abbot india brand name fungizone inj in 50 mg rs 367 per vial and many other also like amphy by intas 2990 and lambin by sun Pharma 4457 etc all are injection

Lipid complex formulations

A number of lipid complex preparations are also available. Abelcet was approved by the FDA in 1995. It consists of amphotericin B and two lipids in a 1:1 ratio that form large ribbon-like structures. Amphotec is a complex of amphotericin and sodium cholesteryl sulfate in a 1:1 ratio. Two molecules of each form a tetramer that aggregate into spiral arms on a disk-like complex. It was approved by the FDA in 1996

By mouth

An oral preparation exists but is not widely available. The amphipathic nature of amphotericin along with its low solubility and permeability has posed major hurdles for oral administration given its low bioavailability. In the past it had been used for fungal infections of the surface of the GI tract such as thrush, but has been replaced by other antifungals such as nystatin and fluconazole.

However, recently novel nanoparticulate drug delivery systems such as Ambionp, nanosuspensions, lipid-based drug delivery systems including cochleates, self-emulsifying drug delivery systems, solid lipid nanoparticles and polymeric nanoparticles such as Amphotericin B in pegylated polylactide coglycolide copolymer nanoparticles have demonstrated potential for oral formulation of amphotericin B.

Management of Mucormycosis

- **Do's –**
  1. Control Hyperglycemia
  2. Monitor blood sugar level post COIVD-19 discharge and also in diabetics.
  3. Use steroid judiciously – correct timing, correct dose and duration.
  4. Use sterile, clean water for humidifiers during oxygen therapy.
  5. Use antibiotics or antifungals judiciously.
- **Don'ts –**
  1. Do not miss warning signs and symptoms.
  2. Do not consider all the cases with blocked nose cases of bacterial sinusitis, particularly in the context of immunosuppression and/or COVID-19 patients on the immunomodulatory.
  3. Do not hesitate to seek the aggressive investigations as appropriate (KOH staining and microscopy, culture) for detecting the fungal etiology.
  4. Do not lose crucial time to initiate the treatment of Mucormycosis.

- **How to Manage –**
  1. Control the diabetic and anti-diabetic ketoacidosis.
  2. Reduce steroids (if patient is still on) with aim to discontinue rapidly.
  3. Discontinue immunomodulating drugs
  4. No antifungal prophylaxis needed.
  5. Intensive surgical Debridment – to remove all necrotic material.
  6. Monitor patient clinically and with radio imaging for response and to detect disease progression.

Some of the Data from Government Websites

Table 2

Presenting signs and symptoms.

Sign/symptom	*n* (%)
Fever	10 (71.4)
Rhinorrhea	8 (57.1)
Cephalea	7 (50)
Ocular pain	4 (28.6)
Vision loss	3 (21.4)
Palpebral edema	3 (21.4)
Facial edema	2 (14.3)
Proptosis	1 (7.1)

Table 1

Demographic data.

	Total (%)	Survivors (%)	Nonsurvivors (%)	*P*
Patients	14 (100)	7 (100)	7 (100)	
Female	5 (35.7)	2 (28.6)	3 (57.1)	0.4
Male	9 (64.3)	5 (71.4)	4 (57.1)	0.5
Age (years)	39.9	27.4	52.4	**0.03** *
DM	10 (71.4)	3 (42.8)	7 (100)	**0.03** *
HM	6 (42.8)	4 (57.1)	2 (28.6)	0.29
CRI	3 (21.4)	0 (0)	3 (42.8)	0.09
KET	4 (28.6)	0 (0)	4 (57.1)	**0.03** *
Hypertension	7 (50)	2 (28.6)	5 (71.4)	0.14
Surgery	11 (78.6)	4 (57.1)	7 (100)	0.09

CRI: chronic renal insufficiency; DM: diabetes mellitus; HM: hematological malignancy; KET: diabetic ketoacidosis. Significant *P* values are indicated in bold. $P \leq 0.05$.

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