WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.084
Volume 10, Issue 12, 334-366. Review Article ISSN 2277–7105

INVASIVE MUCORMYCOSIS (A BLACK FUNGUS); EMERGING CHALLENGE & COMPLICATION IN POST COVID-19 PATIENT

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Article Received on
09 Aug. 2021,

Revised on 30 Aug. 2021,
Accepted on 20 Sept. 2021

DOI: 10.20959/wjpr202112-21675

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ABSTRACT

Even as the world is grappling with the continuing effects of the COVID-19 pandemic, a new health issue appears to be quickly reaching the potential of an outbreak in India & other country is Mucormycosis. Mucormycosis (previously called zygomycosis) is a rare but serious angio-invasive life-threatening infection caused by a group of fungi called mucormycetes. associated with high morbidity and mortality. Rhizopus species are the most causative organisms of this group & species that are most frequently isolated from patients include Mucor, Cunninghamella, Apophysomyces, Lichtheimia (formerly Absidia), Saksenaea, Rhizo mucor. Inhaling fungal spores from the air can affect the lungs and sinuses, the fungus also invades the skin through wounds such as cut, scrape, burn, or other type of skin trauma. Clinical presentation is classified according to the organ involvement. It can be rhino-orbital cerebral, pulmonary, cutaneous, gastrointestinal, or disseminated. Mucormycosis is well known to infect patients with diabetes mellitus, malignancy, chemotherapy, and other immunocompromised conditions. Mucormycosis, aspergillosis and invasive candidiasis, have been reported in patients with severe COVID-19 or those recovering patients with COVID-19. current diagnosis is dependent on culture and histopathological examination is based upon identification of characteristic symptoms, a detailed patient history, a thorough clinical evaluation and a variety of specialized test.Treatment of mucormycosis is Amphotericin B (AmB) is the first-line drug of choice; subsequently, posaconazole and isavuconazole are prescribed reliant on reversal of underlying predisposing factors, surgical debridement of infected tissues and appropriate antifungal therapy & treatment of COVID-19 largely remains systemic steroids and other immunomodulators that add to the risk of invasive fungal infection. Diagnosis and aggressive treatment of mucormycosis, the mortality rate of the disease remains high.

KEYWORDS: Rhizopus oryzae, COVID-19, Amphotericin-B, Diabetes mellitus, antifungal therapy.

INTRODUCTION

Mucormycosis also called as Zygomycosis and Phycomycosis was first described by Paultauf in 1885.

These is the disease caused by the many fungi that belong to the fungal family "Mucorales". Fungi in this family are usually found in the environment – in soil, for example and are often associated with decaying organic material such as fruit and vegetables.

They are a rare fungal infection caused by exposure to mucor mold commonly it affects the sinus, brain and lungs and can be life-threatening in diabetic or severely immunocompromised individuals.

Mucormycosis is an angioinvasive disease that is characterised by tissue infarction and necrosis the member of this family most often responsible for infections in humans is called Rhizopus oryzae.

In India though, found in tropical and subtropical climates, is also common Fungi in the Mucorales family are considered opportunistic, meaning they usually infect people with an impaired immune system, or with damaged tissue. Use of drugs which suppress the immune system such as corticosteroids can lead to impaired immune function, as can a range of other immunocompromising conditions, like cancer or transplants. Damaged tissue can occur after trauma or surgery.

Patients with diabetes mellitus, haematological malignancy and chemotherapy, haematopoietic stem cells, and solid-organ transplant recipients on immunosuppressive therapy, with iron overload, on peritoneal dialysis, extensive skin injury, human immunodeficiency virus (HIV) infection, and voriconazole therapy are at increased risk of acquiring mucormycosis. A considerable number of mucormycosis cases are reported in immunocompetent hosts. Though mucormycosis is globally distributed, certain risk factors, clinical forms, and causative agents of the disease are prevalent in India.

WHAT IS MUCORMYCOSIS?

Black fungus also known as Mucormycosis, is rare but dangerous, invasive & aggressive fungal infection. This fungal infection cause by various genera of class zygomycetes. Caused by getting into contact with fungus spores in the environment. Fungi live in environment particularly soil & decaying organic matter such leave, compost, piles, rotten, wood. The fungus also invades the skin through wounds such as cut, scrape, burn, or other type of skin trauma.

It should be noted usually occur in people who have health problem & Take of drugs which suppress the immune system such as corticosteroids can lead to impaired immune function, as can a range of other immunocompromising conditions. opportunistic, meaning they usually infect people with an impaired immune system, or with damaged tissue.

ETIOLOGY OF MUCORMYCOSIS

- The fungal species that are most frequently isolated from patients with Mucormycosis are *Apophysomyces, Cunninghamella, Lichtheimia, Mucor***,** *Rhizopus,* and *Rhizomucor*.
- The etiology of these infections differs considerably in different countries, but *Rhizopus* spp is the most common cause of these infections in most parts of the world.
- These species exist as spores and thrive in dry, humid, and arid conditions. These transmit through the air and result in mild to severe infections in immunocompromised individuals.
- The Mucoralean fungi are defined by usually abundant and rapidly growing mycelium and other anamorph structures.
- The mycelium is unsepted or irregularly septed, and the anamorphic sporangiospores produce multi-spored sporangia.
- Structures like chlamydospores, arthrospores, and yeast cells are rare in these species. The sporangia consist of the variously shaped columella.
- Some species might exhibit appendages that enable them to switch between the filamentous multicellular state and the yeast-like state.

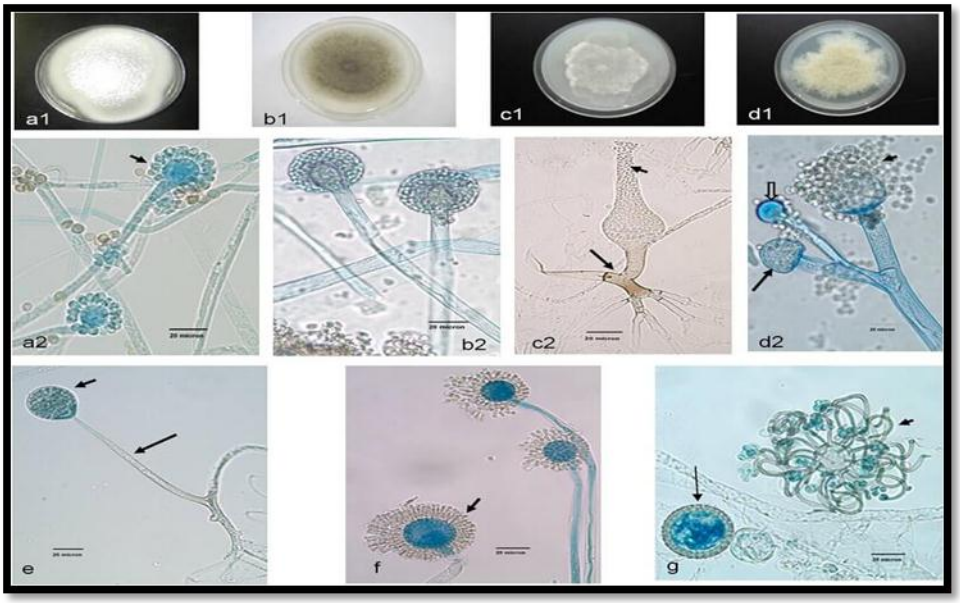

Figure 1

Unusual Mucormycosis. (a2, b2, c2, d2, and e to g) Lactophenol cotton blue mount preparations. (a1, b1, c1, and d1) Potato dextrose agar (PDA) medium plates. (a1) *Cunninghamella bertholletiae* colony surface on a PDA medium plate. (a2) *C. bertholletiae* sporangiophores in terminal swellings called vesicles, with sporangioles (short arrow). (b1) Colony surface of *Rhizomucor pusillus* on a PDA medium plate incubated at 30°C for 96 h. (b2) *R. pusillus* sporangiophores with globose sporangia. (c1) *Saksenaea vasiformis* colony surface on a PDA medium plate incubated at 30°C (48 h). (c2) *S. vasiformis* sporangiophore arising from a "foot cell"-like hyphal element (long arrow), flask-shaped sporangium, and liberated sporangiospores (short arrow). (d1) *Actinomucor elegans* colony surface on a PDA medium plate incubated at 30°C (96 h). (d2) *Actinomucor elegans* branched sporangiophores, sporangium (long arrow), columella (block arrow), and various sporangiospores (short arrow). (e) Unbranched *Apophysomyces elegans* sporangiophore (long arrow) with a pyriform sporangium (short arrow). (f) *Syncephalastrum racemosum* sporangiophores with merosporangia (short arrow). (g) *Cokeromyces recurvatus* sporangiolating vesicle (short arrow) and zygospores (long arrow). Bars, 20 µm.

VIRULENCE FACTORS OF MUCORMYCOSIS

- Iron overload
- High-affinity iron permease (FTR1)
- Rhizoferrin

- Calcineurin
- Spore coat protein

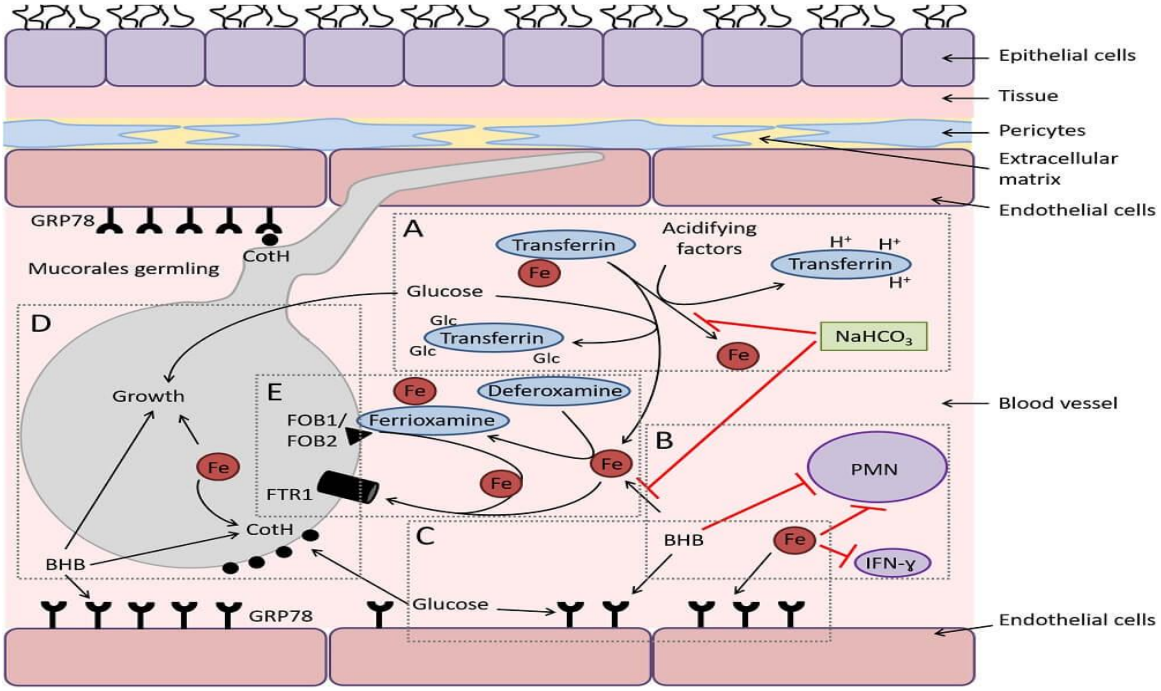

Figure 2.

Diagram depicting the interactions of Mucorales with endothelial cells during hematogenous dissemination/organ seeding and the effect of host factors on these interactions and on the immune response. (A) Hyperglycemia and ketoacidosis result in liberation of iron from serum-sequestering proteins (e.g., transferrin) via glycosylation and protonation, respectively. (B) Ketone bodies (e.g., β-hydroxy butyrate [BHB]) and free iron negatively affect the immune response to the infection, while sodium bicarbonate ($NaHCO_3$) reverses this negative effect by preventing iron release from transferrin and neutralizing acidity. (C) Surface expression of glucose-regulator protein 78 (GRP78) on endothelial cells is enhanced to cope with the stress elicited by hyperglycemia, free iron, and ketone bodies. (D) Glucose, free iron (transported by the high-affinity iron permease [Ftr1p]), and BHB also enhance the expression of fungal cell surface CotH, which results in the invasion of the endothelium and augmentation of fungal growth. (E) In deferoxamine-treated hosts, the iron-rich ferrioxamine binds to its fungal receptor (ferrioxamine binding proteins [Fob1/Fob2]) then releases iron via a reductive step prior to feeding invading Mucorales via Ftr1p transportation.

MECHANISM OF MUCORMYCOSIS IN HEALTHY INDIVIDUALS

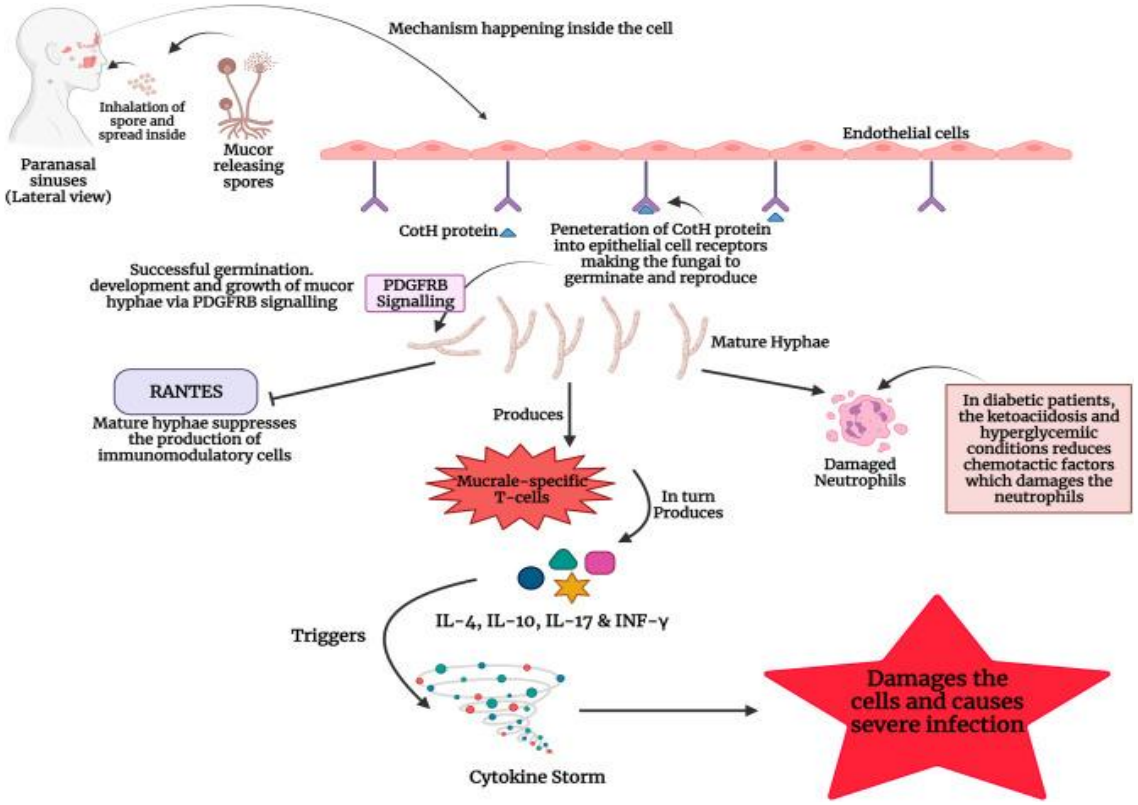

Figure 3.

When the Mucorales enters an immune-compromised patient through inhalation, or through wounds, it is initially gets attached to the epithelial cells receptor using its CotH receptors. Further, the PDGFRB signaling pathways provides essentials for the proper development and growth of the fungal hyphae. Also, if the patients have diabetes, ketoacidosis and hyperglycaemia damage the neutrophils, making it easy for the fungi spread. Once the fungi are developed it starts to produce Mucorales-specific T cells which has various pro-inflammatory cells such as IL-4, IL-10, IL-17, IFN-γ, which triggers the cytokine storm resulting into cellular damages.

TYPE OF MUCORMYCOSIS

1. **Rhinocerebral (sinus, brain and nose)mucormycosis**

Figure 4

Rhinocerebral mucormycosis is a condition caused by filamentous fungi the order Mucorales, which affect organs like the paranasal sinuses, nose, and brain. The disease is most acute, but it can become chronic as the fungus grows rapidly and aggressively. The infection begins in the nasal cavity and slowly moves to the adjacent paranasal sinuses. The fungi then attached themselves to the surface of the sinus and began reproducing as the humid condition of the nose facilitates growth and invasion of the organism.

The initial condition of the infection is associated with the formation of the fungal ball in the maxillary sinus with no bone erosion.

The condition proliferates further depending on the duration of infection, host immunity, and severity of the condition.

It is initiated by the invasion of blood vessels and damage to the endothelial cells resulting in ischemia and tissue necrosis.

The invasion of the brain and orbits of the brain is the result of the invasion of the sphenopalatine and internal maxillary arteries.

Rhinocerebral mucormycosis occurs more commonly in diabetic patients with diabetic ketoacidosis and hyperglycemia.

Commonly observed symptoms include one-sided headache behind the eyes and lethargy.

2. Pulmonary (Lung) mucormycosis

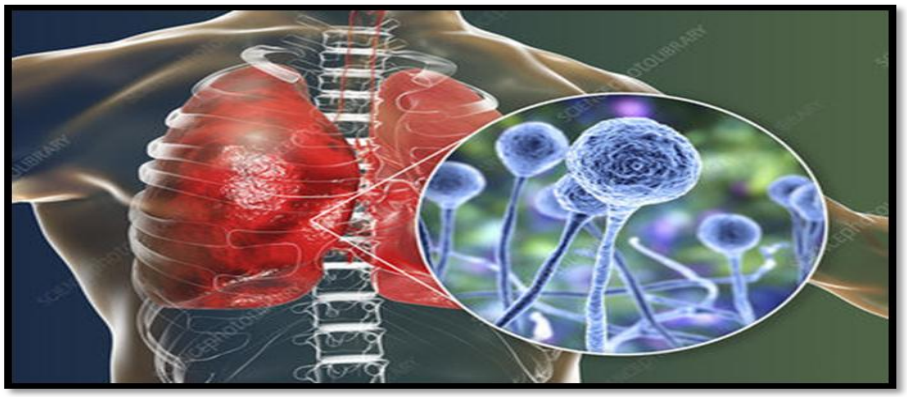

Figure-5

Pulmonary mucormycosis is an uncommon form of mucormycosis but can result in life-threatening opportunistic infections.

It is the second most common mucormycosis infection accounting for about 25% of total mucormycosis infections.

The infection is more frequent in immunocompromised patients with transplants and hematological malignancies.

Pulmonary mucormycosis has a high mortality rate of 40-70%, especially in cases with rapid local progression and angioinvasion.

The infection proceeds from the entry of the organism via inhalation. The organism reaches the lung spaces where it adheres to the endothelial cells to result in tissue damage.

The extent of damage and progression of the infection depends on the immune status of the individual and the underlying conditions.

The diagnosis of the disease is based on intrapulmonary imaging with lobar and segmental consolidation.

The increased mortality associated with the infection is the result of multifocal pneumonia with bilateral consolidation of the lungs. Single or multiple nodules can also be observed in some cases.

The causative agent of pulmonary mucormycosis is mostly *Rhizopus* spp. followed by Mucor and Rhizomucor species.

2. Cutaneous mucormycosis

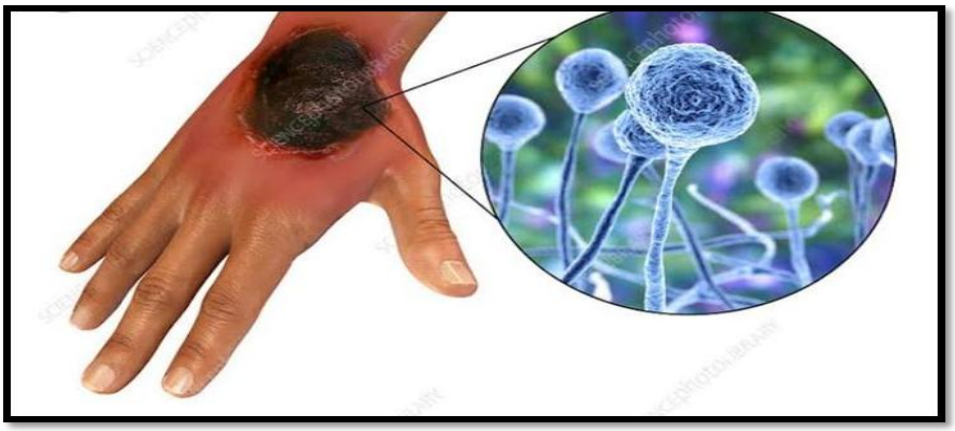

Figure-6

Cutaneous mucormycosis is also a form of mucormycosis either as a localized infection or dissemination disease.

Cutaneous mucormycosis results from the entry of the pathogen through trauma or cuts on the skin as a result of surgery, natural disaster, or inoculation of soil and other contaminated sources.

The infection can spread quite rapidly on the skin to inner layers like the subcutaneous layer, fascia, and bone.

The predominant species involved in cutaneous mucormycosis are Apophysomyces and Saksenaea, both of which are common soil saprophytes.

Cutaneous mucormycosis can be classified as primary and secondary mucormycosis, where Primary infections include infections where the organism infects the individual via direct inoculation.

Secondary mucormycosis involves the dissemination of organisms from other locations, commonly a rhinocerebral infection.

The most commonly affected areas in the case of cutaneous mucormycosis are legs and arms, including other rare cases in the scalp, face, back, thorax, breast, neck, and groin.

Secondary infections result from the spread of rhinocerebral infection, and these are more common than primary infections.

The infection begins with sinusitis which then progresses with the formation of a necrotic eschar.

4. Gastrointestinal mucormycosis

Figure-7

Gastrointestinal mucormycosis is very rare and is observed only in about 2 to 11% of the total cases of mucormycosis.

The organs involved in the infection are the stomach and intestine, but in some cases, the infection can spread to other regions of the infections are mostly mild, but in some cases, these can be fatal. The infection begins with the ingestion of spores with food or other substances that finally make way into the gastrointestinal tract.

Aggressive antifungal treatments and medical therapy with surgeries can be used as a method of treatment the intestinal tract.

5. Isolated renal mucormycosis

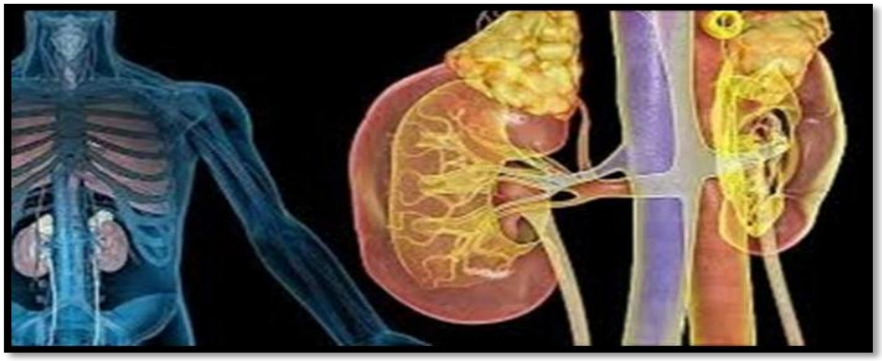

Figure- 8

Isolated renal mucoromycosis in immunocompetent individuals is a rare infection with devastating outcomes isolated involvement of the kidney with mucormycosis has been reported and is presumed to occure via seeding of the kidney during and episode of fungemia. Almost all patients with all renal mucoromycosis have risk factor of fungemia including an intravenous cathetor intravenous drug uses or aids.

6. Disseminated mucormycosis

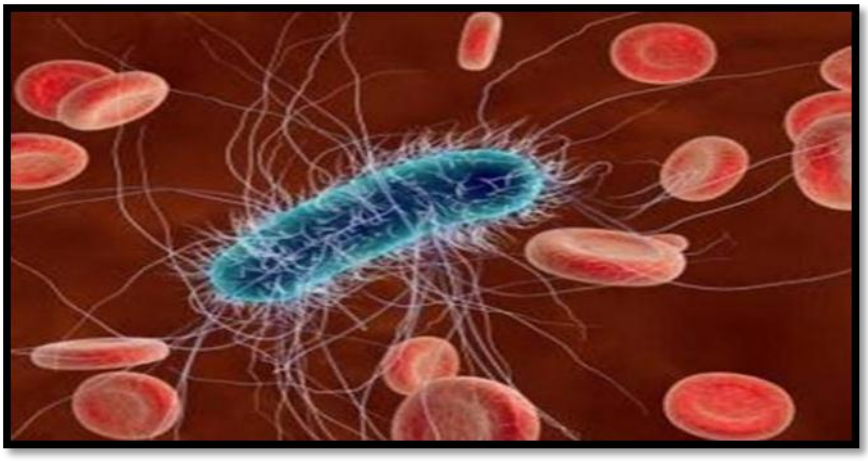

Figure-9.

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.It is the rarest form of mucormycosis that is usually only observed in neutropenic patients.

With hematologic tumors or post-transplant patients. The cases are quite rare but have an extremely high mortality rate of about 90% as the infection tends to be invasive.

The direct inoculation of the fungi is a common mode of transmission where the fungi can infect cutaneous, subcutaneous, fat muscles, and skeletal tissues.

In severe cases, the organism can even reach deep organs and result in localized infections at multiple site.

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PATHOGENESIS OF MUCORMYCOSIS

- The pathogenesis of mucormycosis begins with the inhalation or ingestion of spores from the environment.
- The entry of the spores into healthy individuals results in phagocytosis of the spores with the help of polymorphonuclear phagocytes.
- The persistence of the fungi and their growth is facilitated by defects in the phagocytic activity of the immune cells.
- Conditions like hyperglycemia and acidosis affect chemotaxis and phagocytic killing by the immune cells.
- Fungi like *Rhizopus* secrete the enzyme ketone reductase that supports the growth of fungi in acidic and glucose-rich environments like ketoacidosis.
- The increased virulence in the fungal species results in inherent resistance in these species to human phagocytes.
- Similarly, iron metabolism also plays an important role in the pathogenesis of mucormycosis. Different factors in the fungal species like the iron permeases, rhizoferrin, etc., help in the transition of ferric into soluble ferrous.
- The presence of iron in the serum further supports the growth and survival of the species in the human body.
- The fungi then slowly make their way into the bloodstream by invading blood vessels with resultant thrombosis and tissue necrosis.
- The host-pathogen interaction further results in extensive angioinvasion with ischemic necrosis and tissue damage.
- The movement of the organisms through endothelial cells and the extracellular matrix is the most critical step in the pathogenesis of fungal species like *R. oryzae*.
- The binding of the organism to the host endothelial cells results in endocytosis of the organism, which damages the endothelial cells. It has been recently understood that glucose-regulated protein (GRP78) acts as a receptor to mediate the penetration and damage of these cells.
- Since mucormycosis can occur due to a number of fungal species, the exact mechanism of disease or pathogenesis might not be the same for all species.

- Besides, the dissemination of the organism to a different part of the body can result in different forms of mucormycosis.

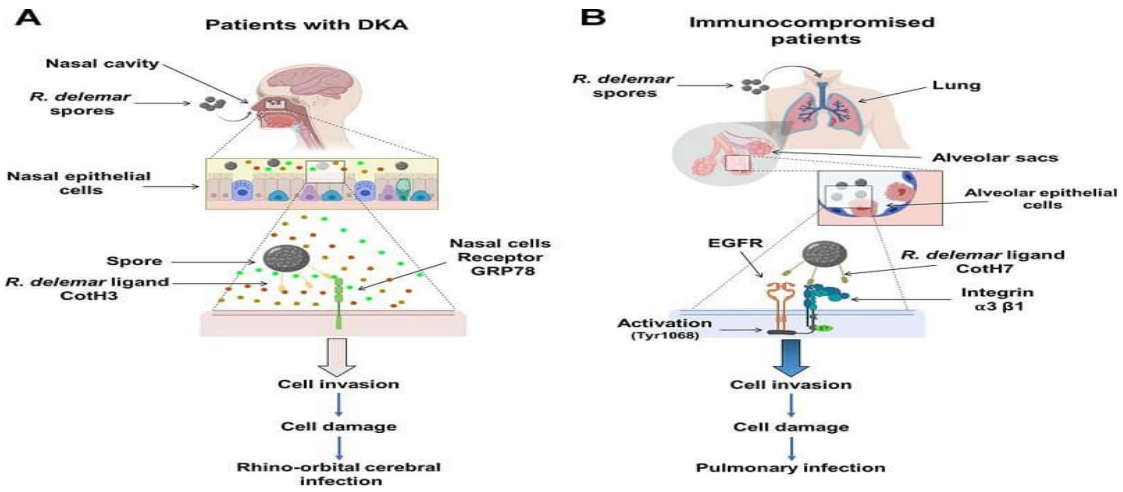

Figure: 10 A diagram showing the molecular pathogenesis of the two main manifestations of mucormycosis. **(A)** *R. delemar* inhaled spores are trapped in the sinus cavities of patients with DKA due to the overexpression of GRP78 on nasal epithelial cells, and the interaction with fungal CotH3 results in rhinoorbital/cerebral mucormycosis. Colored circles represent elevated levels of glucose, iron, and ketone bodies. **(B)** In immunosuppressed patients, inhaled spores reach the alveoli and bind to integrin α3β1 via fungal CotH7, thereby triggering activation of EGFR and subsequent invasion and pulmonary infection.

SYMPTOMS & SIGN OF MUCORMYCOSIS?

Mucormycosis signs and symptoms depend the part of the body the fungus affects

1) **rhinocerebral mucormycosis affect the sinuses, brain, and eyes and nose**

- fever, black patches on the nose and upper inner side of nose, nasal ulcer
- Stuffy nose, facial swelling, vision problems
- Sinus infection, headache

2) **Symptoms of pulmonary mucormycosis affect the lungs and include**

- Cough, chest pain, Shortness of breath
- Pneumonia, fever, hemoptysis may occur in presence of necrosis
- Dyspnea, cavitations

3) **cutaneous mucormycosis affect the skin**

- black skin on the infected area, pain, redness
- swelling, warmth around a wound
- blackened skin patches, blistering, ulceration

4) Gastrointestinal mucormycosis that affects the digestive tract

- Hematochezia,nausea,vomiting
- Massive gastrointestinal haemorrhage,abdominal pain,ulcer
- Gastrointestinal bleeding,peritonitis,bowel infractions(tissue death of the colon

5) Disseminated Mucormycosis

- Headache,fever,
- Brain infection can lead to mental disorders and even coma

6) Isolated Renal Mucoromysis

1) Fever, flank pain

RISK FACTOR OF MUCORMYCOSIS

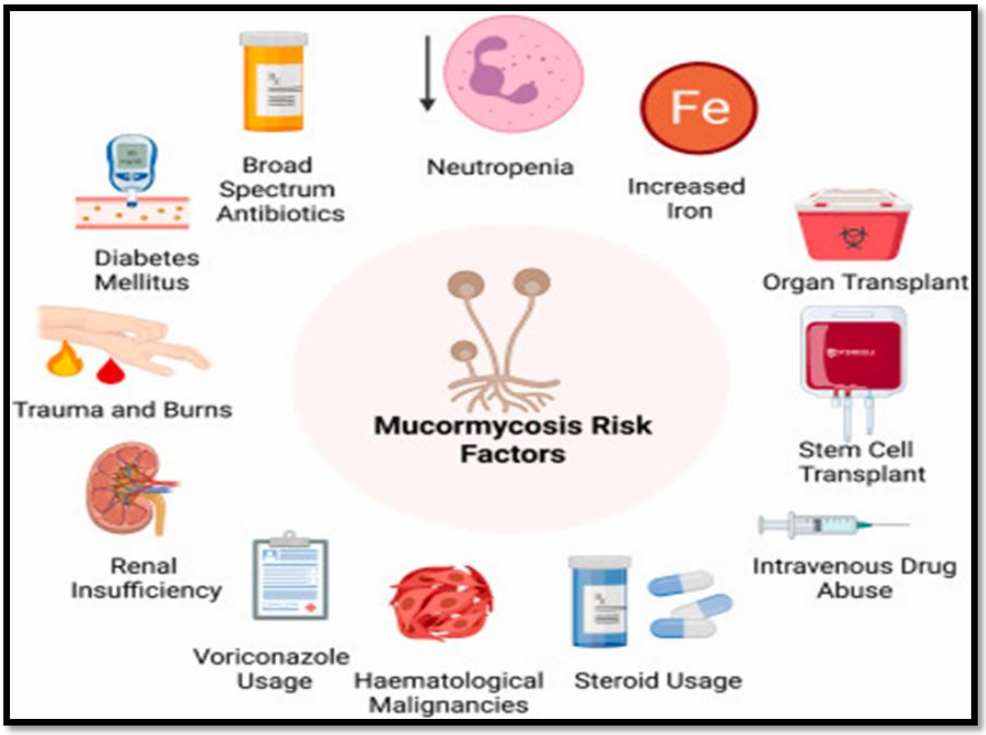

Figure -11

Diabetes patients with diabetes ketoacidosis

It is because diabetic patient have the high glucose level in their blood and *Rhizopus* can thrive in it too.

Dye to the presence of active ketone reductae system *Rhizopus* can survive in high glucose and acidotic conditions.

Due to the impaired glutathione pathway, these patients also have decreased phagocytic activity.

Though the exact phenomenon is unknown, it might be due to the metabolic abnormalities in combination with diabetic patients.

Rhizopus gets inhibited at the normal serum but the growth is stimulated in the patients of diabetic ketoacidosis.

It has been found that the patients on dialysis and iron overload, who are being treated with deferoxamine, an iron chelator are susceptible to mucormycosis.

Other risk factors includes

- Neutropenia (abnormal decrease of the neutrophil in circulating blood)
- High-dose systemic steroids
- Protein-calorie malnutrition
- Solid organ and bone marrow transplantation
- Immunodeficiency
- Leukemia (blood cancer caused by increase in White blood cell)
- Intravenous drug use.

MUCORMYCOSIS & COVID-19

Mucormycosis has been increasingly observed as a form of secondary fungal Infection in COVID 19 patients.

The most common form of mucormycosis in COVID 19 patients is pulmonary mucormycosis, closely followed by rhinocerebral mucormycosis.

The incidence of mucormycosis with COVID 19 isn't unusual as the disease tends to affect the immune status of the patients, resulting in increased chances of mucormycosis.

The use of concurrent immunomodulators drugs and the immune dysregulation as a result of the viral infection further add to the increased risk of the infections following.

- The correlation between COVID 19 and mucormycosis has still not been recognized completely due to the underdiagnoses of these infections.
- Some of the factors that help prevent the infections from turning severe include the control of hyperglycemia with early treatment with appropriate antifungal agent antifungal agent.

POSSIBLE MECHANISM IN MUCORMYCOSIS INFECTED COVID-19 PATIENT

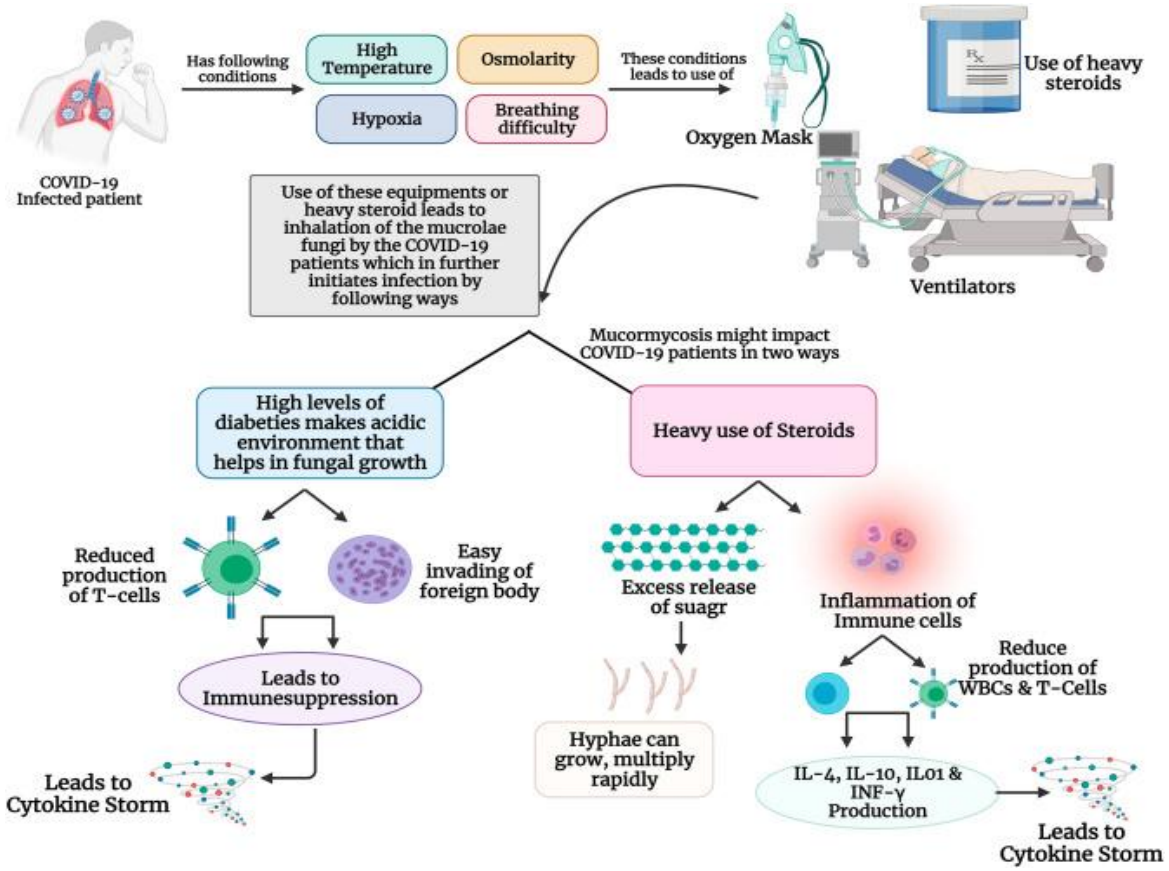

Figure-12

WHY IT IS SEEN MOSTLY IN COVID-19 PATIENT?

Mucormycosis can occur any time after COVID-19 infection, either during the hospital stay or several days to a couple of weeks after discharge.

The COVID-19 causes favourable alteration in the internal milieu of the host for the fungus and the medical treatment given, unwittingly also abets fungal growth. COVID-19 damages the airway mucosa and blood vessels.

It also causes an increase in the serum iron which is very important for the fungus to grow. Medications like steroids increase blood sugar. Broad-spectrum antibiotics not only wipe out the potentially pathogenic bacteria but also the protective commensals. Antifungals like Voriconazole inhibit Aspergillosis but Mucor remains unscathed and thrives due to lack of competition. Long-term ventilation reduces immunity and there are speculations of the fungus being transmitted by the humidifier water being given along with oxygen. All the above make for a perfect recipe for mucormycosis infection.

PREVENTION & CONTROL OF MUCORMYCOSIS

- Maintenance of good hygiene and cleanliness is a must. Regular oral hygiene care with mouthwash, povidone-iodine gargles must be done. While administering oxygen, water for humidification must be sterile and there should be no leakage from the humidifier. Steroid usage must be limited to no more than necessary with strict blood glucose control.
- The high mortality rate of these infections indicates the need for early intervention with immunocompromised individuals.
- It is important that the patients are aware of the infections and their presentations so that they can make an early visit to the hospital.
- The key take-home messages are opportunistic fungal infections are occurring in COVID-19 patients, awareness among health care providers and the public is important, early diagnosis and aggressive treatment are paramount for improving outcomes in an otherwise dismal disease, together we can definitely win this battle against COVID 19 and mucormycosis,"Prevention and control of these infections are based on the early diagnosis of the disease and the maintenance of a proper immune system.Individuals at risk with different underlying conditions should be careful about any possible symptoms and other conditions.
- It has been recommended that the patients take appropriate drugs assigned for their underlying conditions in order to maintain their health.
- The control of the disease can also be made by the use of masks in areas that might contain the spores the causative agents.It is imperative to maintain a healthy diet and appropriate lifestyle in order to prevent severe cases of infection.

DIAGNOSIS

1. Medical History

A detailed medical history will be taken in order to establish where and how the infection was acquired.

2. Clinical Examination

A suspected case will undergo a full clinical examination of the nose and other facial structures for evidence of infection. Since the respiratory tract is the most common route of entry of the pathogen, the nose and sinuses are thoroughly examined for any black crusts and other lesions.

3. Tissue Biopsy

Skin tissue biopsies can be taken if cutaneous mucormycosis is suspected. These biopsy samples are analysed for histopathological evidence of *Mucormycetes* by microscopic examination.

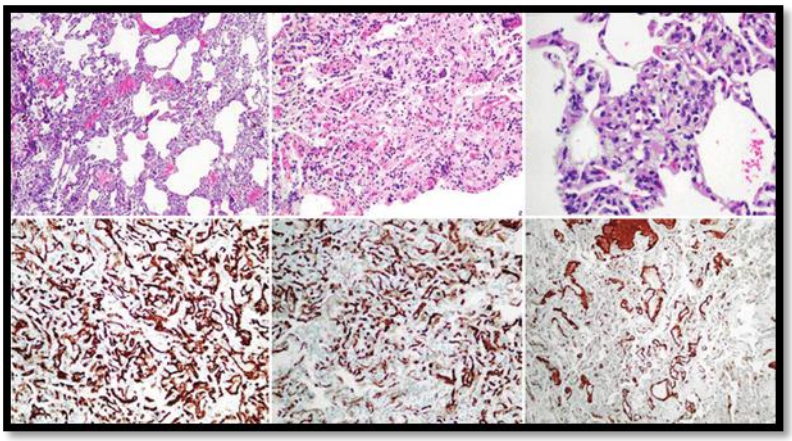

Figure -13 (Tissue biopsy)

4. Imaging

Imaging techniques, such as computed tomography (CT) scans may be used to pinpoint the exact location and extent of the infection in a particular location in the body. A CT scan can be taken of the lungs, sinuses, facial structures, or any other parts of the body, where the infection is suspected to be present.

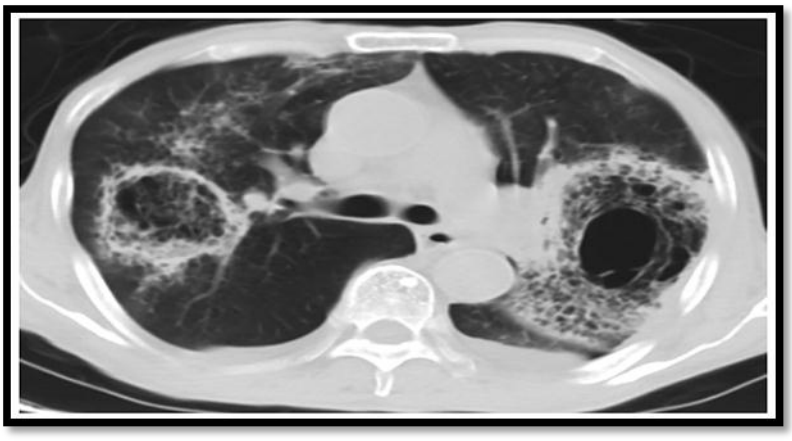

Figure 14 (CT scan image).

5. Fungal Culture

Fluids from the respiratory tract (bronchoalveolar lavage), including sputum can be sent for culture, if pulmonary mucormycosis is suspected. Evidence of the presence

of *Mucormycetes* in the culture fluid indicates a positive and definitive diagnosis. Culture is a method of a definitive diagnosis of mucormycosis and allows both identification to the genus and species level, and antifungal susceptibility testing.

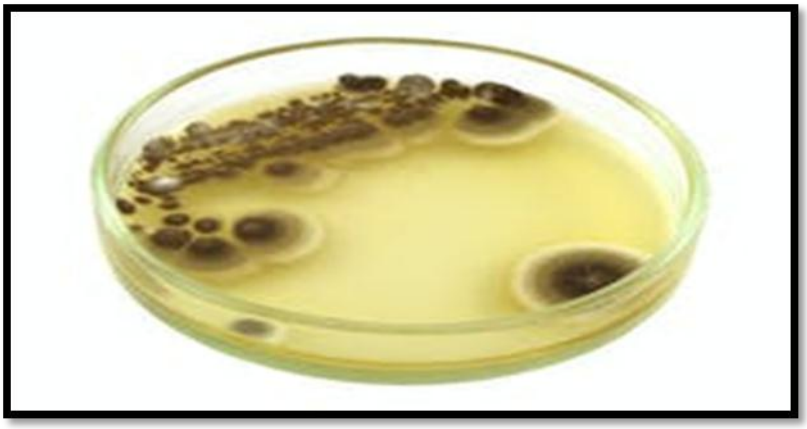

Figure 15: (Fungal Culture).

6. Direct microscopic examination

KOH mounts

For a rapid presumptive diagnosis of mucormycosis, **KOH wet mounts** can be used for direct microscopy KOH when supplemented with fluorescent brighteners such as Blankophor and Calcofluor white, enhance the visualization of the characteristic fungal hyphae but requires fluorescent microscope.

Figure 16: (direct microscopic examination)

7. Histopathological examination

Tissue sections fixed and stained with haematoxylin and eosin (H&E) or specialized fungal stains, such as Grocott methenamine-silver (GMS) or periodic acid-Schiff (PAS) reveal broad-based, ribbon-like, non-septate hyphae with wide-angle branching.

8. Serology

Antibodies to Zygomycetes can be detected by enzyme-linked **i**mmunosorbent assays **(**ELISAs**)**, double diffusion, immunoblot assays but are not in use due to poor specificity and sensitivity, cross-reactivity with ***Candida*** and *Aspergillus* species or showed a lack of clinical validation.

9. Molecular Diagnostics

DNA-based molecular techniques, such as the polymerase chain reaction (PCR) are very promising, but are still in experimental stage. These tests are not.

10. Automated Systems

Proteomic profiling (e.g., MALDI-TOF) is already well established for routine identification of bacteria and yeasts but is difficult in the case of molds due to the presence of complex fungal structures (single or multiple types of conidia, mycelium and/or yeast stages), wide differences of growth rates and lack of valid database.

TREATMENT

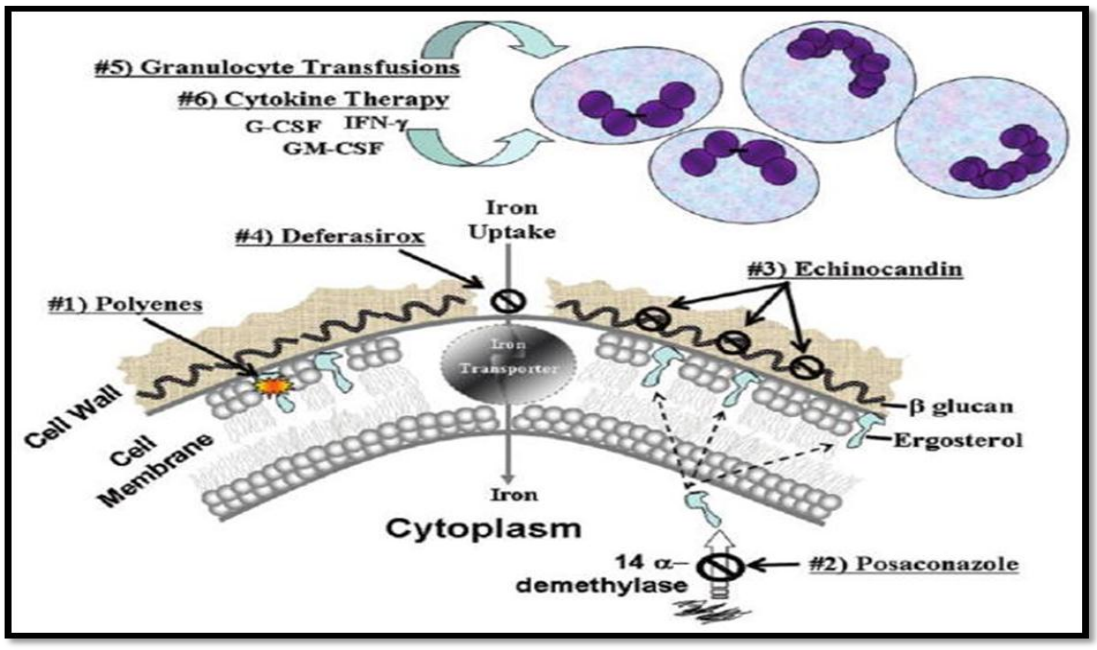

Figure-17.

I. Antifungal agent for mucormycosis

1) Polynes

Amphotericin B deoxycholate (AmB) remains the only licensed antifungal agent for the treatment of mucormycosis. lipid formulations of AmB (LFABs) are significantly less nephrotoxic and can be safely administered at higher doses for a longer period of time than AmB. Amphotericin B lipid complex (ABLC) resulted in a 71% success rate as salvage therapy for mucormycosis treatment with liposomal amphotericin B (LAmB) was associated with a 67% survival rate (16 of 24 patients), compared with 39% survival (24 of 62 patients) with AmB) among patients with cancer who experienced mucormycosis with 39% survival (24 of 62 patients) LFABs appear to be safer, efficacious alternatives to AmB for treatment of Mucormycosis.The response of mucormycosis to antifungal agents is host and site dependent and is particularly problematic in patients with hematological disorders and HSCT recipients.

2) Azoles

Itraconazole is primarily limited to *Absidia* species In contrast, posaconazole has enhanced in vitro activity against the Mucorales, febrile patients with neutropenia or those with invasive fungal infection, posaconazole administered at a dosage of 400 mg orally twice daily resulted in serum levels <1 μg/mL, the treatment of invasive aspergillosis the MICs of *Aspergillus fumigatus* are consistently ≤0.5 μg/mL.Treatment of mucormycosis with posaconazole, particularly among patients at high risk for malabsorption (e.g., patients with mucositis and patients with gastrointestinal graft-versus-host disease).

II. Combination Antifungal Therapy for Mucormycosis

1. Echinocandins

R. oryzae expresses the target enzyme for echinocandins Combination therapy with LAmB plus either micafungin or anidulafungin also improved outcome in neutropenic and disseminated mucormycosis Enhanced exposure of β-glucan on the fungal surface, which results in immune stimulation, combination LFAB-caspofungin therapy was associated with significantly improved outcomes for rhino-orbital-cerebral mucormycosis among patients with diabetes, compared with polyene monotherapy Increasing the dosage of the echinocandins is not advisable because of a paradoxical loss of efficacy against murine mucormycosis at dosages ≥3 mg/kg/day.

2. Iron chelation therapy

Iron chelator, deferoxamine, which increases the risk of mucormycosis, other iron chelating agents, who received deferasirox is that more patients with hematologic malignancy, neutropenia, and/or pulmonary involvement received this agent; determine the possible benefits or harms of deferasirox.

3. Posaconazole combination therapy

Combining posaconazole with AmB enhanced the survival of neutropenic mice infected with *R. oryzae* only when compared to a subtherapeutic dosage (0.3 mg/kg/day) of AmB monotherapy. Combination posaconazole plus LAmB did not improve survival, compared with LAmB monotherapy, in either neutropenic or DKA mice with mucormycosis No clinical studies have evaluated combination posaconazole-polyene therapy for mucormycosis

4. Other adjective therapy

Proinflammatory cytokines, such as interferon-γ and granulocyte macrophage colony-stimulating factor, enhance the ability of granulocytes to damage the agents of mucormycosis Granulocyte colony-stimulating factor–mobilized granulocyte transfusions have been increasingly used for refractory mycoses, including mucormycosis ,granulocyte transfusions is limited, such transfusions may be life-saving for persistently neutropenic patients with mucormycosis**.**

5. Surgery

Surgical intervention with removal of necrotic tissue and debulking infection has been associated with improved survival in anecdotal rhinocerebral and pulmonary infection rhinocerebral infection, debridement to remove all necrotic tissue can often be disfiguring, requiring removal of the palate, nasal cartilage, and the orbit. Endoscopic debridement with limited tissue removal can be accomplished patients with early pulmonary infection who were cured with lobectomies every effort should be made to reverse immunosuppression, optimize underlying medical conditions, and promptly administer antifungals.

6. Salvage therapy

use posaconazole or isavuconazole as salvage therapy for patients who do not respond to or cannot tolerate amphotericin B [Granulocyte colony-stimulating factor–mobilized granulocyte transfusions may provide additional support for persistently neutropenic patients until recovery from neutropenia. Administration of granulocyte macrophage colony-

stimulating factor or interferon-γ may further augment host response and antifungal effect in non neutropenic patients with refractory infection.

7. Total duration of therapy

Total duration of therapy for mucormycosis should be individualized for each patient. Antifungal therapy for mucormycosis should be continued until all of the following objectives are attained.

For patients with mucormycosis who are receiving immunosuppressive medications, secondary antifungal prophylaxis is typically continued for as long as the immunosuppressive regimen is continued.

Posaconazole may be an option if polyenes cannot be used for prolonged periods. For patients with intermittent immunosuppression, such as those receiving intermittent cycles of chemotherapy who have adequate leukocyte counts between cycles, secondary prophylaxis should be reinitiated during neutropenia and should continue until the recovery from neutropenia.

(1) There is resolution or stabilization of residual radiographic signs of disease on serial imaging, and

(2) There is resolution of underlying immunosuppression. Such a case is illustrated in a patient with lymphoma and renal mucormycosis.

8. Hyperbaric Oxygen

Hyperbaric oxygen has been used in some patients with mucormycosis, but the benefit of this therapy has not been establish.

WHAT ARE COMPLICATIONS OF MUCORMYCOSIS ?

The complications of mucormycosis are serious and are related to the body area initially infected but also can occur in other body regions because the fungi often spread to the organs or tissues that physically contact or are near the originally infected area.In addition, because surgical debridement is almost uniformly needed, some normal tissue may be destroyed because the surgeon must remove all tissue that is dead or dying. Unfortunately, that means the surgeon may have to remove some normal tissue to insure all of the fungi are removed An example is infection of the eye orbit; often the whole eye must be removed. Consequently, serious complications may occur, such as.

Blindness, meningitis, brain abscesses, osteomyelitis, pulmonary haemorrhages gastrointestinal haemorrhage, cavity lesions in organ and eventually secondary bacterial infections, sepsis and death.

CONCLUSION

Mucormycosis is an emerging infection in immunocompromised patients, and the mortality with standard therapy remains unacceptably high. Most of the existing epidemiological studies of mucormycosis are retrospective and limited. The incidence of mucormycosis seems to be increasing in leukemic patients and stem cell transplant recipients chronically exposed to Aspergillus-active agents despite the diabetes epidemic in developed countries, the incidence of mucormycosis in diabetics may be decreasing. In contrast, in developing countries, uncontrolled diabetes mellitus and trauma are the most common risk factors for mucormycosis. More representative data on specific groups of patients (eg, leukemic patients, transplant recipients, diabetics) are needed for better evaluation of the infection although research into mucormycosis pathogenesis is considered to be in its infancy, major advances have been achieved recently on how Mucorales causes disease and survives in the host. Most of the work has focused on fungal iron uptake mechanisms, molecular mechanisms of adhesion/invasion, spore size and sex loci and role of innate and adaptive immunity in host defense against Mucorales. A high index of suspicion for mucormycosis based on appropriate risk stratification and improved laboratory diagnosis are important for improving the natural history of this devastating infection.

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