

A Brief Review on Mucormycosis.

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ABSTRACT :

The main goal of the review paper is to overview on causative agent, epidemiology, risk factors diagnostic methods and its treatment .The mucormycosis is also known as black fungus disease. Mucormycosis is a very rare disease which is caused due to fungi mucorales. The exact incidence of mucormycosis infection in our country is unknown due to lack of the population- based studies. The estimated prevalence of mucormycosis infection is about 70 times higher in India than other in global data. Diabetes mellitus is most common risk factor, haematological malignancy and solid-organ transplant are also responsible.

The recent report says that certain COVID-19 patients are suffering from a fungal infection as co-infection commonly known as mucormycosis (black fungus). In our country the outbreak of black fungus in COVID-19 patients has already declared an epidemic. The few reports are noticed in other countries. The country must be focus toward better management of the COVID-19 associated fungal infection. In this review article, we discussed various aspects of black fungus particularly the etiology, tocomy, transmission pathogenesis etc

The Patients with postpulmonary tuberculosis infection and the chronic kidney disease have additional risk of developing mucormycosis infection in our country. Trauma is also a risk factor for cutaneous mucormycosis. Isolated renal mucormycosis in the immunocompetent host is a unique entity in India country It is an angioinvasive fungal infection mainly affects the sinuses or lungs. It occurs due to inhalation of mold spores . The incident cannot be measured exactly but there are processing of population based studies and these

studies shown that the mucormycosis disease were increasing .The infection mainly targets the peoples who have diabetes and also targets the immunocomprised patients. By the awareness of the infection has increased among treating physicians, disease-associated morbidity rate and mortality rate are still high, as patients seek medical attention late in disease process and given the low affordability for the therapy. In conclusion, rise in the number of cases, the emergence of the new risk factors and causative agents, challenges inmanaging the disease are important concerns with mucormycosis infection in India.

KEYWORDS : Mucormycosis, diabetes – mellitus , Mucormycotina , Rhinorbital , Neutropenia , Hematopoietic , Voriconazole .

I. INTRODUCTION :

Mucormycosis is caused by the black fungal infection, which may be harmful for humans. The Mucormycosis is known as Zygomycosis .The Mucormycosis is term find out by American Pathologist R.D. Baker .The term Zygomycosis have used to describe the infection . Mucormycosis is caused by the term Mucorales & term Entomophthorales. Entomophthorales cause by infection in topical areas only and produce chronic subcutaneous and cutaneous infection . Mucorales infection caused by the inhalation of spore, contamination of foods , contamination of open wounds. Mucorales fungi are mostly present in soils , decomposing organic matter and animal manure etc . Mucormycotina are the very common saprobes which are originating from the rotten

matter or soils. The Infection with mucorales are categorized by rapid progression . Mucormycosis is most common in highly caused in immunocompromised hosts in developing countries . Mucormycosis has very strong proclivity for invading blood vessels , causing necrosis thrombosis & tissue infection .

Mucorales are enter in the human body by different process like inhalation , percutaneous inoculation or ingestion .

Term : Mucorales & Entomophthorales

Class : Zygomycosis

Genera :

1)Mucorales : Rhizopus , Mucor , Absidia ,Cunninghamella

2)Entomophthorales : Conidiobolus and Basidiobolus .

Due to the mucorales tissue Infarction occur, they are vasoprotic. The mucormycosis is an angioinvasive disease which is mostly caused by mold fungi belonging to the genus Rhizopus, Mucor, Rhizomucor, Cunninghamella, and Absidia, subphylum Mucormycotina, Order-Mucorales, Class Zygomycetes and is characterized by tissue necrosis and infarction .The mucormycosis Infections mainly caused due to Mucorales are categorized by rapid progression. The Rhizopus Oryzae is the most common types and that is responsible for nearly about 60 percent of mucormycosis cases in humans.

Types of Mucormycosis

- 1 Cutaneous mucormycosis (skin)
- 2 Rhinocerebral mucormycosis (sinus and brain)
- 3 Pulmonary mucormycosis (lung)
- 4 Gastrointestinal mucormycosis
- 5 Disseminated mucormycosis

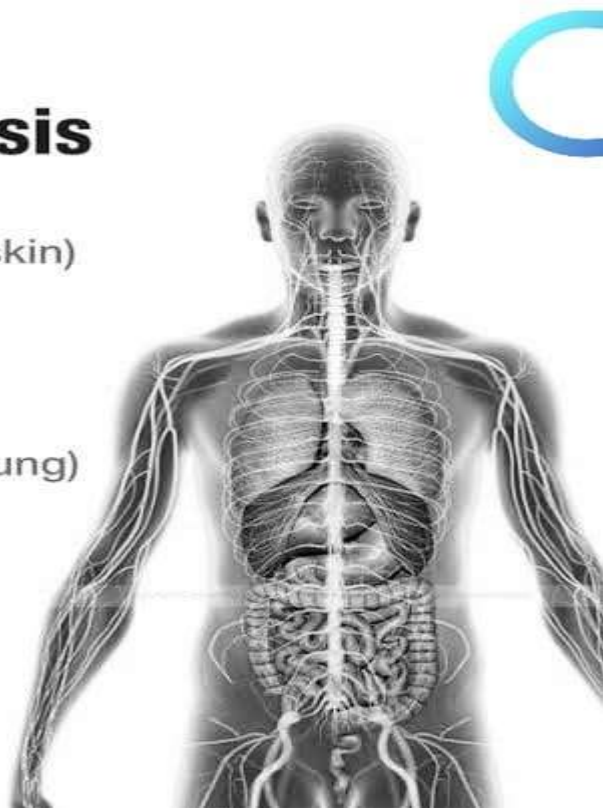


Fig.1 types of Mucormycosis.

The infection mainly caused the infected tissue black. The fatal rate(number of deaths from a specific cause) is estimated to be 40 - 80%. The infection is a life-threatening fungal infection but this are very rare with high morbidity and mortality. The most clinical presentations of mucormycosis are classified on the basis of anatomic localization such like rhinocerebral (It is

a very rare disease which is caused by filamentous fungi involving the nose, paranasal sinuses, and brain) gastrointestinal, cutaneous, pulmonary, renal, and disseminated mucormycosis (The infection spreads through the bloodstream to affect another part of the body) . The increased risk of acquiring mucormycosis are mostly patients with diabetes mellitus, neutropenia (It refers to

abnormally low count of a type of white blood cell hematopoietic stem cell transplantation, hematological malignancy, chemotherapy, the solid-organ transplant recipients on immunosuppressive therapy, in iron overload, extensive skin injury, in human immunodeficiency virus (HIV) infection and immunocompetent patients.

The mucormycosis has also increased majorly in diabetes patients which is the mostly common risk factor around globally. Mucormycosis is globally distributed and the prevalence of the disease is due to different risk factors.

Epidemiology :

The epidemiology of mucormycosis infection is different between the developed and developing countries. In developed countries, the infection is mostly seen in patients with diabetes mellitus and hematological malignancies (It occurs when abnormal cells in the blood will grow out of control) undergoing chemotherapy and allogeneic stem cell transplants. In the country like India the mucormycosis cases of sporadic occur due to uncontrolled diabetes or trauma patients. In places like San Francisco and California the active populations-based surveillance study from 1992 to 1993 shows that the annual incidence of mucormycosis infection was 1.7 cases per 1 million individuals of 500 cases per year. In country like Spain the study was conducted and found to be a lower incidence of 0.43 cases/1 million inhabitants or 0.62/100000 hospital admissions. In country like France the hospital records were analyzed and it resulted in increasing incidence from 0.7/million in 1997 to 1.2/million in 2006 . Roden compiled with 929 mucormycosis infection cases and reported that there are an increased proportion in immunocompromised patients with mucormycosis infection in the year 1980 and 1990. The HIV infection is not inherently predisposing to mucormycosis unless associated with neutropenia, diabetes mellitus, illicit intravenous drug use, hematological malignancy, and hematopoietic stem cell transplantation etc.

Their is a chances of occurring mucormycosis infection is very rare but from the last two decades the cases of this mucormycosis infection was increase abruptly particularly in countries like Belgium, France, Switzerland and India. By the report from National Hospital Discharge Database, the country like France identified 35,876 patients with invasive fungal

infection (IFIs) & it was detected in between 2001 to 2010 among which 1.5% cases was occurs due to mucormycosis itself. Nineteen cases of mucormycosis infection was detected in a single-center study in country like Spain from 2007 to 2015. Same in a tertiary hospital in Geneva, Switzerland, within 1989 to 2003, 3 cases of mucormycosis infection were diagnosed while 16 cases was found in between 2003 to 2008. It was Seen that the people with medication like immunosuppressant and voriconazole were more susceptible to infection of black fungus.

In a report study in Israel, 16 of 19 black fungus cases of rhino-orbito-cerebral mucormycosis was found to be occurs in autumn while in Japan, 6 cases with hematology patient was found be infected during the month August to September. This type of infection in human was resulted from the inhalation of fungal sporangiospores, direct inoculation of pathogens through disrupted skin or mucosa. In a report study in Israel, 16 of 19 black fungus cases of rhino-orbito-cerebral mucormycosis was found to be occurs in autumn while in Japan, 6 cases with hematology patient was found be infected during the month August to September. This type of infection in human was resulted from the inhalation of fungal sporangiospores, direct inoculation of pathogens through disrupted skin or mucosa.

Pathophysiology :

Agents : Fungi are mainly causes of mucormycosis infection, it is a life-threatening fungal infection affecting immunocompromised hosts like, transplant patients diabetics patients, leukopenic patients and patients on dialysis who receive deferoxamine drug in either developing or industrialized countries. The various Species belonging to family Mucoraceae are isolated from patients with Mucormycosis infection. Increasing cases of mucormycosis infection was reported due to infection with *Cunninghamella* spp. The skin have a major role in barrier to fungi which are responsible for causing Mucormycosis infection . The causative agents of Mucormycosis infection are typically incapable of penetrating intact the skin.

Also the condition like burns, traumatic disruption of the skin and persistent maceration of skin enables the organism to penetrate the deeper tissues and which is responsible for infection .The contaminated surgical dressings and adhesive tape also acts as a source of primary cutaneous

Mucormycosis infection. Ingestion is mechanism of transmission occurs in gastrointestinal Mucormycosis .The Inhalation of Mucorales sporangiospores by immune compromised patients

results in development of pulmonary mucormycosis infection.

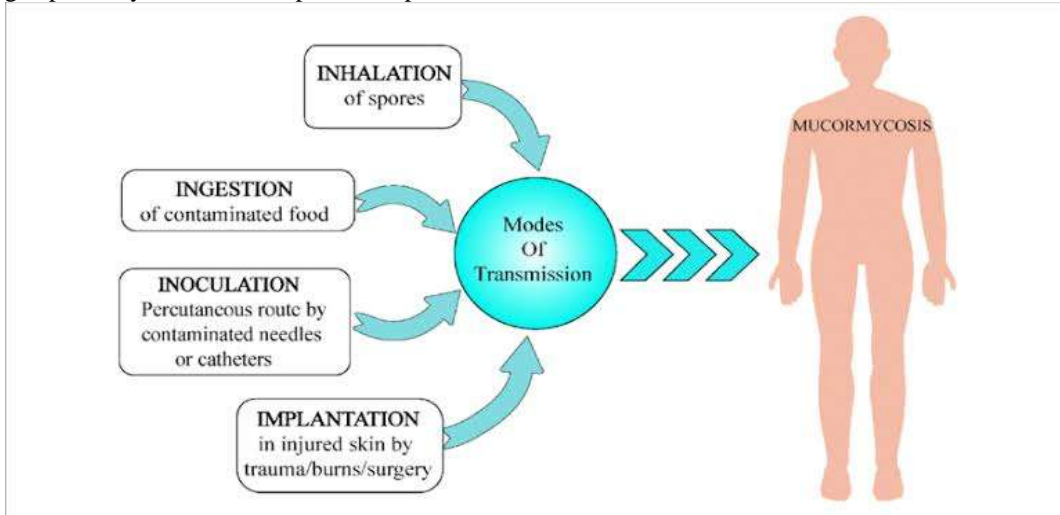


Fig .2 Mode of transmission of Mucormycosis.

CLINICAL MANIFESTATION OF MUCORMYCOSIS :

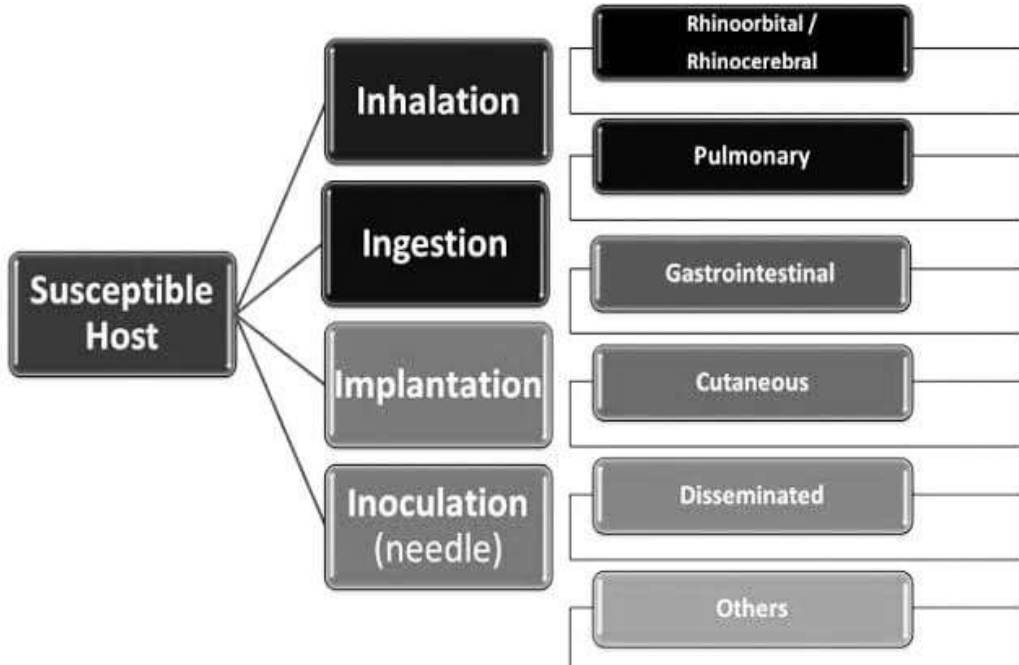


Fig.3 CLINICAL MANIFESTATION OF MUCORMYCOSIS.

1. Rhinoorbital or Rhinocerebral Mucormycosis :

A) Pathogenesis of disease :

It is caused due to Inhalation of sporangiospores develop paranasal sinuses which

can further spread to involve sphenoid sinus, cavernous sinus and brain tissue.

B) Underlying host risk factor :

Malignancy : It refers to the presence of cancerous cells that have ability to spread to other sites in the body

Diabetes mellitus: A disorder in which a person's body unable to control the level of sugar in the blood.

Organ transplant : It refers to an operation in which a organ is transplanted.

C] Clinical manifestations :

Clinical manifestation of Rhinocerebral Mucormycosis is Eye/facial pain ,Sinusitis : Inflammation of nasal passages ,facial numbness,blurry vision , proptosis : It refers to protrusion of the eyeball from the orbit, Headache.

D] Mortality rate : 50% or may be higher

2. Pulmonary Mucormycosis :

A] Pathogenesis of disease :

Pulmonary blood vessel becomes invaded by hyphae which further lead to hemorrhage, ischemia, thrombosis etc.

B] Underlying host risk factor :

Risk factor of pulmonary Mucormycosis is Under chemotherapy,

Neutropenia : It refers to low count of a type of white blood cell & lung transplantation.

C] Clinical manifestations :

Clinical manifestations is Fever,nonproductive cough, endobronchial lesion result in the obstruction of airways

D] Mortality rate : 66% or higher depend on level of the immunosuppression.

3. Gastrointestinal Mucormycosis :

The gastrointestinal Mucormycosis is nonspecific & include Diarrhea , abdominal pain , melena ,hematemesis.

A] Pathogenesis of disease :

It is caused due to ingestion of contaminated milk, breads, alcoholic drinks ,herbal and the homeopathic formulation due to which stomach as well as colon get affected underlying host.

B] Risk factor :

Risk factor of Gastrointestinal Mucormycosis is included Malnourished , Children diabetes mellitus ,premature baby.

C] Clinical manifestations :

The clinical manifestation includes Appendiceal, Gastric perforation, Neutropenic patient with fever, Hematochezia.

D] Mortality rate : 85%

4. Cutaneous Mucormycosis :

Cutaneous Mucormycosis is occur due to the skin or wound injury from surgery , burns , soiled trauma , motor vehicle accidents , bone fracture, intravenous lines , insect bites , cactus spine injury , abrasions , laceration , biopsy sites , allergen patch testing.

A] Risk factor :

Trauma & burn of skin in the susceptible host.

B] Clinical manifestations :

Clinical manifestations Consist of fulminant disease, can lead to gangrene, haematogenous .

C] Mortality rate : 25 %.

5. Disseminated Mucormycosis :

A] Pathogenesis of disease:

Mucormycosis was transferred from one organ to other organ through blood, lungs infection is most commonly happening with dissemination.

B] Risk factor :

Iron overload, excessive

C] Clinical manifestations :

It depend on the site of infection and intensity of invasion.

D] Mortality rate :

May be fatal if deprived of medication.

6. Miscellaneous Mucormycosis:

A] Pathogenesis of disease:

It is the fungal infected or contaminated medical devices, Mucorales contaminated food stuff like barley, wheat, onions, cottons, oranges, honey and tomatoes.

B] Risk factor :

It is included Traumatic inoculation during surgery, Contaminated medical devices (catheters, adhesive tapes), immunosuppressive patients.

C] Clinical manifestations :

Miscellaneous Mucormycosis consist of Infection of skin, prosthetic valve endocarditis, peritonitis, gastrointestinal disease.

D] Mortality rate : The mortality rate depends on site of infection.

Sign & Symptoms :

One-sided facial swelling, Headache,

Sinus congestion (uncomfortable feeling when the tissues lining your sinuses swell up from inflammation).

Chest pain, Shortness of breath,

Abdominal pain,

Nausea and vomiting,

Gastrointestinal bleeding,

Black lesions on the nasal bridge, Fever .

Risk Factor For Mucormycosis :

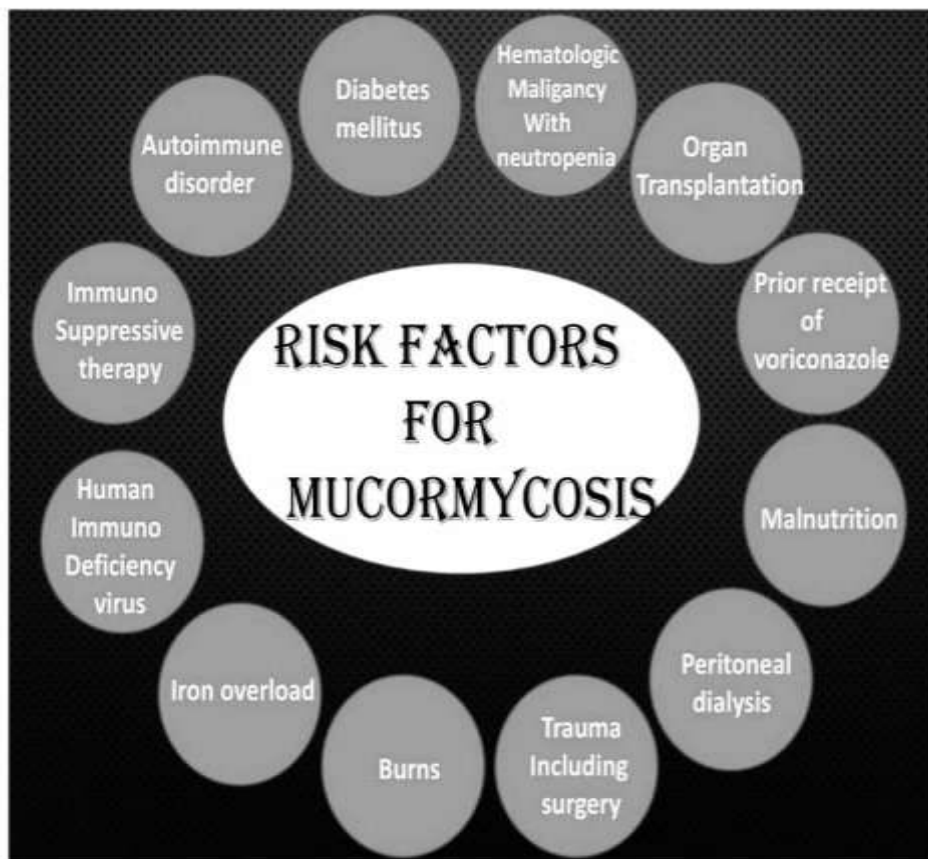


Fig. Risk Factor For Mucormycosis

1] Diabetes mellitus :

The patient with poorly controlled diabetes mellitus which associated with particularly chemotaxis, phagocytosis and macrophages are highly susceptible for acquiring mucormycosis infection. Diabetics mellitus in association with ketoacidosis are at higher risk of developing the rhino-cerebral mucormycosis. In the case of diabetic patients, the common site of the mucormycosis infection is sinuses, but it can easily spread to bone, orbit and brain of the patients. The patients with organ transplant or the hematological malignancies & pulmonary mucormycosis infection are very rare.

The complication of mucormycosis infection was very rare in case of solid organ transplant patients according by the data from U.S Centers of Transplant-Associated Infection Surveillance Network from the year 2001 to 2006 annual incidence of mucormycosis infection in solid organ transplant patients was about 0.07%. The Song et al. was said that from 123 articles which was published between 1970 to 2015, they was found to be 174 cases of mucormycosis infection in renal transplant patients and overall death rate was about 42.5%. Rabin et al. was said that at same center among all 362 heart transplant patients only one case of mucormycosis was found from 1995 to 2012.

2] Solid organ transplant :

3] Hematopoietic stem cell transplant :

In the case of hematopoietic stem cell transplant patients it mainly with graft versus host disease, mucormycosis infection can easily occurs. The retrospective review of Johns Hopkins Hospital (Baltimore, MD) from 2000 to 2009 for hematopoietic stem cell transplant and solid organ transplant, cases of mucormycosis infection was found 8.5% of invasive mold infection . The Center for International Blood and Marrow Transplant Research collected data from 66 worldwide transplant centers and they was reported 72 mucormycosis cases during 1st year of post allogeneic hematopoietic stem cell transplant.

4] Use of corticosteroids and rheumatic disease :

The Long term use of corticosteroids can damage the macrophages, neutrophils and it can induce diabetes mellitus in patients. In case of patients with the systemic lupus erythematosus, disseminated mucormycosis infection was common with higher mortality rate . Other risk factor for the opportunistic mucormycosis involves nephritic syndrome, hypocomplementemia, uremia, diabetes mellitus and leucopenia.

5] Human immunodeficiency virus (HIV) infection or AIDS :

The cases of mucormycosis infection in AIDS patients are very uncommon. From the study of Antinori et al. a retrospective study from 1984 to 2002, in 1630 autopsies patients and it was found that only two patients had mucormycosis. Most of the mucormycosis infection cases are linked with intravenous use of drug in HIV infected patient.

6] Mucormycosis in children :

In children occurrence of mucormycosis infection was very rare. The Zaoutiset al. studied all pediatric cases of mucormycosis infection before 2004 and they found 157 cases, where 64% was male with an average age of 5 years and 28 patients had hematological malignancies and 9 patients had hematopoietic stem cell transplant. The Roilides E et al. reported another 30 pediatric cases of mucormycosis infection from the year 2004 to 2008.

7] Long term use of voriconazole :

The long-term use of the voriconazole in case of hematopoietic stem cell transplant and

hematological malignancies patients can produce the higher risk for mucormycosis infection. Also in place of the voriconazole, use of itraconazole or fluconazole in the allogeneic transplant patients does not produce the risk for mucormycosis.

8] Black fungal infection/mucormycosis in association with COVID-19 :

The newer problem will arising recently in India and also in some other countries is black fungal infection or mucormycosis in COVID-19 as well as post COVID-19 patients. Mucormycosis is mainly arising in COVID-19 patients due to the use of steroids as a medication to suppress highly active immune system, so that it can help COVID-19 patients to protect their lung from damage by a mechanism known as "cytokine storm" Based on the recent scenario of increasing cases of mucormycosis in COVID-19 patients, the physician should keep eyes on their patients even after the complete recovery from this disease.

Diagnostic Method:

Diagnosis of mucormycosis infection includes cautious evaluation of the clinical manifestations, magnetic resonance imaging modalities, utilization of computed tomography (CT) in the early stages, specialist assessment of cytological and the histological provision, finest application of the clinical microbiological technique and execution of molecular detection". The Detection of host factors contribute extensively estimation of a patient's possibility for invasive mucormycosis. The PAS stains, direct examination, calcofluor, histopathological examination, Gomori methen- amine silver stain, culture, the molecular methods and fluorescent in situ hybridization are the various laboratory techniques for detecting mucor. Differential finding of mucormycosis infection include maxillary sinus neoplasia, maxillary sinus aspergillosis, soft tissue infarction, the soft tissue radio necrosis, other deep fungal infections.

Treatment :

The treatment of mucormycosis infection includes the early diagnosis, reversal of underlying predisposing risk factors, surgical debridement and prompt antifungal therapy. . Medicines Amphotericin B is considered to be first-line therapy for treatment of mucormycosis infection . Antifungal therapies like amphotericin B deoxycholate, liposomal amphotericin B (5-10

mg/kg), amphotericin B lipid complex, isavuconazole, and the posaconazole (400mg bid) Second-line treatment of mucormycosis infection includes the mixture of lipid amphotericin B and posaconazole, a combination of lipid amphotericin B and the caspofungin. The Early diagnosis is important to promptly initiate the therapeutic interventions necessary to preventing the progressive tissue invasion, managing the underlying disease, improving outcome and survival the Posaconazole and isavuconazole are used as salvage therapy in mucormycosis treatment. In hematology suffering patients, the monotherapy shows an increase in mortality rate and hence proposed the choice of combination therapy for mucormycosis. The CT scans method are used for detection of pulmonary mucormycosis particularly in cancer patients.

Prevention:

- 1] Avoid the dusty area & construction sites to avoid the infection, wear N95 mask.
- 2] Clean the skin injuries with warm water and antiseptic liquid to avoid from skin infection. Maintain personal hygiene including thorough scrub bath.
- 3] If you have had a stem cell transplant or organ transplant talk to your doctor for antifungal medication to prevent the fungal infections.
- 4] Avoid the activities which has direct contact with dust or soil. Wear shoes, long trousers, long sleeve shirts, gloves while handling soil, moss or manure.

II. CONCLUSION:

The early diagnosis of disease status, recovery from predisposing factors, early intervention with surgical debridement, and prompt antifungal therapy helps to improve disease condition. The Etiopathogenesis of mucormycosis infection remains varied throughout the world and diagnosis of disease manifestation remains a crucial role for the clinicians. Mucormycosis infection is a rare invasive fungal invasion which mainly occur in patient with diabetes mellitus, immuno compromised and iron overload treatment. We observed that, due to extensive shortage of the sterile oxygen, rapid supply of industrial oxygen was provide to save patient due to which pathogens of mucormycosis is entered into immuno compromised patients due which along with COVID-19 they also suffer from Mucormycosis. Medicine Amphotericin B was extensively used for treatment of the infection but if it fails then

combination of posaconazole and caspofungin was found to be effective in infection due to potential synergistic effects.

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