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Recent Advances in the Understanding and Management of Mucormycosis

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Abstract: *Mucormycosis is a fungal infection brimming a war in the shadow of covid-19 in India, Mucormycosis is caused by molds called as mucormycetes, corona virus disease caused by severe acute respiratory syndrome corona virus. (SARS-COV-2) has associated with wide range of bacterial and fungal infection. Aspergillasis and Candida have been reported the main fungal pathogens for co-infection in the people of covid19. Covid-19 increases/ leads to weakened immune system preventing the body form effectively protecting against infection as a result individuals recovering from covid-19 are the risk for Mucormycosis. Steroid treatment for covid-19 may also act to suppress the body's immune response contributing to these increased Mucormycosis infection rate. Mucormycosis is highly tendency for contigenous spread associated with poor progenosis and other immunosuppressive condition including corticosteroid theraphy and other drug theraphy are known risk factor for Mucormycosis.*

Keywords: *Mucormycosis, covid-19, corticosteroid theraphy, drug theraphy, immunosupression, fungal infection*

I. INTRODUCTION

1.1 Mucormycosis

A serious but rare fungal infection caused by a group of molds called as mucormycetes, these molds lives throughout the environment. Mucormycosis mainly affects people who have health Problems or take medicines that lower the body ability to fight germs and sickness. The most commonly affects the sinuses or the lungs after inhaling fungal spore from the air it can also occurred on the skin after a cut, burns or other type of skin injury. The fungi that cause Mucormycosis live in the environment.[1]

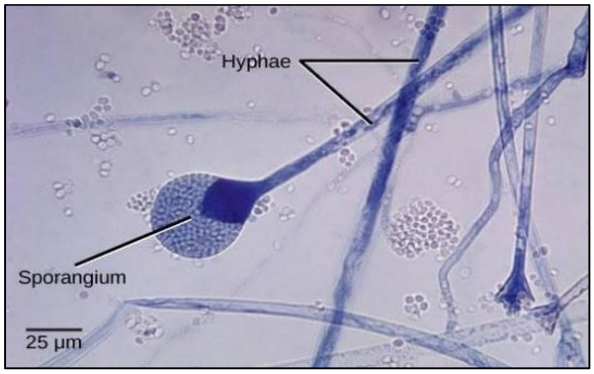

Fig 1. Mucormycosis

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 drug they more common in soil, than air and in summer and fall than in winter or spring. Most people in contact with microscopic fungal spore every day so it probably to completely avoid coming I contact with mucormycetes.[2]

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1.2 What is Mucormycosis? [3]

- Mucormycosis or black fungus is an aggressive and invasive fungal infection caused by a group of molds called mucormycetes.
- Mucormycosis is the general term that indicates any fungal infection caused by various genera of the class *Zygomycetes*.
- Another term used in medical and lay publications that means the same is phycomycosis.
- These forms of mucormycosis usually occur in people who have health problems or take medicines that lower the body's ability to fight germs and sickness.

1.3 Etiology of Mucormycosis: [4-5]

- 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 species present in the order Mucorales display only a small number of distinguishable morphological characteristics that can be used to distinguish between themselves.
- 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.

1.4 Risk Factors

MUCORMYCOSIS AND COVID-19 [6-7]

- Mucormycosis has been increasingly recognized as a form of secondary fungal infection in COVID 19 patients.
- The most common type of mucormycosis in COVID 19 patients is pulmonary mucormycosis, followed closely by rhinocerebral mucormycosis.
- Occurrences of mucormycosis with COVID 19 are uncommon as the disease often impairs the immune system in patients, leading to increased chances of mucormycosis.
- Similarly, glucocorticoids and remdesivir are some of the drugs that have been beneficial in COVID 19; However, the use of glucocorticoids may increase the risk of secondary infection.
- Simultaneous use of antibodies and immunosuppression due to HIV increases the risk of disease.
- The link between COVID 19 and mucormycosis has not been fully identified due to poor diagnosis of these diseases.

1. Organ Transplantation	2. Diabetes Ketoacidosis	3. Neutropenia
4. Protein calorie	5. Malnutrition	6. Iron overload

WHY IS IT OCCURRING IN COVID 19 PATIENTS?

Mucormycosis can occur at any time after COVID-19 infection, either during hospital stay or a few days to a few weeks after discharge. — COVID-19 causes a positive change in the internal condition of the fungus host and the treatment given, unknowingly and inhibits the growth of the fungus. COVID-19 damages the mucous membranes and blood vessels. It also causes an increase in serum iron which is very important for the fungus to grow. Medications like steroids increase blood sugar. Broad-spectrum antibiotics not only eliminate potential viruses but also protective commensals. Antifungals

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like Voriconazole prevent Aspergillosis but Mucor remains undamaged and thrives due to lack of competition. Prolonged exposure to air weakens the immune system and there is a perception that the fungus is dispersed by the hot water supply and oxygen. All of the above make up the perfect recipe for mucormycosis infection" [8]

PREVENTION AND CONTROL OF MUCORMYCOSIS [9-10]

- Ensuring personal hygiene through proper bathing and washing, especially after returning from work, exercising or visiting neighbors, relatives, friends.
- Wear a face mask and face mask when going to dirty places such as construction sites
- Make sure you wear fully covered hiking boots, long pants, long-sleeved shirts and gloves while touching the ground, moss, manure, as in garden work.
- It is important for patients to know about their illnesses and presentations so that they can visit the hospital early.
- Prevention and control of these diseases is based on the early diagnosis and maintenance of the immune system.
- Vulnerable people with different conditions should be aware of any possible symptoms and other conditions.
- It is important to maintain a healthy diet and healthy lifestyle to avoid severe cases of infection.

DIAGNOSIS OF MUCORMYCOSIS [11-15]

A systematic, step-by-step approach is adopted for the diagnosis of mucormycosis, involving the following strategies-

- **Medical History**: A detailed medical history will be taken in order to establish where and how the infection was acquired.
- **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.
- **Tissue Biopsy**: Skin tissue biopsies canbe taken if cutaneous mucormycosis is suspected. These biopsy samples are analyzed for histopathological evidence of Mucormycetes by microscopic examination.
- **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.

Fig 2. Fungal Culture.

- **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.
- **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 fully standardized, and have not been clinically evaluated and are currently unavailable for commercial use.

TREATMENTS FOR MUCORMYCOSIS: [16-19]

There are two main types of treatment - antifungal treatment and surgery. Apart from this, complementary therapies have been suggested as well as to control the basic immune system. This is briefly discussed below-

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- Antifungal Therapy: Immediate control of antifungals is important in killing infectious fungi and preventing them from causing further damage. This treatment needs to be timely and very important in improving the outcomes of patients with mycormycosis. The most effective antimicrobials for the treatment of mucormycosis include amphotericin B, posaconazole, and isavuconazole. Although amphotericin B can only be administered intravenously (IV), posaconazole and isavuconazole can be administered via both the IV route, and the oral route.
- Surgery: Surgical removal and resuscitation of infected or dead tissue is usually necessary and should be performed as soon as the diagnosis is confirmed. In the event of cutaneous mucormycosis, damaged skin and connective tissue under the skin may need to be removed and surgically removed. Patients with rhinocerebral mucormycosis may show significant changes in facial features. Specific surgical procedures usually vary with the location, severity and severity of the disease.
- Adjunctive Treatment: Adjunctive treatment is defined as an alternative treatment, in addition to the primary treatment. Hyperbaric oxygen therapy is one of the accompanying therapies. This treatment involves exposing the patient to fresh, pressed air, either in the pressure chamber or through a tube. Although hyperbaric oxygen has been shown to be effective in treating some forms of disease, its effectiveness in treating mucormycosis has not been fully established. Further research and major clinical trials are needed to determine the effectiveness of this combination therapy.
- Salvage therapy: If desease refractory or intolerance toward previous antifungal therapy.
    - Posaconazol (A)
    - Posaconazole (B) + polymers
    - Lipid complex, liposomal colloidal dispersion (B)
    - Polyenes + caspofungin (C)
- The new generation antifungal therapeutics including Amphotericin-B, Ketaconazole, Itraconazole and Variconazole, Amphotericin-B, Ketaconazole and Itraconazole was similar MIC, Variconazole has higher MIC, and there are several formations of Amphotericin-B available like, Liposome's, Lipid base Amphotericin, colloidal dispersion of Amphotericin-B for most common infection to human. The combination of antifungal medication along broad spectrum antibiotics like trovafloxacin or ciprofloxacin effective suppresses pulmonary zygomycosis in marine model.

COMPLICATIONS OF MUCORMYCOSIS: [20-22]

Mucormycosis complications are serious and are related to the initially infected area but may also occur in other parts of the body because the fungus usually spreads to organs or tissues that come in contact with or near the original infected area.

In addition, because surgical removal is almost equally necessary, certain normal tissues may be destroyed because the surgeon must remove all dead or dying tissue. Unfortunately, this means that the surgeon may need to remove the normal tissue to ensure that all the molds 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 hemorrhages,
- Gastrointestinal hemorrhages,
- Cavitary lesions in organs and eventually secondary bacterial infections, sepsis, and death.

Drug Theraphy used in covid-19:

In general the use of drug against viral diseases and against SARS-COV-2 and their mechanism action are below.

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Remdesivir

A new antiviral drug of the class of nucleotide analogues. What can be done mechanically to the ATP analogue that inhibits the viral RNA polymerase enzyme, an effective form of Remdesivir drug as a nucleoside analogue, is in a state of competing with the adenosine triphosphate (ATP) metabolite to join the newly produced RNA line. giving Remdesivir digested metabolism and converted to NTP, will stop RNA synthesis. [23]

Fig 3: Remdesivir injection

Iveramectin

Iveramectin cause an increases in permeability of chloride ions by hyperpolarisation of the nerve or muscle cell, the result in deactivation of the channel by manipulating chloride level, in studies it was found that it is highly effective against SARSCOV-2 and to stop the virus in the replication stage. [24]

Corticosteroids theraphy

According to WHO the panel made two recommendations, a strong recommendation for systemic (i.e. intravenous or oral) corticosteroid theraphy. (e.g. 6mg dexamethasone orally or intravenously daily or 50mg of hydrocortisone intravenously every 8 hours)for 7 to 10 days on patient with severe and critical covid-19 and a conditional recommendation not to use corticosteroid theraphy in patient with nonsevere covid-19. [25]

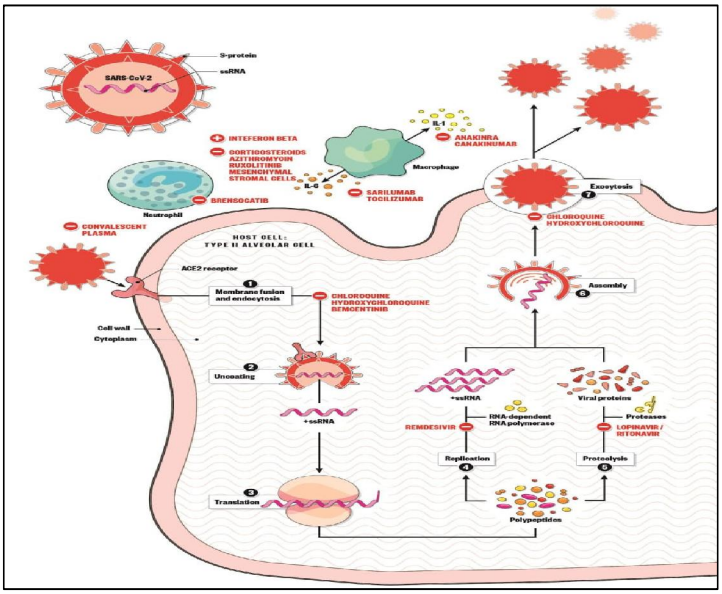

Figure 4: Mechanism of action of several medicines that are being put through clinical trial for covid

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How Mucormycosis rise in the covid-19 patient: [26-27]

The main apparent cause of mucoralates' growths in people with covid-19 is good for low O2 (hypoxia), high glucose, acidic medium 9metabolic acidosis, diabetes, steroid, hyperglycemia, weight loss phagocytic of WBC's. to immunosupression (SARS-COV-2) mediated, mediated steroid associated with a few other risk factors such as prolonged hospital stay with a ventilator. the accumulated dose of prednisone greater than 600mg or a total dose of methyl prednisone 12-7gm given a month before prednisone Immunocompromised to mucormycosis. In a recent systemic review conducted until April9, 2021 by toh.et.al reported the diagnosis of 41 confirmed cases of mucormycosis in people with covid-19, DM in 93% of cases, 88% receiving corticosteroid, 101 cases of mycormycosis (as confirmed. and 6 suspects) in covid-19, more than two thirds (76.3%) found the causes of corticosteroid.covid-109 usually cause, endothelial damage thrombosis , lymphoneia and decreased CD4 and CD8 levels and levels and thus jeopardized secondary or opportunistic fungal infections. . The median time between covid-19 detection and the onset of symptoms of mucormycosis was 156 + / 9.6 days.

Deferoxamine

A medication of Deferoxamine infection acquire iron from the affected individuals, Deferoxamine leads to growth and spread of infection and use of this drug is another risk factor for mucormycosis.

Toclizumab

According to European organization for research and treatment of cancer and the mycoses study group of education and research consort ion CEORTC/MSGEROA consensus, prolonged use of corticosteroid at therapeutic dose of 0.3mg/kg of least 3weeks in past 60days in considered risk factor for invasive fungal disease,further more IL-6 inhibiting drug such Toclizumab may cause immune degranulation and increases risk of secondary infection without providing substantial clinical benefits in the patient with covid-19. [28]

Mucormycosis in covid-19 summary of 82 Case report India up to may 2021: -

LFU: - Lost to follow-up, LAMA: - Left against medical advice.

Role of pharmacist in covid-19 treatment: [29-30]

Role as front line worrier pharmacist-

Pharmacists ought to have consistently been considered frontline workers, however particularly in the midst of COVID-19. Pharmacists are as of now among those medical care experts on the front line, giving fundamental medical services administrations during this time. Pharmacists are the most available medical care suppliers and the first touch point of patient commitment with the medical services system. Pharmacists are at the forefront giving basic patient consideration administrations during this general wellbeing emergency in COVID 19.

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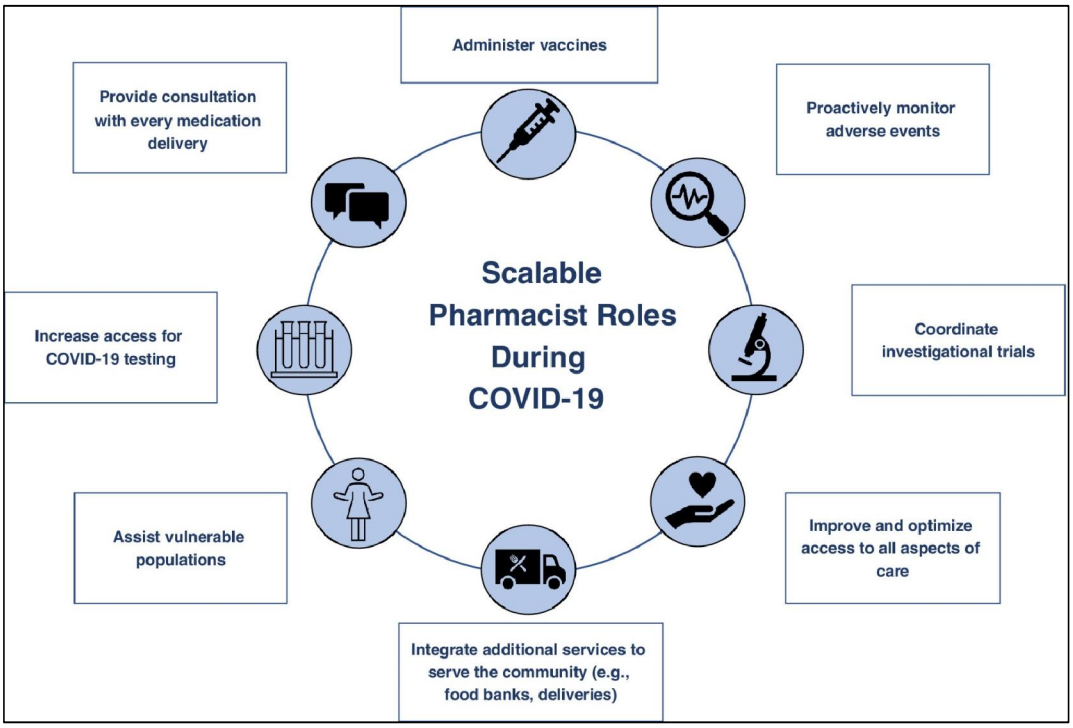

Fig 5 : Role of pharmacist in covid-19

II. CONCLUSION

To conclude, mucormycosis is a disease which usually shows aggressive and an alarming mortality rate. However the actual etiopathogenesis remains varied throughout the world, diagnosis of this disease remains a challenge for the clinicians. But still in the view of its high mortality rate, (i) early and prompt diagnosis, (ii) recovery from the predisposing factors, (iii) early intervention with surgical debridement and therapeutic drugs are the only hopes to improve the condition from this devasting disease. A major use of Toclizumab, Deferoxamine, Dexamethasone (Corticosteroid) in a background of covid-19 appears to increases mucormycosis. All efforts' should be made to maintain optimal glucose and only judicious use of Toclizumab, Dexamethasone, Deferoxamine, Corticosteroids in patient with covid-19.

III. RESULT

Characteristics of 82 patients of mucormycosis causes with covid-19 studied in which 82 patient are caused with mucormycosis in which 58/82 person taking steroid and 8/82 person taking Toclizumab and 10/82 taking Remdesivir. And few cases were received all 3 drugs for covid19 and 77/82 was Confirmed test for mucormycosis and 5 was Suspected all these patient are treating with covid-19 drug and some of diabetic patient.

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