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Review Article

AN OVERVIEW OF MUCORMYCOSIS

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ABSTRACT

Mucormycosis is an angioinvasive infection caused by Zygomycosis in the order of Mucorales. It is mainly affected in immunocompromised individuals followed by risk factors such as diabetes mellitus, stem cell transplantation, organ transplantation, hematological malignancy, and more intake of steroids. Rhino-orbito-cerebral mucormycosis, pulmonary mucormycosis, cutaneous mucormycosis, gastrointestinal mucormycosis, and disseminated mucormycosis are the most common types. Moreover, it can be diagnosed to overcome this infection using the following methods such as histopathology cultures, computed axial tomography, and resonance imaging. Moreover, it can be treated with amphotericin B, the first-line drug, and posaconazole and isavuconazole are also used. The *in vitro* studies reveal the antifungal drugs which show the best activity against mucormycosis. The main aim of this review shows the detailed study of mucormycosis and the outcome of this infection.

Keywords: Amphotericin B, Angioinvasive infection, Mucormycosis, Zygomycosis.

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INTRODUCTION

Mucormycosis is the term introduced by American pathologist, R.D. Baker. It is a severe sickness caused by organisms from the Mucorales order. Zygomycosis is another name for it [1]. Mucormycosis is an invasive Angioinvasive infection characterized by tissue death. It is regularly influenced by immunocompromised patients [2]. They normally involved growths of the Rhizopus, Lichtheimia, Mucor, and Rhizomucor, and other uncommon families of organisms are Apophysomyces, Saksenaea, Cunninghamella, and Syncephalastrum [2]. The growths, for the most part, found in rotting matter, have changed the climate, and caused their development as a potential pathogenic life form that prompts high morbidity and extremely high mortality. These molds can go into the human body through the respiratory portion or skin and less normally into the gastrointestinal portion get an inflammatory reaction. Normally, the illness is caused in immunocompromised patients and the disease expanded with diabetes mellitus, hematological risk, solid organ transplantation, HIV, intravenous drug addiction, voriconazole treatment, and corticosteroid treatment [2,3]. The infection can be communicated by the inward breath of spores or direct immunization of spores into disturbed skin or mucosa. Either the inward breath of air-borne spores or ingestion or immunization on direct skin, the hyphae attack veins causing tissue localized necrosis and decomposition. Patients suffering from neutropenia or ketoacidosis, as well as those with high iron serum concentrations, are at a higher risk of developing mucormycosis [4]. Mucorales can produce minor contaminations, but they can swiftly proceed to obtrusive delicate tissue, rhinocerebral-orbital, gastrointestinal, and pneumonic disorders. Mucormycosis is a fungal infection that affects the rhino-orbital-cerebral, pulmonary, and cutaneous areas, as well as the gastrointestinal, disseminated, and renal regions. In any case, rhino-ocular-cerebral mucormycosis and pulmonary mucormycosis are common features of most typical appearances. The most well-known indication in hematological individuals is pulmonary mucormycosis. Contrasted with other contagious, for example, *Aspergillus fumigatus* or *Candida albicans*, just little is known so far on parasitic properties lead to abundant disease and the host's harmless reaction to the different agents of the Mucorales.

Mucormycosis is mainly an opportunistic disease with grave results in case it is not examined and treated at the time. Furthermore, the different analysis techniques utilized to examine these contaminations include computed tomography, magnetic resonance imaging, direct microscopy, based on cultures, and histopathologic examinations. The difficulty in diagnosis antifungal treatment is incomplete because of intensely innate protection from large numbers of the generally utilized antifungal medications still it causes high mortality [5,6]. Amphotericin B was utilized as a first-line drug. Other antifungal medications are itraconazole and posaconazole which are utilized. The identified proof of Syncephalastrum species utilizing molecular techniques, for example, DNA sequencing or protein profile-based strategies, such as matrix-assisted laser desorption ionization-time-on-flight mass spectroscopy (MALDI-TOF-MS). Furthermore, corona infection is an illness that influences the respiratory system severely by COVID (SARS-COV-2) and is related to bacterial and fungal contaminations; a few examples of coronavirus are related to mucormycosis which has been expanded as of late [7].

The German pathologist Fubringer describes the disease in 1876 and 1885; Arnold Paltauf publishes Mycosis Mucorina, the first case of mucormycosis. Furthermore, later, the American pathologists introduced the term mucormycosis [1]. This contamination rose during the 1980s and 1990s, among immunocompromised people on frequency rate in France, it shows intensification by 7.4% per year [8].

MICROBIOLOGY

Mucormycosis is caused by fungi from the Mucorales order, which is divided into six families, that is, Mucoraceae, Cunninghamellaceae, Mortierellaceae, Saksenaceae, and Thamnidaceae. The classification is shown in Table 1 says Bouza *et al*.

Rhizopus species are the most important. Mucorales grow quickly on both selective and non-selective media. The mycelium seems fibrous or cotton candy-like, and the growth is rapid. According to macroscopic and microscopic criteria, the identified agents are responsible for mucormycosis. Hyaline appearance, strong development, light

coloration on the rear side of the plate (i.e. tan to yellow for most species), and variable coloration on the sporulating surface of the colonies are the macroscopic characteristics. Identification is aided by macroscopic criteria, which are confirmed by microscopic inspection following staining.

EPIDEMIOLOGY

Mucormycosis is thought to be an uncommon infection that affects <1.7 billion people each year. Infection is mostly human impacts due to inhalation of fungi that are expelled into the air or direct inoculation of organisms into damaged skin or membranes. Cases with mucormycosis have reportable everywhere. The annual reports of mucormycosis-affected patients are reportable in India within Table 2. The data from 2001 to 2020 are collected by Chakrabarti *et al*., Prakash *et al*., and Manesh *et al.*

Table 1: Classification of species

Family	Genes	Species
Mucoraceae	Absidia	*A. corymbifera*
	Apophysomyces	*A. elegans*
	Mucor	*M. circinelloides*
	Rhizopus	*M. hiemalis*
		M. racemosus
		M. ramosissimus
		M. rouxianus
		M. pusillus
		R. arrhizus
		R. azygosporus
Cuninghamellaceae	Cunninghamella	*C. bertholletiae*
Mortierellaceae	Mortierella	-
Saksenaceae	Saksenaea	*S. vasiformis*
Syncephalastraceae	Syncephalastrum	*S. racemosum*
Thamidaeceae	Cokeromyces	*C. recurvatus*

The causative fungi are extremely obsessed with the location. Most agents cause infections within the Mucorales. The Mucorales contains 261 species in 55 genera. Some Mucoralean species supported the taxonomy given within Table 3. Another predisposing factor related to mucormycosis in India. Diabetes is a common disease followed by hematological malignancies and solid organ transplants, diabetes-related mucormycosis shows 54–74% of cases and hematological malignancy shows 1–9% in India. Numerous studies have documented the most significant risk factor/underlying disease.

PATHOGENESIS

Mucorales attack deep tissues through the ingestion process or inhalation of spores and infusion of spores [9]. The spores penetrate the lungs or and so the first line of defense action in associate degree extremely using oxidative metabolites and cationic peptides, the dense body eliminates spores [1,10,11].

Host defense

The synthesis of oxidative metabolites and cationic peptides by both molecular and polymorphonuclear phagocytes of typical hosts such as fungal order Mucormycosis is fought by phagocytes, which are a type of white blood cell. Consider: Neutropenic patients have a higher risk of mucormycosis. Mucormycosis is more common in people who have phagocytes that are malfunctioning. Symptoms and pathologies are employed to disable phagocytes' ability to travel toward and destroy pathogens through either oxidative or non-oxidative mechanism. Corticosteroid therapy also affects bronchoalveolar macrophages, preventing spore development *in vitro* or after intranasal administration activates *in vivo* infection. The precise processes by which ketoacidosis, diabetes, and steroids affect phagocyte function are unknown [1,10].

Role of iron

Some clinical aspects have recently been established that the contamination is increased impotence due to mucormycosis in patients

Table 2: Annual incidence and risk factors of mucormycosis in India

Parameters	Chakrabarti *et al*., 2001; 2006; 2009	Manesh *et al*., 2019	Chander *et al*., 2018	Patel *et al*.,	Prakash *et al*., 2020
Study center	1	1	1	2	4
Study period	1990–2004; 2006–2007	2005–2015	2010–2014	January 2013–May 2015	2013–2015
Study duration	15 years 6 months	10 years	5 years	2 years 5 months	3 years
Place of study	Chandigarh (North India)	Tamil Nadu (South India)	Chandigarh	Gujarat	North and South India
Total cases	382	184	82	27	388
Mean annual incidence	24.5	18.4	16.4	-	-
Male: female ratio	2.4:1	21:1	2.04:1	231	23:1
Pediatric (10–16 years)	30 (7.9)	7 (3.8)	4 (4.9)	-	46 (11.9)
Adult's n (%)	352 (92.1)	177 (96.2)	78 (95.1)	-	342 (89.1)
Total number of patients with underlying risk factors	349[s]	184	82	27	303
Diabetes mellitus	187 (53.6)	120 (65.2)	51 (62.2)	15 (55.6)	172 (56.8)
Diabetic ketoacidosis	21 (21.6)	16.9%	-	-	31 (10.2)
Solid organ transplantation	9 (26)	-	-	3 (11.1)	19 (6.3)
HSCT	-	4 (2.2)	-	-	1 (0.3)
Hematological and solid organ malignancy	16 (4.6)	14 (7.6)	-	1 (3.7)	23 (7.6)
Branch of skin (trauma due to accidents, burns, and injection site)	35 (10)	20 (10.9)	12 (14.6)	6 (22.2)	31 (10.2)
Pulmonary disease	1 (0.6)	-	-	2 (7.4)	21 (6.9)
Neutropenia	11 (14.6)	-	-	-	18 (5.9)
Steroid therapy	28 (8)	-	-	6 (22.2)	30 (9.9)
Chronic alcoholism	15 (5.9)	-	-	-	28 (9.2)
Chronic kidney disease	24 (32)	1 (0.5)	1 (1.2)	1 (3.7)	27 (8.9)
Human immunodeficiency virus	2 (0.8)	-	-	-	3 (1)
Immunocompetent host	45 (12.9)	10 (5.4)	16 (19.5)	7 (25.9)	32 (10.6)
Miscellaneous	53 (31)	15 (8.2)	8 (9.8)	6 (22.2)	6 (2.0)

Table 3: Current nomenclatures of medically important Mucoralean species according to updated taxonomy

Current species names	Previous name/synonyms
Lichtheimia corymbifera	*Absidia corymbifera*, *Mycocladus corymbifer*
Lichtheimia ornate	*Absidia ornate*
Lichtheimia ramosa	*Absidia ramose, Mycocladus ramosus*
Mucor ardhlaengiktus	*Mucor ellipsoideus, Mucor circinelloides f. circinelloides*
Mucor circinelloides	*Rhizomucor regularior, Rhizomucor variabilis var. regularior*
Mucor griseocyanus	*Mucor circinelloides f. griseocyanus*
Mucor irregularis	*Rhizomucor variabilis*
Mucor janssenii	*Mucor circinelloides f. janssenii*
Mucor lusitanicus	*Mucor circinelloides f. lusitanicus*
Rhizopus arrhizus	*Rhizopus oryzae*
Rhizopus microsporus	*Rhizopus microsporus var. azygosporus, var. chinensis, var. oligosporus, var. tuberosus.*

with elevated accessible body serum iron. Invasive mucormycosis is more common in patients who are given the iron chelator deferoxamine. Iron chelator with a deferoxamine degree determined by the human host. Deferoxamine is used as a siderophore by *Rhizopus* species to create inaccessible iron. Deferoxamine provides more iron to *Rhizopus* species. Furthermore, since the administration of deferoxamine, evidence from animal models have shown the critical role of iron in *Rhizopus* pathogenicity. Finally, animal models show that the fungus does not use various iron chelators as siderophores [1,10].

Fungal endothelial interactions

Mucormycosis infection is defined as the presence of a wide range of living forms with the ability to hematogenously transmit infection from the initial site to other organs. As a result, the organism's pathogenic strategy requires penetration through endothelial cells lining blood vessels. *R. oryzae* spores, but not germlings (i.e. pre-germinated spores), are able to follow subendothelial matrix proteins, as well as laminin and type 4 collagen. *In vitro R. oryzae* spores adhere to subendothelial network proteins [10].

The risk factors incorporate uncontrolled inherited disease, considerably ketoacidosis, steroid use, blood disorder, etc., considerably AIDS, renal insufficiency organ, or stem cell transplantation, intravenous drug abuse. In diabetic patients, it occurs as a dangerous and probably basic condition due to the augmented availability of micronutrients and diminished defense mechanisms of the body. Seriously neutropenic patients and those who lack phagocytic function are more prone to mucormycosis. Mucormycosis infection is characterized as the presence of a diverse range of live organisms capable of spreading infection hematogenously from the initial site to other organs. As a result, the organism's pathogenic strategy necessitates penetration of blood artery endothelial cells. *R. oryzae* spores can follow subendothelial matrix proteins, as well as laminin and type 4 collagen, but not germlings (i.e. pre-germinated spores) [1,10].

TYPES

The disease is caused by the order Mucorales. The underlying medical conditions are associated with which type of mucormycosis.

Rhino-orbital-cerebral mucormycosis

This is a hazardous infection brought about by saprophytic growths. *C. bertholletiae* or *Cunninghamella* species are responsible for the clinical course of this infection. In immunocompromised people, the infection is almost always present [12]. This infection progresses rapidly within an hour to days leading to cranial nerve paralyzes and highlighting CNS involvement. In patients with diabetic ketoacidosis or diabetes mellitus under control, ROCM is usually normal. Unstable rhino-sinus mucormycosis will be impacted by thrombosis of the cavernous sinuses. Reddish-black nasal turbinate and septum showed up alongside a nasal release is also seen [1]. Cunninghamella disease is diagnosed in an immunocompetent host, and the tooth is extracted and treated with Am B deoxycholate [12]. The microscopic examination of impacted tissues revealed granulomatous aggravation, degradation, and acute necrosis all over, but little angioinvasion, indicating a maintained immune response. Around 33–50% of individuals are influenced by this disease [1,11]. The few risk factors are solid organ transplant, corticosteroid treatment, chronic kidney infection, and intravenous medications. The normal signs and indications are fever, migraine, facial swelling, facial pain, nasal discharge, epistaxis, sinusitis, hemiplegia, nasal ulceration, toothache, facial numbness, bone destruction, and altered mental status. Eye pain, decreased vision, proptosis (11–16%), chemosis (4.5–9%), ptosis (3.5–18%), orbital cellulitis (2–16%), periorbital discoloration, and necrosis are some of the indications and adverse effects (2–4%). From the sino-nasal region and retro-orbital area, the infection spreads to the brain. Cerebral mucormycosis can also spread through the bloodstream, affecting specific organs. Early imaging is helpful in determining the amount of a deadly disease's involvement, which necessitates prompt and vigorous therapy. Imaging investigations aid in determining the amount of tissue invasion. Mucosal thickness, sinusitis, and bone degeneration in the nasal septa, orbit, maxilla, and mandible can all be seen on CT and MRI scans of paranasal sinus mucormycosis [13,14].

Pulmonary mucormycosis

Pulmonary mucormycosis is an invasive infectious disease caused by the Mucorales order [15], which is more common in immunocompromised persons. The major infection site of *C. bertholletiae* was discovered [12]. The pulmonary system is the most prevalent place, and it is frequently encountered in hematological patients and transplant recipients. In pulmonary mucormycosis, hematological danger is the most significant risk factor (32–40%), followed by diabetes mellitus (32–56%), hematopoietic stem cell transplant (1–9.8%), solid organ transplant (6.5–9%), and renal disease (13–18%), according to Hariprasath Prakash *et al*. Fever (3870%), cough (50–61%), pleuritic chest discomfort (22–37%), dyspnea (19–34%), lung infiltration, and consolidation are among the symptoms and manifestations seen in the patients (58–96%) [12]. This sign shows that the pulmonary mucormycosis can be analyzed early and quite challenging. Imaging studies can be non-specific. These infections finding requires histopathological assessment of the contaminated tissues get profound tissue examination, for example, transbronchial lung biopsies (TBLBs) from hematologic patients. To detect exactly, the culture and histopathology independent diagnostic tests are utilized. Mucorales DNA is detected in peripheral blood tests from patients with hematologic malignancies and is closely linked to pulmonary mucormycosis. Targeted treatment with liposomal amphotericin B, based on Mucorales molecular evidence, was successful for the afflicted patients. The widespread use of glucocorticoids can result in the spread of secondary bacteria or fungal infections. COVID-19 is being hampered by pulmonary aspergillosis [16-18].

Cutaneous mucormycosis

Mucormycosis of the skin can be both primary and secondary. Direct immunization infects the skin in the primary stage. This condition is still restricted to the entire depth of the skin, with 24% of cases extending to bone or muscle and 20% of cases spreading to non-contagious organs. Initial lesions in primary connective tissue mucormycosis are indurated plaques, which evolve into necrosis with an erythematous halo and eventually eschar. Burns commonly manifest as cellulitis and necrosis in people with surgical wounds. Secondary mucormycosis is additional frequent than primary mucormycosis. Its acute onset and high mortality alternative signs are fever, periorbital cellulitis, loss of vision, and other neurological deficits. The clinical manifestations of this illness are amorphous. Early detection is critical for determining the most effective antifungal treatment. Direct KOH, microscopic examination, and the presence of non-septate, hyaline, and hyphae primarily around the lesion's periphery are typically used to detect it. The diagnostic test should be collected from the lesion's center, together with subcutaneous

tissue fat. The RT-PCR method is used to determine the order of events. Mucorales with high specificity in clinical isolates and tissue samples. The antifungal medicine of choice for treating cutaneous infections is deoxycholate amphotericin B (d-AmB). In mucormycosis, posaconazole has been characterized as a second-line treatment. The risk factors are open wound trauma (21%), surgery (8–30%), burns (5–11%), and scratches (9%), reported by Hariprasath *et al*. regarding 43–67% of the patients were incident on cutaneous mucormycosis [12].

Gastrointestinal mucormycosis

The abdomen is the most prevalent site of mucormycosis, followed by the colon and small intestine, and is frequently associated with extensive diffused mucormycosis [19]. According to Hariprasath *et al*., it affects immunocompromised patients as well as patients with solid organ transplantation (52%), neutropenia (38%), hematological malignancies (35%), diabetes (12.2%), and malnutrition (16.7%) [12]. The symptoms of this infection differ depending on the place of infection. Nausea and vomiting are common signs and symptoms. Moreover, it is diagnosed during surgery or inspection by a diagnostic test of the suspected space. Gastric aspirants and wooden tongue depressors were cultured to develop the description. By reporting to Hariprasath *et al*., the foremost common site of infections is in the gut (1.3–2%), abdomen (33.6%), and gut (28.4%) [20]. It is rarely occurred in a patient who has transplantation of their liver and heart.

Disseminated mucormycosis

It is a rare entity and mostly seen in neutropenic patients with hematological malignancies, post-transplants, or in patients on deferoxamine therapy. It indicates the involvement of two or additional contagious organ systems with Zygomycetes [21]. According to the study, 13% of the population lives in poverty. It is a rare syndrome that primarily affects neutropenic persons with hematological malignancies, transplant recipients, and deferoxamine users, passes from one portion of the body to another through the bloodstream. It always occurs as a result of a hematogenous spread of a localized respiratory organ infection. The original respiratory organ or cutaneous tissue site of inoculation was the source of most disseminated infections [16]. The varied signs and symptoms are fever, fatigue, myalgia, arthralgia, metastasis distress, loss of consciousness, cardiovascular disease, and blood disease. It should be diagnosed the patients by autopsy, the organs and tissues affected were the lungs (81%), heart (62%), spleen (57%), brain (48%), GIT (24%), and skin (24%).

Miscellaneous

Endocarditis is an uncommon infection of the prosthetic valve. In a patient with myelodysplastic syndrome, an unusual case of order Mucorales causes aortic thrombosis. When traumatic inoculation or surgical intervention results in osteomyelitis. The illness hematogenous osteomyelitis is extremely rare. The solitary involvement of the kidney causes renal mucormycosis. It happens as a result of a kidney transplant.

SYMPTOMS

Mucormycosis symptoms vary depending on where the fungi develop in the body.

If the skin is infected and seems damaged, red, or swollen, it will turn black or feel heated or painful after a few days. It also travels through the blood to other parts of the body. Disseminated mucormycosis is another name for this condition. In severe circumstances, it might result in coma or death. The infection began in the mouth or nose and spreads to the central nerve system through the eyes.

One-sided facial swelling, headache, nose or sinus congestion, black lesions on the nasal bridge, or higher within the mouth that soon become more serious and fever are all signs of rhino orbital cerebral mucormycosis. Fever, cough, chest pain, and shortness of breath are signs of pulmonary mucormycosis. Blisters or ulcers may appear as a result of cutaneous mucormycosis, and the diseased region may turn black.

Rhino orbital cerebral mucormycosis is characterized by one-sided face swelling, headache, nose or sinus congestion, black lesions on the nasal bridge or higher in the mouth that quickly grows more serious, and fever. Symptoms of pulmonary mucormycosis include fever, cough, chest pain, and shortness of breath. As a result of cutaneous mucormycosis, blisters or ulcers may form, and the affected area may turn black.

RISK FACTORS

Mucormycosis is uncommon, but it is frequent in persons with health issues or who use medications that reduce the body's capacity to fight infections and illness. People with diabetes, diabetes with ketoacidosis, cancer, organ transplantation, stem cell transplant, neutropenia, long-term corticosteroid use, intravenous drug abuse, too much iron in the body, skin injury due to surgery, burns or wounds, prematurity, and low birth weight (for neonatal gastrointestinal mucormycosis) are more likely to develop mucormycosis. For example: Inhaling spores from the air can cause the infection to spread to the lungs or sinuses. The fungus enters the skin through a scrape, burn, or other sort of skin damage, resulting in a skin infection. Because the fungi that cause mucormycosis are prevalent in the environment, it is impossible to avoid breathing in fungal spores.

Diabetes mellitus

It is a common underlying illness in mucormycosis patients. Diabetes mellitus was the most common underlying disease in 40% of cases, and ketoacidosis was found in 20%. Diabetic ketoacidosis is observed in 90% of diabetic ketoacidosis cases in North India and 10% in South India [5].

Hematological malignancies (HMs) and Hematopoietic stem cell transplantation (HSCT)

In some nations, mucormycosis is the most frequent disease. In India, however, HM and HSCT are risk factors for 1–9% and 1% of the population, respectively. When a patient has experienced chronic neutropenia, this is a common risk factor [5].

Solid organ transplantation (SOT) and Solid organ malignancies (SOM)

HM and HSCT are more common than SOT and SOM. The chances of this happening vary depending on the organs that are being transplanted. Infection rates range from 0.6% to 23% in this group [5].

Corticosteroids and immunosuppressive agents

The most major risk factor for mucormycosis is these. These are the medications that are used to treat cancers, transplants, and autoimmune diseases. Mucormycosis is caused by a high dose of corticosteroids. Anna Skiada *et al*. reported that 46% of patients had corticosteroids a month before the diagnosis of mucormycosis, and 44% receive immunosuppressive agents [5].

PREVENTION

There is no vaccine to prevent this infection. There are also some ways to protect people to lower the possibility of developing mucormycosis. They defend themselves against the environment. After a natural disaster stay away from stagnant water, damaged buildings, and floodwater. Avoid activities like gardening or yard work that involve close contact with dirt or dust. It is not potential, though.

1. When undertaking outdoor activities such as horticulture, yard maintenance, or visiting a wooded area, wear shoes, long trousers, and a long-sleeved shirt.
2. When handling items such as dirt and manure, wear gloves.
3. Clean skin injuries thoroughly with soap and water to limit the risk of infection, especially if they must be exposed to soil or dirt.
4. Take antifungal drugs if you're at high risk of mucormycosis, such as after a transplant or a vegetative cell transplant.

DIAGNOSIS

Early identification of this infection is almost important. It may improve the outcome of this infection. Identification consists of recognition

of risk factors, assessment of clinical manifestation, and strategies supported by histopathology, cultures, and advanced techniques such as computed axial tomography and resonance imaging.

Clinical diagnosis
The clinical approach shows low sensitivity and specificity. Pathogens such as fungal genus, Fusarium, Pseudallescheria, and Scedosporium, will be diagnosed differentially in immunocompromised individuals with necrotic cutaneous lesions caused by mucormycosis infection [5,22]. The diabetic patient with sinusitis undergoes a thorough examination. Corzo *et al*. presented a method for detecting and treating rhino-orbito-cerebral mucormycosis in a diabetic patient [5,23]. Nerve palsy, nasal discomfort, and proptosis are all danger signals. The discovery of some symptoms prompts rapid testing, including blood tests, eye imaging, and antifungal medication. A reverse of halo sign (RHS) on a CT scan could indicate respiratory organ mucormycosis. The RHS was seen in 54% of mucormycosis patients [24]. Detailed identification necessitates the use of laboratory techniques such as histology and culturing.

ROUTINE LABORATORY IDENTIFICATION

Laboratory identification includes histopathology, direct examination, and culture.

Histopathology
Fungi biopsies of afflicted tissues or bronchoalveolar lavage (BAL) in patients with respiratory organ mucormycosis were supported by this type of identification. It is an important tool for determining the presence of an associated infection. It distinguishes the presence of fungus as an infectious agent in the specimen from the presence of fungus in a culture. It will also disclose any coinfections with other molds. The fungus is highlighted with Grocott Methenamine Silver (GMS) and periodic acid–Schiff (PAS) staining. Furthermore, PAS allows for a better view of the surrounding tissues than GMS [5,11].

Direct examination
For early diagnosis, direct examination and KOH wet mounts are used. Fluorescent brighteners such as blankophor and calcofluor white with KOH are used to improve visualization. Direct evaluation of fresh material is inexpensive, and histopathological methodology recommends it. Under the microscopic genus and species, the appearance of the fungi varies, the appearance varies, but it includes wide, ribbon-like filaments and septa that do not branch at right angles [5].

Culture
The essential approaches to the identification of mucormycosis are culture. It helps to identify the genus and species level and antifungal susceptibility testing, Mucorales order is rapidly growing at 37°C temperature, matrix-assisted laser desorption ionization-time-of-flight mass spectroscopy to identify cultured Mucorales (MALDI-TOF) [5,22,25]. The positive culture from a sterile site ensures identification at a non-sterile site due to contamination and should be combined with clinical and tomography information to determine a correct identification [5]. The diagnostic test sample is cultured and does not offer a result as the organisms are fragile.

Applied and emerging molecular methods
It is a useful tool to verify the infection and determine the strains. For tissue detection, many approaches are developed such as PCR, RTPCR, and nested PCR combined with RFLP. Principally molecular test target 18s rRNA genes and other targets were additionally investigated. This method includes 28r DNA, mitochondrial gene, cytochrome b gene, or Mucorales-specific cot H gene [5].

TREATMENT

Mucormycosis is uncommon contamination that could be treated properly because prompts death. For the effective treatment it requires (1) Early diagnosis, (2) Reversal of underlying disease (3) Surgical debridement, (4) Antifungal treatment [7,26].

Early diagnosis
Early analysis of mucormycosis is allowed to initiate the antifungal treatment early. Some diagnostic approaches are created. The quantitative polymerase chain reaction (PCR) framework is developed, allowing for quick analysis. Patient's most widely recognized CT findings for detecting Orbital and CNS involvement. A CT scan was used to detect pulmonary mucormycosis early.

Reversal of an underlying disease
It is critical to prevent defects in host defense. While treating mucormycosis, the immunosuppression drug portion should be decreased or stopped. Administration of iron should be avoided.

Surgical debridement
Mucormycosis is characterized by widespread angioinvasion caused by blood vessel thrombosis and tissue necrosis. It is caused by antifungal drugs not getting to the infection site. The surgical excision of necrotic tissues may be necessary for complete eradication. Patients who did not have surgery died at a far higher rate than those who had surgery.

Antifungal therapy
The infection is examined, and the appropriate antifungal treatment is administered. Patients can overcome this infectious condition with the right treatment. The first-line treatment for mucormycosis infection is amphotericin B, which is used in the lipid formulation. Posaconazole and itraconazole are two more antifungals widely used to treat this illness.

Amphotericin B

Amphotericin B. It is used as a first-line medication against fungus in the form of a lipid formulation. It is used to treat infections that are life threatening. The Am B's efficacy has been demonstrated in both *in vitro* and *in vivo* investigations. Lipid amphotericin B is less nephrotoxic, and it can be safely administered at a greater dose for an extended length of time. Liposomal Am B had a survival rate of 67%, while Am B had a survival rate of 39%. In this way, liposomal Am B is commonly preferred for the treatment of mucormycosis.

Posaconazole

It is the first-line medication to show a wide range of action against Zygomycetes. Posaconazole shows great action against the fungi. It is given orally or by intravenous route. For the most part, suspension form is utilized to treat this infection. Other than the oral form, it should be taken intravenous route containing β cyclodextrin for the better pharmacokinetic property.

Isavuconazole

It is a new Zygomycetes-fighting broad-spectrum triazole derivative medicine. It is administered both orally and intravenously. When compared to other azole derivatives, it possesses a wide range of pharmacokinetic and safety properties. Other antifungal compounds used to treat mucormycosis contamination include voriconazole, caspofungin, and echinocandins.

IN VITRO STUDIES OF ANTIFUNGAL DRUGS

Mucormycosis has become much more common in recent years, particularly among immunocompromised people. Amphotericin B is the treatment of choice for this illness. Furthermore, this treatment has a variety of outcomes [27,28], and toxicity is common. The usual procedures for testing mold sensitivity to antifungal drugs were outlined by Dannaoui *et al.* and Alastruey *et al*.

The CLSI standard reference broth dilution method is the primary approach.

They recommend using Standard RPMI-1640 stock non-germinated conidial inoculum suspension in this paper.

Incubation at 350C for 24 h for Rhizopus species.

The European Committee for Antimicrobial Susceptibility Testing (EUCAST) developed an alternative standard for conidia producing molds through its antifungal susceptibility testing (AST) subcommittee. The differences between CLSI and other approaches are as follows:
To achieve a glucose concentration of 2%, RPMI 1640 is supplemented with glucose.

Chrysanthou and Cuenca Estrella are distinguished by their inoculum size, which is consistent between the two procedures.

Amphotericin B
Cunninghamella species and *Rhizopus* species have greater minimum inhibitory concentrations (MICs) than Am B, which display the best *in vitro* efficacy against majority of the species responsible for Mucormycosis (zygomycosis). The sickness caused by *Cunninghamella* species is responsible for the greatest number of failures [27]. When the lipid formulation of Am B is used for treatment, retrospective studies show an increase in survival rates.

Isavuconazole
It is not an effective treatment for mucormycosis; only a few patients benefit from it [29,30]. Isavuconazole has stronger efficacy against Zygomycetes than voriconazole in these trials, and a few strains are blocked by a modest dose of isavuconazole. Singh *et al*. studied mice using 15 Zygomycetes strains and discovered that isavuconazole has a lower MIC. As a result, in some cases of zygomycosis, isavuconazole is beneficial. Isavuconazole has a low MIC in *Rhizopus* and *Syncephalastrum*.

Voriconazole
It has no effect on Zygomycetes. The MIC in these *in vitro* studies is >2 mg/L. The most of azole medicines have been found to have concentrations of >8 mg/L [31].

Posaconazole
It is the first-line treatment for Zygomycetes that has broad-spectrum action. This research demonstrates strong antifungal action [28,32,33]. Similarly, experimental models such as mice have been used to illustrate the medication's *in vivo* activity. Posaconazole and amphotericin B, both used as prophylaxis in neutropenic mice, produced similar effects [34]. Van Burik *et al*. and Sun *et al*. reported 60% and 79% responses in 91 and 24 patients, respectively [35,36]. Finally, some case reports of zygomycosis patients who were successfully treated have been published [37-39]. Posaconazole is a crucial antibiotic for treating this infection. This infection is treated with AmB, which is the first-line treatment for this infection and causes toxicity. As a result, this medicine provides an alternative treatment. As a result, the alternate treatment is posaconazole, which is the second most active against fungal Zygomycetes. The use of echinocandins in combination with other treatments enhances the survival of patients infected with Zygomycetes.

Combination therapy
It is difficult to deal with this infection, because of the limited number of medications active against zygomycosis. *In vitro* action against fungus Zygomycetes is the subject of a few research. The combination between AmB and caspofungin or posaconazole enhances fungal survival in animal models. Caspofungin coupled with Am B is also more effective in patients than AmB alone. In a patient with hematological malignancy, a combination medication is used to treat rhinocerebral mucormycosis [27].

CASE STUDY

Kazuko lno *et al*. conducted a polymerase chain reaction (PCR) assay targeting these fungi in blood for four patients with hematological malignancies who were strongly suspected of having pulmonary mucormycosis. *Rhizopus* species have been discovered in two of the four patients. Based on molecular findings, every one of the patients was effectively treated with liposomal AmB and the species *Cunninghamella* and *Absidia* found in the other two patients, respectively. They conclude in this study that PCR-based methodology allows for highly sensitive and specific Mucorales detection, as well as information that can be used to manage pulmonary mucormycosis in high-risk patients with hematological malignancies, particularly those who have not undergone histopathological examinations [16].

Erick *et al*. investigated rhino-ocular-cerebral mucormycosis in a 46-year-old woman who had bilateral blepharoedema, corneal opacity in the left eye, and poorly controlled diabetes. The patient had a total maxillectomy and was treated with Am B. A direct mycological investigation with KOH 10% revealed that the patient had hyaline. Using rRNA gene amplification and sequencing, *Apophysomyces ossiformis* was discovered from a maxillary biopsy.

Finally, the reason for this being the first case of rhino orbital cerebral mucormycosis. ossiformis, which was deadly. They highlight the importance of employing molecular approaches to identify the fungus that causes mucormycosis in order to treat patients effectively. They highlight the importance of employing molecular approaches to identify the fungus that causes mucormycosis to treat patients effectively [16].

Chelsea Gummer *et al*. investigated disseminated mucormycosis. They described a patient with T-cell lymphoblastic leukemia who received severe treatment in this study. They looked at the first case of a patient who survived disseminated mucormycosis with infection in five places: The lungs, appendix, pancreas, left occipital lobe, and right kidney, all of which were treated with a combination of antifungal drugs. Finally, successful therapy of disseminated mucormycosis and patient survival were found to be: (1) A high index of clinical suspension of disseminated fungal infection. (2) Early antifungal treatment with a mix of drugs. (3) Fungi foci must be surgically debrided.

PROGNOSIS AND MORBIDITY RATE

The prognosis is mostly determined by the severity of the disease's clinical manifestations and the effectiveness of treatment undertaken in response to the infection. Patients with this condition have a general survival rate of roughly 50%. Rhinocerebral mucormycosis was almost always lethal, with a high mortality rate. By and large, the survival rate is around 50%, with some cases reaching 85%. The survival rate of rhino-orbito-cerebral mucormycosis is higher than that of pulmonary or disseminated mucormycosis. The most well-known fundamental infection is rhino-orbito-cerebral. In contrast, pulmonary mucormycosis has 32–40%. Cutaneous mucormycosis has 43–67%, gastrointestinal mucormycosis has 12.5–52%, and disseminated mucormycosis has 13%. In general, the disease is a large part of the body carefully removed the infected tissues and diagnosis should be possible early then death rate is additionally decreased.

CONCLUSION

The infections caused by the fungus in the order Mucorales mostly affect immunocompromised patients and at present coronavirus-influenced individuals are also affected. This shows an alarming mortality rate. Physicians and clinicians alike continue to struggle with disease diagnosis. It is critical to get a diagnosis as soon as possible. Mucormycosis cases multiplied in the future as the number of immunocompromised patients increased. Amphotericin B, as well as several antifungal medications, is the treatments of choice for treating this infection. Surgical debridement is used to remove necrotic tissues in severe infections. Because antifungal

medications have weak penetration properties, it may be difficult to thoroughly remove the necrotic tissues. Patients who do not undergo surgery have a higher mortality risk than those who get surgical debridement.

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CONFLICTS OF INTEREST

None.

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