INDO AMERICAN JOURNAL OF PHARMACEUTICAL RESEARCH

MUCORMYCOSIS: AN OVERVIEW

Surushe C., Karpe M., Kadam V.
Bharati Vidyapeeth's College of Pharmacy, Belapur, CBD, Navi Mumbai, 400614, India.

ARTICLE INFO

Article history
Received 28/08/2021
Available online
30/09/2021

Keywords
Mucormycosis,
Types of Mucormycosis,
Mucormycosis in COVID-19.

ABSTRACT

Mucormycosis is termed as an angio-invasive fungal infection, connected with high morbidity and mortality. An alteration in the epidemiology of mucormycosis has been discovered in recent years with the rise in frequency, newfound causative agents and susceptible population. The rise has been perceived globally, but it is very advanced in the Asian continent. Though diabetes mellitus surpass all other risk factors in Asia. Post-tuberculosis and chronic renal failure have appeared as a new risk groups. The rhino cerebral mucormycosis is most usually seen in patients with diabetes mellitus. Although considered to be a infrequent infection, mucormycosis (zygomycosis) has emerged as the second most common invasive mould infection. Despite the advent of newer fungicidal agents, mortality rate of mucormycosis resides exceedingly higher. Successful direction of mucormycosis requires early identification, reversal of underlying predisposing risk number, surgical debridement and prompt administration of active antifungal agents. However, mucormycosis is not always amenable to cure. There are challenging obstacles that lead to exertion in management of Amphotericin B. These include unique host-based risk factors for mucormycosis, the fungus' resistance to innate hostdefences and distinctive features of its immunopathogenesis, such as extensive angioinvasion, increased virulence and use of chelators by the fungus as siderophores.

DOI NO: 10.5281/zenodo.5541154

Corresponding author
Surushe C.
Bharati Vidyapeeth's College of Pharmacy,
Belapur, CBD, Navi Mumbai, 400614, India.
chaitanyasurushe31@gmail.com

*Please cite this article in press as **Surushe C.** et al. Mucormycosis: an Overview. Indo American Journal of Pharmaceutical Research.2021:11(09).*

INTRODUCTION

Mucormycosis (Zygomycosis) is caused by fungi from the Mucorales order. Is also known as Black Fungus. Inhalation of sporangiospores, consumption of tainted food, or traumatic inoculation are the most common ways for humans to become infected. Mucorales fungi are widespread, and their hyphae appear to be broad, aseptate, or coarsely septate ribbon-like hyphae. Mucorales has eleven genera and 27 species that are linked to human illnesses. The most common cause of mucormycosis is Rhizopus arrhizus, which is followed by Apophysomyces, Lichtheimia, Rhizomucor, Mucor, and Cunninghamella species. Between the Western world and Asian countries, there has been a change in the predominance of risk factors/underlying illness and mucormycosis causative agents. In Asia, diabetes mellitus is the most common risk factor, while in Europe and the United States, haematological malignancies and transplantation are substantial risk factors. In healthy people, a large proportion of cases are reported after a traumatic event. Health-care related to mucormycosis has become increasingly reported in recent years.Health-care related to mucormycosis has become increasingly reported in recent years. The current study examines the global incidence of mucormycosis as a function of changes in epidemiological characteristics such as risk factors, causative agents, and underlying disease. [1-12]

TYPES OF MUCORMYCOSIS

Invasive mucormycosis is divided into one of six major clinical forms based on its clinical presentation and anatomic location:
(1) Rhinocerebral Mucormycosis
(2) Pulmonary Mucormycosis
(3) Cutaneous Mucormycosis
(4) Gastrointestinal Mucormycosis
(5) Disseminated Mucormycosis
(6) Endocarditis, osteomyelitis, peritonitis, and kidney infection are uncommon rare types. [13–15]

RHINOCEREBRAL MUCORMYCOSIS

The most frequent type of Mucormycosis is Rhinocerebral Mucormycosis (ROCM), which is primarily encountered in people with Diabetes Mellitus. Patients with underlying malignancies, recipients of solid organ transplants or haematopoietic stem cell transplants, and people with other risk factors are all at risk. Inhalation of fungal sporangiospores in the paranasal sinuses causes this fungus to grow. The infection can quickly spread to nearby tissues. When the invading fungus germinates, it might spread inferiorly to the palate, posteriorly to the sphenoid sinus, laterally in the cavernous sinus to the orbits, or cranially to the brain. The fungus kills the host by attacking the cranium through the orbital apex or cribriform plate of the ethmoid bone. However, imaging tests are nonspecific for ROCM, and histological confirmation of fungal tissue invasion is always required to diagnose ROCM. Given the rapid progression of ROCM and the significant increase in death rate when the fungus penetrates the cranium, every diabetic patient with a headache and visual abnormalities should be evaluated as soon as possible with imaging studies and nasal endoscopy to rule out mucormycosis. [16-19]

PULMONARY MUCORMYCOSIS

Pulmonary mucormycosis is particularly common in neutropenic cancer patients receiving induction chemotherapy and those who have had HSCT and developed graft-versus-host disease. Patients with pulmonary mucormycosis have a high overall mortality rate (76%) that is significantly higher in critically immunocompromised patients. Pulmonary mucormycosis has nonspecific clinical characteristics that are difficult to distinguish from pulmonary aspergillosis. Patients frequently have a high-grade fever (38°C) that does not respond to broad-spectrum medications. Hemoptysis, pleuritic chest pain, and dyspnea are the most prevalent symptoms, while hemoptysis, pleuritic chest pain, and dyspnea are less prevalent. Pulmonary mucormycosis can show as an endobronchial or tracheal lesion in rare cases, especially in diabetics. Endobronchial mucormycosis can produce an obstruction in the airway, resulting in lung collapse, as well as invasion of the hilar blood vessels, culminating in significant hemoptysis. Pulmonary mucormycosis can affect the mediastinum, pericardium, and chest wall, as well as the lungs. On chest imaging, the symptoms of pulmonary mucormycosis are nonspecific and distinct from those of pulmonary aspergillosis.Consolidation, infiltration, nodules, cavitations, atelectasis, effusion, posterior tracheal band thickening, hilar or mediastinal lymphadenopathy, and even normal findings are the most common results.[20–28].

CUTANEOUS MUCORMYCOSIS

Direct immunisation of fungal spores in the skin causes cutaneous mucormycosis (Zygomycosis), which can progress to widespread illness. The opposite (distribution of blood from internal organs to the skin) is extremely uncommon. Only 6 examples were identified by Roden et al as having an inverted distribution (3%). cutaneous mucormycosis is characterised as localised when it affects only the skin or subcutaneous tissue, deep extension when it attacks muscle, tendons, or bone, and circularise when it affects other noncontiguous organs, depending on the severity of the illness. The clinical signs and symptoms of cutaneous mucormycosis differ. A necrotic eschar with surrounding induration and erythema is the typical presentation (demonstration) of cutaneous Zygomycosis. A nonspecific erythematous macule, on the other hand, may represent the cutaneous manifestation of widespread disease in an immunocompromised patient, despite its tiny size and apparent insignificance. When cutaneous mucormycosis is accompanied by necrotic eschars, the lesions can resemble bacterial synergistic gangrene, pyoderma gangrenosum, or other bacterial or fungal infections. [29-35].

Image- Cutaneous Mucormycosis

GASTROINTESTINAL MUCORMYCOSIS

In surviving patients, gastrointestinal mucormycosis is both uncommon and common. In such circumstances, diagnosis can take a long time, and the mortality rate can be as high as 85%. Only 25% of gastrointestinal mucormycosis cases are detected antemortem, and the condition has been linked to preterm neonates, HMs, malnourished children, diabetes mellitus, and a history of corticosteroid usage, according to reports. Consumption of pathogens in foods such as fermented milk and dried bread items causes GI mucormycosis. Gastric mucormycosis may be exacerbated by the consumption of fermented porridges and alcoholic beverages made from corn. Finally, in a hematology-oncology clinic, one group of sources reported on a series of instances of gastrointestinal mucormycosis thought to have been transmitted orally by sporangiospore-infected tongue depressors used for oropharyngeal examinations. Mucormycosis of the gastrointestinal tract can affect any portion of the digestive system, although the stomach is the most commonly afflicted, followed by the colon and ileum.

The infection usually manifests as a cecal, appendiceal, or ileac mass, as well as a gastric perforation, which is typically accompanied by severe upper gastrointestinal tract bleeding. Neutropenic fever, typhlitis, and hematochezia are among conditions that can affect neutropenic patients. Because of the generic nature of gastrointestinal mucormycosis, diagnosis is generally delayed, requiring a high level of suspicion and prompting the use of endoscopic biopsy analysis. Mucormycosis of the gastrointestinal tract can potentially affect the liver, spleen, and pancreas.The fungus can induce peritonitis, bowel perforation, sepsis,and extensive gastrointestinal haemorrhage,which is the leading cause of death.[1],[36-52].

Image- Gastrointestinal Mucormycosis.

DISSEMINATED MUCORMYCOSIS

Mucormycosis in one organ can spread to other organs hematogenously. The lung is the organ most usually associated with dispersion. Dissemination can also happen through the gastrointestinal tract, severe skin lesions, or burns. Although the brain is a common location of spread, lesions in the liver, spleen, heart, and other organs can also be discovered. Patients with high iron levels (particularly those on deferoxamine), severe immunosuppression (e.g., allogeneic stem cell transplant recipients with graftversus-host disease treated with corticosteroids), or profound neutropenia and active leukaemia are all at risk for disseminated mucormycosis. The host, as well as the location and degree of vascular invasion and tissue infarction in the affected organs, influence the symptoms and progression of disseminated mucormycosis. To change early diagnosis, the varied depiction of disseminated mucormycosis necessitates a high index of suspicion. Disseminated mucormycosis is frequently diagnosed postmortem. Early detection relies heavily on the presence of a metastatic skin lesion. Disseminated mucormycosis is invariably lethal if not treated properly. [53-62]

UNCOMMON FORMS OF MUCORMYCOSIS

Endocarditis, osteomyelitis, peritonitis, and pyelonephritis are some less common or different localised types of mucormycosis. Mucormycosis is a relatively uncommon cause of prosthetic or native valve endocarditis. The most common risk factor is intravenous drug usage. Endocarditis is a type of infection that develops on or around prosthetic valves and can lead to aortic thrombosis. Surgical intervention (e.g., tibial pin placement, anterior cruciate ligament repair) or traumatic inoculation are the most common causes of osteomyelitis. The tibia, calcaneus, femur, cuboid, humerus, scapula, metacarpals, phalanges, and sternum have all been recorded to develop osteomyelitis. Hematogenous osteomyelitis is quite uncommon. Zygomycetes' involvement in the peritoneal cavity in individuals undergoing continuous ambulatory peritoneal dialysis is also uncommon. Peritonitis is a slow-progressing infection, but the attributable death rate in individuals who get delayed or improper treatment has reached as high as 60%. In all cases of catheter-related mucormycosis, the catheter should be removed as soon as possible, and systemic antifungal medication should be used for many weeks. [58,59,6381]

ETIOLOGY

Mucormycosis is a fungal infection caused by certain moulds. Mucormycetes are the scientific name for these moulds. They can be found/discovered in the soil and decaying organic materials, such as rotting plant, and can be found/discovered all over nature (ubiquitous). Despite the fact that they are commonly found in nature, these moulds rarely create difficulties. They can, however, cause serious, even life-threatening illness in people who have a weaker or compromised immune system. To the highest degree most people develop this infection by breathing in mold spores.Infection can spread more rarely when spores enter the body through a cut or open wound. There are certain persons who are more susceptible to mucormycosis than others. Persons who have low amounts of neutrophils (neutropenia), which are white blood cells that help fight infection, and are taking broad-spectrum antibiotics, as well as people who are taking medicines that decrease the immune system's functioning, are at risk (immunosuppressive drugs). Neutropenia can be seen in and immunosuppressive drugs can be taken over for cancer, particularly blood (hematologic) cancers.

Mucormycosis is a fungal infection that affects persons who have recently had a hematopoietic stem cell transplant (HSCT). Hematopoietic stem cells are cells that grow into red blood cells, white blood cells, and platelets and are present in the bone marrow. The current bone marrow is removed and replaced with bone marrow from a healthy donor during a transplant. Immunosuppressive medications must be taken by infected people to help them fight rejection, but this can make them more vulnerable to infection, including HIV. People who get immunosuppressive medicines for other reasons, such as an organ transplant, are also at risk of contracting this illness. Some diabetics are at risk of acquiring mucormycosis, particularly if their diabetes is poorly managed and they develop diabetic ketoacidosis. Ketoacidosis is a diabetic condition in which the body produces high quantities of blood acids called ketones. Ketoacidosis can manifest itself in a variety of ways. The exact reasons why people with poorly controlled diabetes are more prone to mucormycosis are unknown, however it could be because these patients have more iron in their tissues.Mucormycosis is also a concern for those who have too much iron in their bodies (iron overload), which can occur as a result of frequent blood transfusions or certain blood illnesses. Researchers believe that these moulds can develop and spread by utilising the extra iron. Mucormycosis infection can use a medicine called deferoxamine, which is used to get rid of excess iron in the body, to get iron from the sick person. The usage of dexeroxamine promotes infection growth and dissemination, making it another risk factor for mucormycosis infection. Other factors that increase the risk of developing mucormycosis include kidney failure, HIV/AIDS, the use of contaminated medical equipment near or in open wounds, long-term use of corticosteroids, which are extremely powerful anti-inflammatory medications, skin trauma such as burns or other skin injuries, extreme malnutrition, and illegal drug use involving needles. Immature neonates are more susceptible to infection, particularly mucormycosis. Some patients get mucormycosis without having any recognised risk factors, which happens seldom.Mucormycosis infection has a strong affinity for blood arteries, according to researchers. This suggests that the illness frequently affects blood vessels, however researchers aren't sure why. Infection of blood arteries can reduce blood flow, depriving tissues of oxygen and resulting in tissue death (necrosis).

SIGNS AND SYMPTOMS

A sinus infection (sinusitis) is the most common symptom, which is accompanied by nasal congestion, nasal discharge, and sinus pain. It's also possible to get a temperature and a headache. If the infection spreads beyond the sinuses, symptoms may include disintegration of the septum, a thin cartilage and bone wall that divides the nostrils, tissue loss (necrosis) of the palate, swelling of the area around the nose (perinasal area), and redness (erythema) of the skin overlying the sinus and the eye socket (orbit). Due to a lack of oxygen, there is often a blue-colored discoloration of the skin near the sinuses or the eye socket (cyanosis). Blurry vision or double vision might occur at times. If left untreated, substantial tissue death (necrosis) and infection can occur, causing considerable damage to facial features. Mucormycosis can sometimes extend to the brain. This might result in lethargy, impaired speech, seizures, partial paralysis, cranial neuropathies (abnormalities of the nerves of the face and eyes), a brain abscess, altered consciousness, and coma..This infection is known as rhinocerebral mucormycosis when it affects the sinuses and brain. When an infection spreads to the eye, it can cause swelling (periorbital edoema), bulging or displacement of the eye (proptosis), visual loss, and maybe blindness owing to fluid buildup near to the eyes. Ophthalmoplegia is a condition in which the muscles that move the eyes are paralysed or weak, making it difficult or painful to move the eyes. Mucormycosis can cause pulmonary mucormycosis, which occurs when spores are breathed in and spread throughout the respiratory system.Pulmonary mucormycosis is a fast-progressing infection that is characterised by fever and a cough that produces no mucus (nonproductive cough). Chest pain, spitting or coughing up blood (hemoptysis), and difficulty breathing (dyspnea) are less common symptoms.

When mucormycosis affects the skin (cutaneous zygomycosis), patients can develop a single, painful, hardened region of skin as well as underlying tissue inflammation. The skin around you may become reddish, heated, swollen, and uncomfortable.

Open sores (ulcers) and blisters can develop, and tissue loss (necrosis) can occur, resulting in the affected tissue turning black. A fever is possible in those who are afflicted.Cutaneous mucormycosis can be mild or severe, with a rapid start (fulminant). The gastrointestinal system might be affected in some cases. This is most likely caused by spores being swallowed, inhaled into the mouth, or eating infected food.

Symptoms include stomach pain and blood vomiting (hematemesis). Lesions can form in the stomach or intestines, causing a hole to appear (perforation). Peritoneum infection (peritonitis) is an infection of the membrane that borders the abdominal wall and covers the organs inside the abdomen. Due to a lack of blood flow (bowel infarction), acute discomfort in the intestines can occur, and affected persons may fall into shock as a result of massive blood loss (hemorrhagic shock). Disseminated mucormycosis is a rare type of mucormycosis that affects people with weakened immune systems. In this state, the infection has migrated to other parts of the body and has the potential to become widespread (disseminated). The brain, spleen, skin, heart, and other organs are among the numerous organs that can be impacted. Mucormycosis can impact or spread to the kidneys, the inner lining of the heart chambers and heart valves (endocarditis), and the bone in rare cases (osteomyelitis). The signs and symptoms of disseminated mucormycosis vary a lot depending on which organ system is affected.

Most common symptoms observed are -

- ✞ Pain in face
- ✞ Cheek swelling
- ✞ Eye swelling
- ✞ Loss of Vision
- ✞ Stuffy nose
- ✞ Brownish/Bloody Nasal Discharge
- ✞ Dental pain
- ✞ Ulcer on palate
- ✞ Loosening of Teeth
- ✞ Swelling on Palate
- ✞ Headache

DIAGNOSIS

CLINICAL DIAGNOSIS

A strong index of suspicion, identification of host variables, and timely assessment of clinical symptoms are all required for the diagnosis of mucormycosis. Diplopia in a patient with diabetes or pleuritic discomfort in a neutropenic host could be signs of infection, prompting the use of imaging modalities and the following collection of samples for microbiology, histology, and advanced molecular testing. Mucorales infection most commonly manifests as rhinocerebral, soft tissue, pulmonary, and disseminated disease, but it can affect practically any organ. Mucormycosis is characterised by tissue necrosis, however a diagnosis based on representation and syndromes lacks sensitivity and specificity. Other fungus, such Aspergillus or Fusarium, can cause the same symptoms.

Furthermore, in tuberculosis-endemic nations, the two illnesses may coexist, as in the case of a diabetic patient. There are, however, several characteristics that should raise your suspicion of invasive pulmonary mucormycosis. A history of past prophylaxis with voriconazole or the appearance of breakthrough fungal infection in an immunocompromised patient receiving antifungal medications active against Aspergillus but not Mucorales are examples of these. *Corzo-Leon et al.* proposed a diagnostic method for diabetic patients with rhinocerebral mucormycosis.Signs and symptoms that can be considered "red flags" include cranial nerve palsy, sinus pain, diplopia, periorbital edoema, proptosis, orbital apex syndrome, and palate ulcers. Mucormycosis is said to be more common in radiological terms, with numerous nodules and pleural effusion. The reverse halo sign is another finding on a computed tomography (CT) scan that appears to suggest the presence of mucormycosis (RHS). The RHS was detected in 15 of 16 patients (94 percent) during the first week of the disease in a recent investigation of consecutive thoracic CT scans in leukemic patients with neutropenia. Other radiologic abnormalities, such as numerous nodules, were detected later. The presence of the RHS on CT was a strong predictor of pulmonary mucormycosis in neutropenic leukemic individuals with lung infection, according to the source. Patients with mucormycosis had a higher RHS (54%) than those with aspergillosis (6%, P.001), while aspergillosis patients had more airway-invasive characteristics such as clusters of peribronchial consolidations, centrilobular nodules, and bronchial wall thickening. While these results aren't conclusive, they can be utilised as a starting point for more aggressive diagnostic laboratory procedures. PET/CT with is another emergent imaging tool that may potentially aid in the diagnosis and therapy of mucormycosis. Fluorodeoxyglucose is a kind of fluorodeoxyglucose (FDG). When feasible, endobronchial ultrasound-guided fine needle aspiration is also a useful diagnostic tool. [82-89]

MICROSCOPIC EXAMINATION AND CULTURE

The cornerstones of diagnosing mucormycosis are microscopy (direct and histopathological) and culture of various clinical specimens. Direct microscopy of clinical specimens, in combination with optical brighteners such as Blankophor and Calcofluor White, provides for a rapid presumptive diagnosis of mucormycosis. Mucorales hyphae range in width from 6 to 25 metres, are nonseptate or pauci-septate, and have an uneven, ribbon-like appearance. The branching angle is varied, including wide-angle (90) bifurcations**.** The distinction between hyphae of Aspergillus or morphologically related fungi and hyphae of Mucorales may not always be valid based on histopathological analysis of tissue specimens. Tissue identification, on the other hand, is a critical diagnostic technique since it distinguishes the existence of the fungus as a pathogen in the collection from a culture contaminant. On virtually fungal culture media, such as Sabouraud agar and potato dextrose agar cultured at 25°C to 30°C, all Mucorales grow quickly (3–7 days). A microaerophilic environment improves culture yield for some species. Surprisingly, even when fungal hyphae are visible in histopathologic study, only 50% of fungal cultures are positive. Because hyphae are brittle, they can be destroyed during tissue manipulation (avoidance of excessive tissue homogenization is recommended). For immunohistochemistry examination, a particular mouse monoclonal anti-Rhizomucor antibody was used nevertheless, this test has already been found to react with different Mucorales and Entomophthorales.*In situ* hybridization targeting 5S and 18S ribosomal RNA sequences40 is still being researched. [90-99]

SPECIFIC IDENTIFICATION AND FUNGAL SUSCEPTIBILITY TESTING.

Identification of species is important for a better epidemiological understanding of mucormycosis and could be useful in epidemic investigations. On cultivation, Mucorales fungus are easily recognised from Aspergillus fungus. *Alvarez et al.* revealed that morphological functions alone can give a high level of accuracy when assessed by those with experience in fungal evidence. Identification of morphological taxonomic groups, on the other hand, is challenging and may be linked to speciation failures.42 ID32C kit (bio Merieux, *Marcy l'Etoile,* France) has been successfully used to identify Lichtheimia corymbifera and R. pusillus, while API 50CH (bioMerieux)has been used to identify Mucor species. Both tests failed to distinguish M. circinelloides and M. rouxii. L. ramosa is detected using ID32C and positive melezitose assimilation. MALDITOF mass spectrometry (matrix-assisted laser desorption/ionisation time-of-flight) is a promising method, however it is not yet valid for all Mucorales. The use of molecular-based tests concentrating on the internal transcribed spacer region is another reliable method. M. circinelloides has a high minimum inhibitory concentration (MIC) in the presence of posaconazole, while Rhizopus and Cunninghamella have a high MIC in the presence of amphotericin B. a The MIC of several Apophysomyces isolates against amphotericin B has also increased. The role of such data is unclear for patient treatment but needs to be later analyzed. [100-106]

SEROLOGY

Enzyme-linked immunosorbent assays, immunodiffusion tests, and immunoblots have all been tried with varying degrees of success. An enzyme-linked immunospot (ELISpot) assay was used to identify Mucorales specific T cells in three haematological patients who had developed invasive mucormycosis. Mucorales-specific T cells were never seen in any of the controls. Later research will look into the usage of such unique T cells as surrogate diagnostic markers. [107-110]

MOLECULAR ASSAY

Conventional polymerase chain reaction (PCR), restriction fragment length polymorphism examination (RFLP), DNA sequencing of defined gene regions, and melt curve analysis of PCR products are all examples of molecularbased tests. All of the above assays can be used to detect Mucorales signals or to identify them. The internal transcribed spacer or the 18S rRNA genes are the targets of the vast majority of molecular experiments. Various studies have been conducted utilising formalin-fixed, paraffin-embedded, or fresh tissue samples39, with varying results.

The investigations conducted have different degrees of sensitivity (70–100%) and specificity (not estimated to 100%), with the superior drawback being the small number of patients analysed. Because the efficacy of these inhouse tests has not been properly investigated and clinically evaluated, they cannot be recommended as a standalone, single strategy in clinical routine diagnostics. Recent attempts to diagnose diseases using molecular markers in blood and serum have generated promising clinical results. When compared to culture, molecularbased identification from serum resulted in earlier diagnosis and overall confirmed culture-proven instances. Currently, molecular-based diagnostic assays can be suggested as valuable add on tools that complement conventional diagnostic procedures. [98],[101],[102],[108-120]

TREATMENT

Treatment must address the patient's fundamental medical issue and reduce immunosuppression. Diabetics may have a better chance of succeeding than non-diabetics. *Yohai et al.* reported a coverall survival rate of 77 percent in diabetics and 34 percent in nondiabetics for rhinoorbito-cerebral mucormycosis. In patients with rhino-orbitocerebral mucormycosis, it is found that diabetics had a 60% survival rate and nondiabetics had a 20% survival rate. Those with serious illnesses, such as leukaemia and lymphoma, have a poor prognosis. With a combined surgical and medical therapy, the death rate for isolated pulmonary mucormycosis ranges from 9.4 to 27 percent, compared to 50–55 percent for patients treated just medically. In reported instances and candidates for different types of therapy, there is inherent selection bias. Antifungal therapy with an amphotericin B preparation, surgery and, if possible, repair of the underlying medical condition are the cornerstones of treatment. The only fungicidal agent with substantial *in-vitro* efficacy against Zygomycetes is amphotericin B. Mucorales are resistant to caspofungin and 5-flucytosine in vitro.Mucormycosis has been successfully treated with amphotericin B and its lipid formulations . Amphotericin B susceptibility varies between Mucorales species. The mean inhibitory concentrations (MIC) of Cunninghamella clinical isolates range from 1 lg mL to 100 lg mL. They primarily described a case of C. bertholletiae infection in an allogeneic bone marrow transplant patient who was unresponsive to two distinct forms of amphotericin B lipid formulations (amphotericin B liposomal and lipid complex). According to the National Committee for Clinical Laboratory Standards (NCCLS) recommendations, the MIC was 4 lg mL. After receiving more than 10 g of liposomal amphotericin, amphotericin B lung concentrations from surgically detained tissue averaged 9.5 lg mL. Because of thrombosis and tissue infarction, amphotericin B levels at the site of involvement may not be enough. Itraconazole and Flucanazole have been used to treat mucormycosis in anecdotal case reports.

A 29-year-old woman with acute myelogenous leukaemia and pulmonary mucormycosis responded to fluconazole clinically and radiographically. Despite this, the reaction could have been a result of a recovering neutrophil count. Azole effectiveness has been proven to be poor in most *in vitro* and animal experiments. In guinea pig and murine models, azoles were ineffective against Rhizopus infection in mouse models of disseminated Absidia and Rhizopus infection, Itraconazole was mainly inferior to amphotericin B. Fluconazole in combination with trovafloxacin or Ciprofloxacin has been shown to be effective in the treatment of pulmonary mucormycosis in experimental mice. *In vitro*, voriconazole has little antimicrobial action against Mucorales. Posaconazole, a novel triazole in development, offers promise as a viable alternative to Mucorales. As seen by a rare instance of reported cavitary pulmonary mucormycosis caused by Rhizopus sp. that resolved without antifungal therapy after diabetic ketoacidosis was corrected, the underlying condition must be corrected for successful therapy.

To cure mucormycosis, a multimodal approach is required. Antifungal medicines must be given early, and metabolic imbalances must be corrected quickly. For diabetic people, sodium bicarbonate (together with insulin) can restore ketoacidosis, regardless of how severe the acidosis is. This can also stop Mucorales from invading hosts. Drugs like corticosteroids should aid in early diagnosis and tissue invasion prevention. Mucormycosis exhibits characteristics similar to thrombosis and tissue necrosis in a vase angio artery. A lipid formulation of amphotericin B has been proposed at a European conference as a solution to such a violent invasion. For injection into the central nervous system, the recommended dose is 5mg/kg/day up to 10mg/kg/day. The response rate for individuals with mucormycosis ranged from 78 percent in week one to 87 percent in week 12. Salvage treatment, which combines the effects of liquid amphotercin B with caspofungin or posaconazole, has shown to improve survival rates in individuals with rhino orbital cerebral mucormycosis. The use of hyperbaric oxygen to enhance the cytokine environment in order to reduce fungal cell area is effective in a high proportion of cases. This oxygen aids in the simulation of a granulocyte-macrophage colony, allowing for the production of interferon gamma to combat Mucorales. The drug VT-1161, a fungus inhibitor with selective activity, can be used for the final treatment. They suppress ergosterol formation and are a useful tool in the fight against mucormycosis. [121-136]

DRUGS USED IN TREATMENT

Sr.No.	Class of Drugs	Drugs
1.	Amphotericin-B	Liposomal Lyophillised Lipid Emuldion Deoxychelate Sonication
2.	Isavuconazole	
3.	Posaconazole	

Urgent Surgical debridement and strict glycemic control.
Inj. Amphoterecin B (1.0-1.5 mg/kg/day) or Inj. Amphoterecin B 5-10 mg/kg/day)
Intracranial Involvement (10mg/kg/day) OR Inj.Amphoterecin B lipid Complex (5mg/kg/day)

PRINCIPLE IN MANAGEMENT OF MUCORMYCOSIS

1. Early diagnosis
2. Early Surgery with Wide excision
3. Maximum Medical Management
4. Management of Complications (especially of Medical Management)
5. Team Approach [ENT + Opthalmologist + Anaesthetist+ Physician + Infectious Disease Specialist + Endocrinoligist + GI Medicine + Nephrologist + Neurologist + Neurosurgeon + Dentist + Psychiatrist]

MUCORMYCOSIS IN COVID-19

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)-caused Coronavirus Disease 2019 (COVID19) has been linked to a variety of opportunistic bacterial and fungal diseases. The predominant fungal pathogens for co-infection in persons with COVID-19 have been identified as Candida and Aspergillosis. Recently, multiple occurrences of mucormycosis in COVID19 patients have been recorded around the world, particularly in India.The capital reason that seems to be assisting Mucorales spores to germinate in people with COVID-19 is an perfect environment of low oxygen (hypoxia), steroid-induced hyperglycemia), acidic medium (metabolic acidosis, diabetic ketoacidosis [DKA]), high iron levels (increased ferritins) ,high glucose (diabetes), new-onset hyperglycemia, and decreased phagocytic activity of white blood cells (WBC) due to immunosuppression (SARSCoV-2) mediated, steroid-mediated or background comorbidities) coupled with various other shared risk factors including elongated hospitalization with or without mechanical ventilators.

Paltauf first identified Phycomycosis or Zygomycosis in 1885, which was later renamed Mucormycosis in 1957 by Baker, an American pathologist, for a belligerent Rhizopus infection. Mucormycosis is a rare but deadly fungal infection that mostly affects those with weakened immune systems. Mold fungi of the genus Rhizopus, Rhizomucor, Mucor, Cunninghamella, and Absidia of the Order Mucorales, Class Zygomycetes cause mucormycosis. The Rhizopus Oryzae is the most common form, accounting for approximately 60% of human mucormycosis cases, as well as Journal. 90% of the Rhino-orbital-cerebral (ROCM) form is pre-proofed. The inhalation of fungus spores is the mode of contamination. According to a recent projection for the year 2019-2020, the prevalence of mucormycosis ranged from 0.005 to 1.7 per million people worldwide, with a ratio approximately 80 times greater (0.14 per 1000) in India than in developed countries. To put it another way, India has the largest number of mucormycosis cases in the world. Despite this, India has the world's second-largest diabetes mellitus (DM) population and was, until recently, the world's diabetes hotspot. Importantly, in India, diabetes mellitus is the most prevalent risk factor for mucormycosis, whereas in Europe and the United States, haematological malignancies and organ transplant take the lead. DM, on the other hand, remains the leading risk factor for mucormycosis worldwide, with a fatality rate of 46%. While long-term use of corticosteroids has been linked to opportunistic fungal infections such as aspergillosis and mucormycosis, even a short course of corticosteroids has lately been linked to mucormycosis, particularly in persons with diabetes. Mucormycosis caused by even a short period (5–14 days) of steroid medication is uncommon, especially in patients with diabetes]. In the European Confederation of Medical Mycology research, 46 percent of the patients had received corticosteroids within one month of the diagnosis of mucormycosis. In patients with COVID-19, there has been an increase in case reports/series of mucormycosis, particularly in India. Several case reports have also been received from various parts of the world.When mucormycosis spreads to the brain, the mortality rate rises to as high as 90%. Furthermore, the pace with which mucormycosis spreads is an rare phenomena, and even a 12-hour delay in diagnosis can be lethal, which is why 50 percent of cases of zygomycosis have traditionally been detected only in post-mortem autopsy series.

MUCORMYCOSIS IN DIABETES MELLITUS PATIENT

- If people acquire symptoms of mucormycosis, they should see a doctor very away, especially diabetics (Black fungus infection).
- Patients get this illness either after recovering from COVID-19 or after testing positive for COVID-19. They all have one thing in common: they're diabetics.
- The coronavirus can affect the pancreas and cause blood sugar levels to fluctuate, either as a result of the disease or as a result of treatment.
- Sugar provides a favourable environment for mucormycosis to develop when the immune system of the body gets weakened, especially in uncontrolled diabetic patients with extremely high blood sugar levels. It's critical to maintain blood sugar levels under control both during and after therapy.
- Patients with diabetes must keep their blood sugar levels under control by taking medications as directed by their doctors, eating a balanced diet, and exercising regularly.
- Blood sugar levels must be checked on a daily basis. Whether or whether they have symptoms of mucormycosis, they should see a doctor if the level is high.
- Diabetics should be extremely cautious about following the safety precautions to avoid contracting COVID-19.

CONCLUSION

Mucormycosis is becoming more common in people with weakened immune systems, and the fatality rate from current treatment remains unacceptably high. Although research into the pathophysiology of zygomycosis is still in its early stages, substantial breakthroughs have recently been made in understanding how Mucorales produces disease and lives in the host. The majority of the research has been on fungal iron uptake methods, molecular processes of adhesion/invasion, sex loci, spore size, and the involvement of innate and adaptive immunity in Mucorales host defence.The lack of interest from pharmaceutical corporations in a condition with a tiny market revenue opportunity is the biggest roadblock to turning novel technology into genuine therapeutics. As a results federally sponsored research methods must back up newly promising treatment/diagnostic discoveries for unique diseases that pose a public health danger.

This study is being done in order to distribute information on Mucormycosis, as well as the signs and symptoms of the disease, in order to prevent it.

Acknowledgement-

I'd like to express our gratitude to our mentor, Dr. Manisha Karpe mam, of the Pharmaceutics Department, for her unwavering support and encouragement during the project.

List of Abbrevations-

ROCM : Rhinocerebral Mucormycosis
HIV : Human Immuno Deficiency virus
AIDS : Acquired Immuno Deficiency Syndrome

Conflict of interest

The author declares there's no conflict of interest.

REFERENCES

1. Ribes, J.A.; Vanover-Sams, C.L.; Baker, D.J. Zygomycetes in Human Disease. Clin. Microbiol. Rev. 2000, 13,236–301.
2. Richardson, M. The ecology of the Zygomycetes and its impact on environmental exposure. Clin. Microbiol.Infect. 2009, 15, 2–9.
3. Roden, M.M.; Zaoutis, T.E.; Buchanan, W.L.; Knudsen, T.A.; Sarkisova, T.A.; Schaufele, R.L.; Sein, M.; Sein, T.Chiou, C.C.; Chu, J.H.; et al. Epidemiology and outcome of zygomycosis: A review of 929 reported cases. Clin. Infect. Dis. 2005, 41, 634–653.
4. Jeong, W.; Keighley, C.; Wolfe, R.; Lee, W.L.; Slavin, M.A.; Kong, D.C.M.; Chen, S.C.A. The epidemiology and clinical manifestations of mucormycosis: A systematic review and meta-analysis of case reports.Clin. Microbiol. Infect. 2019, 25, 26–34.
5. Prakash, H.; Ghosh, A.K.; Rudramurthy, S.M.; Singh, P.; Xess, I.; Savio, J.; Pamidimukkala, U.; Jillwin, J.;Varma, S.; Das, A.; et al. A prospective multicenter study on mucormycosis in India: Epidemiology, diagnosis,and treatment. Med. Mycol. 2018.
6. Rees, J.R.; Pinner, R.W.; Hajjeh, R.A.; Brandt, M.E.; Reingold, A.L. The epidemiological features of invasive mycotic infections in the San Francisco Bay area, 1992–1993: Results of population-based laboratory active surveillance. Clin. Infect. Dis. 1998, 27, 1138–1147.
7. Torres-Narbona, M.; Guinea, J.; Martínez-Alarcón, J.; Muñoz, P.; Gadea, I.; Bouza, E. Impact of zygomycosis on microbiology workload: A survey study in Spain. J. Clin. Microbiol. 2007, 45, 2051– 2053.
8. Bitar, D.; Van Cauteren, D.; Lanternier, F.; Dannaoui, E.; Che, D.; Dromer, F.; Desenclos, J.C.; Lortholary, O.Increasing incidence of zygomycosis (mucormycosis), France, 1997–2006. Emerg. Infect. Dis. 2009, 15,1395–1401.
9. Ambrosioni, J.; Bouchuiguir-wafa, K.; Garbino, J. Emerging invasive zygomycosis in a tertiary care center: Epidemiology and associated risk factors. Int. J. Infect. Dis. 2010, 14, e100–e103.
10. Chakrabarti, A.; Das, A.; Mandal, J.; Shivaprakash, M.R.; George, V.K.; Tarai, B.; Rao, P.; Panda, N.;Verma, S.C.; Sakhuja, V. The rising trend of invasive zygomycosis in patients with uncontrolled diabetes mellitus. Med. Mycol. 2006, 44, 335–342.
11. Skiada, A.; Pagano, L.; Groll, A.; Zimmerli, S.; Dupont, B.; Lagrou, K.; Bouza, E.; Klimko, N.; Gaustad, P.Lass-Florl, C. et al. Zygomycosis in Europe: Analysis of 230 cases accrued by the registry of the European Confederation of Medical Mycology (ECMM) Working Group on Zygomycosis between 2005 and 2007. Clin.Microbiol. Infect. 2011, 17, 1859–1867.
12. Rammaert, B.; Lanternier, F.; Zahar, J.-R.; Dannaoui, E.; Bougnoux, M.-E.; Lecuit, M.; Lortholary, O. Healthcare-associated mucormycosis. Clin. Infect. Dis. 2012, 54 (Suppl. 1), S44–S54.
13. Goodman NL, Rinaldi MG. Agents of mucormycosis. In: Balows A, Hausler WJ, Herrmann KL, Isenberg HD, Shadoomy HJ, eds. Manual of clinical microbiology. 5th ed. Washington, DC: ASM Press, 1991: 674–92.
14. Lopes JO, Pereira DV, Streher LA, Fenalte AA, Alves SH, Benevenga JP. Cutaneous mucormycosis caused by Absidia corymbifera in a leukemic patient. Mycopathologia 1995; 130:89–92.
15. Stas KJF, Louwagie GLH, Van Damme BJC, Coosemans W, Waer M, Vanrenterghem YFC. Isolated mucormycosis in a bought living unrelated kidney transplant. Transplant Int 1996; 9:600–2.
16. Roden MM, Zaoutis TE, Buchanan WL, et al. Epidemiology and outcome of mucormycosis: a review of 929 reported cases. Clin Infect Dis 2005; 41:634–53.
17. Skiada A, Pagano L, Groll A, et al. Zygomycosis in Europe: analysis of 230 cases accrued by the registry of the European Confederation of Medical Mycology (ECMM) Working Group on Zygomycosis between 2005 and 2007. Clin Microbiol Infect 2011; 17:1859–67.
18. Meyer RD, Rosen P, Armstrong D. Phycomycosis complicating leukemia and lymphoma. Ann Intern Med 1972; 77:871–9
19. Hosseini SM, Borghei P. Rhinocerebral mucormycosis: pathways of spread. Eur Arch Otorhinolaryngol 2005; 262:932–8.
20. Torres-Narbona M, Guinea J, Martinez-Alarcon J, et al. Impact of mucormycosis on microbiology overload: a survey study in Spain. J Clin Microbiol 2007; 45:2051–3.
21. Tedder M, Spratt JA, Anstadt MP, Hegde SS, Tedder SD, Lowe JE. Pulmonary mucormycosis: results of medical and surgical therapy. Ann Thorac Surg 1994; 57:1044–50.
22. Gupta KL, Khullar DK, Behera D, Radotra BD, Sakhuja V. Pulmonary mucormycosis presenting as fatal massive haemoptysis in a renal transplant recipient. Nephrol Dial Transplant 1998; 13:3258–60.
23. Kitabayashi A, Hirokawa M, Yamaguchi A, Takatsu H, Miura AB. Invasive pulmonary mucormycosis with rupture of the thoracic aorta. Am J Hematol 1998; 58:326–9.
24. Passamonte PM, Dix JD. Nosocomial pulmonary mucormycosis with fatal massive hemoptysis. Am J Med Sci 1985; 289:65–7.
25. Connor BA, Anderson RJ, Smith JW. Mucor mediastinitis. Chest 1979; 75:525–6.
26. Hsu JW, Chiang CD. A case report of novel roentgenographic finding in pulmonary mucormycosis: thickening of the posterior tracheal band. Kaohsiung J Med Sci 1996; 12:595–600.
27. Rubin SA, Chaljub G, Winer-Muram HT, Flicker S. Pulmonary mucormycosis: a radiographic and clinical spectrum. J Thorac Imaging 1992; 7:85–90.
28. McAdams HP, Rosado de Christenson M, Strollo DC, Patz EF Jr. Pulmonary mucormycosis: radiologic findings in 32 cases. Am J Roentgenol 1997; 168:1541–8.
29. Spellberg B, Edwards J Jr, Ibrahim A. Novel perspectives on mucormycosis: pathophysiology, presentation, and management. Clin Microbiol Rev 2005; 18:556–69.
30. Roden MM, Zaoutis TE, Buchanan WL, et al. Epidemiology and outcome of mucormycosis: a review of 929 reported cases. Clin Infect Dis 2005; 41:634–53

31. Oliveira-Neto MP, Da Silva M, Monteiro PCF, et al. Cutaneous mucormycosis in a young, immunocompetent girl. Med Mycol 2006; 44:567–70.
32. Hampson FG, Ridgway EJ, Feeley K, Reilly JT. A fatal case of disseminated mucormycosis associated with the use of blood glucose self-monitoring equipment. J Infect 2005;269–72.
33. Hocker TL, Wada DA, Bridges A, El-Azhary R. Disseminated mucormycosis heralded by a subtle cutaneous finding. Dermatol Online J 2010; 16:3.
34. Rubin AI, Grossman ME. Bull's-eye cutaneous infarct of mucormycosis: a bedside diagnosis confirmed by touch preparation. J Am Acad Dermatol 2004; 51:996–1001.
35. Kerr OA, Bong C, Wallis C, Tidman MJ. Primary cutaneous mucormycosis masquerading as pyoderma gangrenosum. Br J Dermatol 2004; 150:1212–34.
36. Diven SC, Angel CA, Hawkins HK, Rowen JL, Shattuck KE. Intestinal mucormycosis due to Absidia corymbifera mimicking necrotizing enterocolitis in a preterm neonate. J Perinatol 2004; 24:794–6.
37. Mitschell SD, Gray J, Morgan ME, et al. Nosocomial infection with Rhizopus microsporus in preterm infants: association with wooden tongue depressors. Lancet 1996; 348:441–3.
38. Michalak DM, Cooney DR, Rhodes KH, Telander RL, Kleinberg F. Gastrointestinal mucormycoses in infants and children: a cause of gangrenous intestinal cellulitis and perforation. J Pediatr Surg 1980; 15:320–4.
39. Garg PK, Gupta N, Gautam V, Hadke NS. Gastric mucormycosis: unusual cause of gastric perforation in an immunocompetent patient. South Med J 2008; 101:449–50.
40. Bittencourt AL, Ayala MA, Ramos EA. A new form of abdominal mucormycosis different from mucormycosis: report of two cases and review of the literature. Am J Trop Med Hyg 1979; 28:564–9.
41. . Oliver MR, Van Voorhis WC, Boeckh M, et al. Hepatic mucormycosis in a bone marrow transplant recipient who ingested naturopathic medicine. Clin Infect Dis 1996; 22:521–4.
42. Ismail MH, Hodkinson HJ, Setzen G, Sofianos C, Hale MJ. Gastric mucormycosis. Trop Gastroenterol 1990; 11:103–5.
43. Lyon DT, Schubert TT, Mantia AG, Kaplan MH. Phycomycosis of the gastrointestinal tract. Am J Gastroenterol 1979; 72:379–94.
44. Geramizadeh B, Modjalal M, Nabai S, et al. Gastrointestinal mucormycosis: a report of three cases. Mycopathologia 2007; 164:35–8.
45. Echo A, Hovsepian RV, Shen GK. Localized cecal mucormycosis following renal transplantation. Transplant Infect Dis 2005; 7:68–70.
46. Virk SS, Singh RP, Arora AS, Grewal JS, Puri H. Gastric mucormycosis—an unusual cause of massive upper gastrointestinal bleed. Indian J Gastroenterol 2004; 23:146–7.
47. Azadeh B, McCarthy DO, Dalton A, Campbell F. Gastrointestinal mucormycosis: two case reports. Histopathology 2004; 44:298–300.
48. Park YS, Lee JD, Kim TH, et al. Gastric mucormycosis. Gastrointest Endosc 2002; 56:904–5.
49. Siu KL, Lee WH. A rare cause of intestinal perforation in an extreme low birth weight infant— gastrointestinal mucormycosis: a case report. J Perinatol 2004; 24:319–21.
50. Cherney CL, Chutuape A, Fikrig MK. Fatal invasive gastric mucormycosis occurring with emphysematous gastritis: case report and literature review. Am J Gastroenterol 1999; 94:252
51. Ibrahim A, Edwards JE Jr, Filler SG, eds. Mucormycosis. Philadelphia: Harcourt Brace, 2004
52. Ribes JA, Vanover-Sams CL, Baker DJ. Zygomycetes in human disease. Clin Microbiol Rev 2000; 13:236–301.
53. Liu MF, Chen FF, Hsiue TR, Liu CC. Disseminated mucormycosis simulating cerebrovascular disease and pulmonary alveolar haemorrhage in a patient with systemic lupus erythematosus. Clin Rheumatol 2000; 19:311–14
54. Tomita T, Ho H, Allen M, Diaz J. Mucormycosis involving lungs, heart and brain, superimposed on pulmonary edema. Pathol Int 2005; 55:202–5
55. Fujii T, Takata N, Katsutani S, Kimura A. Disseminated mucormycosis in an acquired immunodeficiency syndrome (AIDS) patient. Intern Med 2003; 42:129–30.
56. Richardson MD, Warnock DW. Mucormycosis. In: Richardson MD, Warnock DW, eds. Fungal infection diagnosis and management. Oxford, United Kingdom: Blackwell, 2003:230–40.
57. Ingram CW, Sennesh J, Cooper JN, Perfect JR. Disseminated mucormycosis: report of four cases and review. Rev Infect Dis 1989; 11:741–54.
58. Virmani R, Connor DH, McAllister HA. Cardiac mucormycosis: a report of five patients and review of 14 previously reported cases. Am J Clin Pathol 1982; 78:42–7.
59. Sanchez-Recalde A, Merino JL, Dominguez F, Mate I, Larrea JL, Sobrino JA. Successful treatment of prosthetic aortic valve mucormycosis. Chest 1999; 116:1818–20.
60. Prabhu RM, Patel R. Mucormycosis and entomophthoramycosis: a review of the clinical manifestations, diagnosis and treatment. Clin Microbiol Infect 2004; 10(Suppl 1):31–47.
61. Gonzalez CE, Rinaldi MG, Sugar AM. Mucormycosis. Infect Dis Clin North Am 2002; 16:895–914, vi.
62. McNab AA, McKelvie P. Iron overload is a risk factor for mucormycosis. Arch Ophthalmol 1997; 115:919–21.
63. Mishra B, Mandal A, Kumar N. Mycotic prosthetic-valve endocarditis. J Hosp Infect 1992; 20:122–5.
64. Solano T, Atkins B, Tambosis E, Mann S, Gottlieb T. Disseminated mucormycosis due to Saksenaea vasiformis in an immunocompetent adult. Clin Infect Dis 2000; 30:942–3.

65. Zhang R, Zhang JW, Szerlip HM. Endocarditis and hemorrhagic stroke caused by Cunninghamella bertholletiae infection after kidney transplantation. Am J Kidney Dis 2002; 40:842–6.
66. Kalayjian RC, Herzig RH, Cohen AM, Hutton MC. Thrombosis of the aorta caused by mucormycosis. South Med J 1988; 81:1180–2.
67. Mehta NN, Romanelli J, Sutton MG. Native aortic valve vegetative endocarditis with Cunninghamella. Eur J Echocardiogr 2004; 5:156–8.
68. Gubarev N, Separovic J, Gasparovic V, Jelic I. Successful treatment of mucormycosis endocarditis complicated by pulmonary involvement. Thorac Cardiovasc Surg 2007; 55:257–8.
69. Sanchez-Recalde A, Merino JL, Dominguez F, et al. Successful treatment of prosthetic aortic valve mucormycosis. Chest 1999; 116:1818–20.
70. Burke WV, Zych GA. Fungal infection following replacement of the anterior cruciate ligament: a case report. J Bone Joint Surg Am 2002; 84A:449–53.
71. Pierce PP, Wood MB, Roberts GD, Fitzgerald RH, Robertson C, Edson RS. Saksenaea vasiformis osteomyelitis. J Clin Microbiol 1987; 25:933–5.
72. Holtom PD, Obuch AB, Ahlmann ER, Shepherd LE, Patzakis MJ. Mucormycosis of the tibia: a case report and review of the literature. Clin Orthop 2000; 381:222–8.
73. Wanishsawad C, Kimbrough RC, Chinratanalab S, Nugent K. Mucormycotic osteolytic rib lesion presenting as subacute pleural effusion. Clin Infect Dis 1996; 22:715–16.
74. Meis JF, Kullberg BJ, Pruszczynski M, Veth RP. Severe osteomyelitis due to the zygomycetes Apophysomyces elegans. J Clin Microbiol 1994; 32:3078–81.
75. Chaudhuri R, McKeown B, Harrington D, Hay RJ, Bingham JB, Spencer JD. Mucormycosis osteomyelitis causing avascular necrosis of the cuboid bone: MR imaging findings. Am J Roentgenol 1992; 159:1035–7.
76. Echols RM, Selinger DS, Hallowell C, Goodwin JS, Duncan MH, Cushing AH. Rhizopus osteomyelitis. A case report and review. Am J Med 1979; 66:141–5
77. Nayak S, Satish R, Gokulnath, Savio J, Rajalakshmi T. Peritoneal mucormycosis in a patient on CAPD. Perit Dial Int 2007; 27:216–17.
78. Ram R, Swarnalatha G, Prasad N, Dakshinamurty KV. Exit site infection due to mucormycosis resulting in abdominal wall necrosis in a continuous ambulatory peritoneal dialysis patient. Nephrol Dial Transplant 2007; 22:266–7.
79. Serna JH, Wanger A, Dosekun AK. Successful treatment of mucormycosis peritonitis with liposomal amphotericin B in a patient on long-term peritoneal dialysis. Am J Kidney Dis 2003;14–17
80. Fergie JE, Fitzwater DS, Einstein P, Leggiadro RJ. Mucor peritonitis associated with acute peritoneal dialysis. Pediatr Infect Dis J 1992; 11:498–500.
81. Chayakulkeeree M, Ghannoum MA, Perfect JR. Mucormycosis: the re-emerging fungal infection. Eur J Clin Microbiol Infect Dis 2006; 25:215–29.
82. Petrikkos G, Skiada A, Lortholary O et al. Epidemiology and clinical manifestations of mucormycosis. *Clin Infect Dis*. 2012; 54: S23–S34.
83. Aggarwal D, Chander J, Janmeja AK, Katyal R. Pulmonary tuberculosis and mucormycosis coinfection in a diabetic patient. *Lung India*. 2015; 32: 53–55.
84. Chamilos G, Marom EM, Lewis RE et al. Predictors of pulmonary zygomycosis versus invasive pulmonary aspergillosis in patients with cancer.*Clin Infect Dis*. 2005; 41: 60–66.
85. Legouge C, Caillot D, Chretien ML et al. The reversed halo sign: pathognomonic pattern of pulmonary mucormycosis in leukemic patients with neutropenia *Clin. Infect Dis*. 2014; 58: 672–678.
86. Jung J, Kim Y, Lee HJ et al. Comparison of computed tomographic findings in pulmonary mucormycosis and invasive pulmonary aspergillosis. *Clin Microbiol Infect*. 2015; 21: e11–684.e18.
87. Liu Y, Wu H, Huang F, Fan Z, Xu B. Utility of 18F- FDG PET/CT in diagnosis and management of mucormycosis. *Clin Nucl Med*. 2013; 38: e370–e371.
88. Nair V, Sharma RK, Khanna A, Talwar D. Pulmonary mucormycosis diagnosed by convex probe endobronchial ultrasound-guided fifine needle aspiration of cavity wall. *Lung India*. 2017; 34: 179–181.
89. Frater JL, Hall GS, Procop GW. Histologic features of zygomycosis: emphasis on perineural invasion and fungal morphology. *Arch Pathol Lab Med*. 2001; 125: 375–378.
90. Lass-Florl C. Zygomycosis: conventional laboratory diagnosis. *Clin Microbiol Infect*. 2009; 5: 60–65.
91. Lass-Florl C, Resch G, Nachbaur D et al. The value of computed tomography-guided percutaneous lung biopsy for diagnosis of invasive fungal infection in immunocompromised patients. *Clin Infect Dis*. 2007; 45: e101–104.
92. Monheit JE, Cowan DF, Moore DG. Rapid detection of fungi in tissues using calcoflfluor white and flfluorescence microscopy. *Arch Pathol Lab Med*. 1984; 108: 616–618.
93. Spellberg B, Edwards J, Ibrahim A. Novel perspectives on mucormycosis: pathophysiology, presentation and management. *Clin Microbiol Rev*. 2005; 18: 556–569.
94. Ribes JA, Vanover-Sams CL, Baker DJ. Zygomycetes in human disease. *Clin Microbiol Rev*. 2000; 13: 236–301.
95. Chakrabarti A, Das A, Mandal J et al. The rising trend of invasive zygomycosis in patients with uncontrolled diabetes mellitus. *Med Mycol*. 2006; 44: 335–342.

96. Lass-Florl C. Diagnosing invasive fungal diseases—limitations of microbiological diagnostic methods. *Expert Opin Med Diagn*. 2009; 3: 461–470.
97. Walsh TJ, Gamaletsou MN, McGinnis MR, Hayden RT, Kontoyiannis DP. Early clinical and laboratory diagnosis of invasive pulmonary, extrapulmonary and disseminated mucormycosis (zygomycosis). *Clin Infect Dis*. 2012; 54: S55–S60.
98. Lackner M, Caramalho R, Lass-Florl C. Laboratory diagnosis of mucormycosis: current status and future perspectives. *Future Microbiol*. 2014; 9: 683–695.
99. Hayden RT, Qian X, Procop GW, Roberts GD, Lloyd RV. *In situ* hybridization for the identification of fifilamentous fungi in tissue section. *Diagn Mol Pathol*. 2002; 11: 119–126.
100. Bonifaz A, Stchigel AM, Guarro J et al. Primary cutaneous mucormycosis produced by the new species *Apophysomyces mexicanus*. 2014; 52: 4428– 4431
101. Alvarez E, Sutton DA, Cano J et al. Spectrum of zygomycete species identified in clinically signifificant specimens in the United States.*J Clin Microbiol*. 2009; 47: 1650–1656.
102. Yang M, Lee JH, Kim YK, Ki CS, Huh HJ, Lee NY. Identification of mucorales from clinical specimens: a 4-year experience in a single institution. *Ann Lab Med*. 2016; 36: 60–63.
103. Ramani R, Gromadzki S, Pincus DH, Salkin IF, Chaturvedi V. Effificacy of API 20C and ID 32C systems for identification of common and rare clinical yeast isolates. *J Clin Microbiol*. 1998; 36: 3396– 3398.
104. Schwarz P, Lortholary O, Dromer F, Dannaoui E. Carbon assimilation profiles as a tool for identification of zygomycetes. *J Clin Microbiol*. 2007; 45: 1433–1439. 105
105. Schrodl W, Heydel T, Schwartze VU et al. Direct analysis and identifification of pathogenic *Lichtheimia* species by matrix-assisted laser desorptionionization "Time of Flight" analyzer-mediated mass spectrometry. *J Clin Microbiol*. 2012; 50: 419–427.
106. Vitale RG, de Hoog GS, Schwarz P et al. Antifungal susceptibility and phylogeny of opportunistic members of the order mucorales. *J Clin Microbiol*. 2012; 50: 66–75.
107. Sandven PER, Eduard W. Detection and quantitation of antibodies against *Rhizopus* by enzyme-linked immunosorbent assay. *APMIS*. 1992; 100: 981–987.
108. Wysong DR, Waldorf AR. Electrophoretic and immunoblot analyses of *Rhizopus arrhizus* antigens. *J Clin Microbiol*. 1987; 25: 358–363.
109. Jones KW, Kaufman L. Development and evaluation of an immunodiffusion test for diagnosis of systemic zygomycosis (mucormycosis): preliminary report. *Clin Microbiol*. 1978; 7: 97–101.
110. Potenza L, Vallerini D, Barozzi P et al. *Mucorales*-specifific T cells emerge in the course of invasive mucormycosis and may be used as a surrogate diagnostic marker in high-risk patients. *Blood*. 2011; 118: 5416–5419.
111. Hsiao CR, Huang L, Bouchara J-P, Barton R, Li HC, Chang TC. Identification of medically important molds by an oligonucleotide array. *J Clin Microbiol*. 2005; 43: 3760–3768.
112. Nagao K, Ota T, Tanikawa A et al. Genetic identifification and detection of human pathogenic *Rhizopus* species, a major mucormycosis agent, by multiplex PCR based on internal transcribed spacer region of rRNA gene. *J Dermatol Sci*. 2005; 39: 23–31.
113. Larche J, Machouart M, Burton K et al. Diagnosis of cutaneous mucormycosis due to *Rhizopus microsporus* by an innovative PCR-restriction fragment-length polymorphism method. *Clin Infect Dis*. 2005; 41: 1362– 1365.
114. Machouart M, Larche J, Burton K et al. Genetic identifification of the main opportunistic mucorales by PCR-restriction fragment length polymorphism. *J Clin Microbiol*. 2006; 44: 805–810.
115. Nyilasi I, Papp T, Csernetics A, Krizsan K, Nagy E, Vagvolgyi C. High affifinity iron permease (*FTR1*) gene sequence-based molecular identifification of clinically important Zygomycetes. *Clin Microbiol Infect*. 2008; 14: 393–397.
116. Springer J, Lackner M, Ensinger C et al. Clinical evaluation of a Mucorales-specifific real-time PCR assay in tissue and serum samples. *J Med Microbiol*. 2016; 65: 1414–1421.
117. Kasai M, Harrington SM, Francesconi A et al. Detection of a molecular biomarker for zygomycetes by quantitative PCR assays of plasma, bronchoalveolar lavage, and lung tissue in a rabbit model of experimental pulmonary zygomycosis. *J Clin Microbiol*. 2008; 46: 3690–3702.
118. Guinea J, Escribano P, Vena A et al. Increasing incidence of mucormycosis in a large Spanish hospital from 2007 to 2015: epidemiology and microbiological characterization of the isolates. *PLoS One*. 2017; 12: e0179136.
119. Ino K, Nakase K, Nakamura A et al. Management of pulmonary mucormycosis based on a polymerase chain reaction (PCR) diagnosis in patients with hematologic malignancies: a report of four cases. *Intern Med*. 2017; 56: 707–711.
120. Millon L, Herbrecht R, Grenouillet F et al. Early diagnosis and monitoring of mucormycosis by detection of circulating DNA in serum: retrospective analysis of 44 cases collected through the French Surveillance Network of Invasive Fungal Infections (RESSIF). *Clin Microbiol Infect*. 2016; 22: e1–810.e8.
121. Roy V, Ali LI, Carter TH, Selby GB. Successful non-surgical treatment of disseminated polymicrobial fungal infection in a patient with pancytopenia and graft-versushost disease. J Infect 2000; 41: 273–5.
122. Garey KW, Pendland SL, Huynh VT, Bunch TH, Jensen GM, Pursell KJ. Cunninghamella bertholletiae infection in a bone marrow transplant patient: amphotericin lung penetration, MIC determinations, and review of the literature. Pharmacotherapy 2001; 21: 855–60.
123. Kocak R, Tetiker T, Kocak M, Baslamisli F, Zorludemir S, Gonlusen G. Fluconazole in the treatment of three cases of mucormycosis. Eur J Clin Microbiol Infect Dis 1995; 14: 559–61.

124. Funada H, Miyake Y, Kanamori K, Okafuji K, Machi T, Matsuda T. Fluconazole therapy for pulmonary mucormycosis complicating acute leukemia. Jpn J Med 1989; 28: 228–31.
125. Mosquera J, Warn PA, Rodriguez-Tudela JL, Denning DW. Treatment of Absidia corymbifera infection in mice with amphotericin B and itraconazole. J Antimicrob Chemother 2001; 48: 583–6.
126. Mendoza-Ayala R, Tapia R, Salathe M. Spontaneously resolving pulmonary mucormycosis. Clin Infect Dis 1999; 29: 1335–6.
127. Odds FC, Van Gerven F, Espinel-Ingroff A et al. Evaluation of possible correlations between antifungal susceptibilities of fifilamentous fungi in vitro and antifungal treatment outcomes in animal infection models. Antimicrob Agents Chemother 1998; 42: 282–8.
128. Sun QN, Fothergill AW, McCarthy DI, Rinaldi MG, Graybill JR. In vitro activities of posaconazole, itraconazole, voriconazole, amphotericin B, and flfluconazole against 37 clinical isolates of zygomycetes. Antimicrob Agents Chemother 2002; 46: 1581–2.
129. Pfaller MA, Messer SA, Hollis RJ, Jones RN and the Sentry Participants Group. Antifungal activities of posaconazole, ravuconazole, and voriconazole compared to those of itraconazole and amphotericin B against 239 clinical isolates of Aspergillus spp. and other fifilamentous fungi: report from sentry antimicrobial surveillence program, 2000. Antimicrob Agents Chemother 2002; 46: 1032–7.
130. Gomez-Lopez A, Cuenca-Estrella M, Monzon A, Rodriguez-Tudela JL. In vitro susceptibilities of clinical isolates of Zygomycota to amphotericin B, flflucytosine, itraconazole, and voriconazole. J Antimicrob Chemother 2001; 48: 919–21.
131. Sugar AM, Liu XP. Combination antifungal therapy in treatment of murine pulmonary mucormycosis: roles of quinolones and azoles. Antimicrob Agents Chemother 2000; 44: 2004–6.
132. Sahin B, Paydas S, Cosar E, Bicakci K, Hazar B. Role of granulocyte colony-stimulating factor in the treatment of mucormycosis. Eur J Clin Microbiol Infect Dis 1996; 15: 866–9.
133. MacKenzie KM, Baumgarten KL, Helm BM et al. Innovative medical management with resection for successful treatment of pulmonary mucormycosis despite diagnostic delay. J State Med Soc 2002; 154: 82–5.
134. Garcia-Diaz JB, Palau L, Pankey GA. Resolution of rhinocerebral zygomycosis associated with adjuvant administration of granulocyte-macrophage colonystimulating factor. Clin Infect Dis 2001; 32: 145–50.
135. Lanternier F, Poiree S, Elie C et al. Prospective pilot study of high-dose (10 mg/kg/day) liposomal amphotericin B (L-Amb) for the initial treatment of mucormycosis. J Antimicrob Chemother. 2015; 70: 3116-3123.
136. Wiederhold NP. Pharmacokinetics and safety of posaconazole delayed-release tablets for invasive fungal infections. Clin Pharmacol. 2016; 8: 1-8.

5487847845**1210813**