SJIF Impact Factor: 5.464

WORLD JOURNAL OF ADVANCE HEALTHCARE RESEARCH

ISSN: 2457-0400
Volume: 5.
Issue: 3.
Page N. 551-560
Year: 2021

Review Article www.wjahr.com

UNREST SITUATIONS OF MUCORMYCOSIS OVER COVID-19 PANDEMIC: RISK FACTORS, PATHOPHYSIOLOGY AND TREATMENT OPTIONS AVAILABLE FOR VIABLE ERADICATION

Tharun K.*, Pooja Reddy, Likhitha K., Chetan Sai P. and Sannihitha C.

Doctor of Pharmacy IV year, Department of Pharmacy Practice, Sri Venkateswara College of Pharmacy, Madhapur, Telangana, India.

Received date: 21 April 2021 **Revised date:** 11 May 2021 **Accepted date:** 01 June 2021

***Corresponding author: Tharun K.**

Doctor of Pharmacy IV year, Department of Pharmacy Practice, Sri Venkateswara College of Pharmacy, Madhapur, Telangana, India.

ABSTRACT

Since January 2020 world has been gripped by corona virus disease 2019 (covid-19), which is mainly caused by sever acute respiratory syndrome coronavirus-2 (SARS-COV-2). Covid 19 patients with other comorbid conditions like diabetes, malignancies, recent organ transplants and patients on long term steroids therapy are at a greater risk of developing opportunistic fungal infections . One such infection is mucormycosis (The black fungal infection). Mucormycosis is an angio invasive infection that occurs due to fungi mucorales. It is a rare disease with almost 50 % mortality rate even with appropriate treatment, so early diagnosis and treatment may help patient. The main agenda of this review is to provide an overview of etiology and pathogenesis followed by brief idea on clinical presentation, diagnosis and treatment options available to treat mucormycosis. **KEYWORDS:** mucormycosis, covid-19, diabetes ketoacidosis, steroids, amphotericin B, posaconazoile, isavuconazole

INTRODUCTION

Mucormycosis (Previously called as zygomycosis) is a rare, insidious fungal infection with high morbidity and mortality. Mucormycetes belong to the order mucorales, sub phylum mucormycotina.[1] These are ubiquitous moulds, abundantly found in the environment on decaying organic matter. This has recently emerged as the life threatening complication of covid-19 and most common in patients with uncontrolled diabetes mellitus, hematological malignancy, solid organ transplantations and corticosteroid therapy.[2,3] The two most important manifestations of mucormycoses in Covid patients include rhino orbital cerebral mucormycoses and pulmonary mucormycoses.[4]

Besides mucormycoses, there are some other fungal co-infections in covid-19 patients and these include:[7]

1. Invasive aspergillosis
2. Invasive candidiasis
3. Invasive crytococcosis

Mucormycosis is difficult to manage for several reasons. Firstly, it is difficult to diagnose mucormycosis because of non specific clinical findings and lack of appropriate diagnostic tools. Secondly, if the treatment has to be effective it must be started as early as possible and requires combination of antifungal drugs, surgical interventions and reversal of underlying risk factors.

Epidemiology

The incidence of mucormycoses is rising globally, but the rise is very high among patients with uncontrolled diabetes in India and china.[2,5] A recent multivariable logistic regression analysis by W. Jeong et al., on 851 cases over the period January 2000 to January 2017, showed that majority of cases were from Europe (34%) followed by Asia (31%) and north or south America (28%). The remaining cases were from Africa (3%), Australia and Newzeland (3%).[6]

Recently black fungus is being detected frequently among Covid-19 patients in some states of India. According to the latest news reports more than 9000 cases of mucormycosis cases have been reported in India. The infection has claimed over 200 lives so far. Maharashtra and Gujarat topped the list of states with highest number of mucormycosis cases. Few states and union territories have already declared mucormycosis as epidemic and few reported it as notifiable disease.

Etiology and Risk factors

Mucormycosis is a rare and serious fungal infection. It is mainly caused by the mould belonging to the order mucorales. Rhizopus oryzae is the common organism associated with mucormycosis and accounts for about 70% of all the cases. Other isolated species of mucoraceae family causing similar spectrum of fungal infections are[8,9]

- Cunninghamella spp
- Apophysomyces elegans
- Rhizopus microsporus var. rhizopodiformis
- Rhizomucor pusillus
- Saksenaea

There are three ways in which humans can contact mucormycosis:

- By inhaling spores.
- By swallowing spores in food or medicines
- When spores contaminate wounds (burns and traumatic disruption of skin enables the spores to enter deeper tissues)

According to the study by Arunaloke et al the risk of angio invasive zygomycosis was noted higher among patients with uncontrolled diabetes mellitus (73.6%). This was compared to 36% patients with diabetes in the review of Roden et al. they also concluded that rise of invasive mucormycosis may be correlated with an increase in the population of diabetes.[10,11]

Patients at a higher risk of mucormycosis include immunocompromised host with diabetes especially with ketoacidosis, patients on long term or high dose steroid therapy, neutropenic patients, hematologic and solid malignancies, malnourished individuals, renal failure patients, IV drug use, desferroxamine therapy and other causes leading to iron overload, streptococcal toxic shock syndrome.[12]

An alarming rise of potentially fatal black fungal cases in Covid 19 patients is mainly due uncontrolled diabetes during course of infection, non judicial use of steroids, use of humidifiers and oxygen pipes contaminated with spores.

Pathogenesis of mucormycosis

Overview of pathogenesis:

Several characteristics of Mucorales that contribute to the aggressive nature of disease include,

· Rapid growth

· Ability to bind on endothelial surfaces

· Ability to obtain iron from host organism

· Down regulation of host defense genes implicated in pathogen recognition, immune defense, and tissue repair

· Inhibition of interferon-gamma expression

· An evolutionary duplication of systems implicated in energy use and virulence.

Fungal spores are easily aerosolized and may enter the human organism through inhalation, local inoculation (e.g., skin lesion), or ingestion through the gastrointestinal tract. Regardless of point of entry, few critical steps are required for the development of mucormycoses, they include the following,

· Inoculation of spores into host tissue

· Evading phagocytosis by macrophages and neutrophils and germination into hyphae

· Increasing their growth and virulence by taking advantage of other pathogenic host conditions (e.g., hyperglycemia, ketoacidosis, iron overload, functional or quantitative neutropenia)

· Attaching through the specific receptors to the endothelium and inducing endocytosis and causing endothelial damage

· Leading to clinically apparent disease through hemorrhage, tissue necrosis and thrombosis.

· Entry into the circulation and disseminating hematogenously, which leads to systemic disease and multi-organ involvement.[13]

Interaction of the pathogen with immune system

1. ***Phagocytes*:** phagocytes are most important line of host defense mechanism against the fungi. The three main groups of phagocytes include mononuclear cells, macrophages, and neutrophils. The composition of the spore wall of the fungi appears to determine the recognition and the intracellular killing by the phagocytes. Through various pathogen-associated molecular patterns, the fungi bind to the pattern recognition receptors of phagocytes [among the receptors, toll like receptor-2 play a major role in the early proinflammatory response], this leads to activation and transduction of intracellular signals. In a study it was observed that, stimulated Keto acidic conditions prevented the cytotoxic action of phagocytes and enhanced the growth of R.oryzae, an effect that got completely reversed after the reversal of acidosis.

The oxidation of L-arginine to nitrite was found to play an important role in the inhibition of the germination of R.oryzae spores in murine alveolar macrophages, whereas gamma interferon and endotoxins were essential for the prevention of germination of R.oryzae spores in human macrophages. In an experimental study it was observed that, exposure to corticosteroids render murine pulmonary alveolar macrophages unable to prevent sporangiospore germination. Any lack or delay in the early inflammatory response can rapidly lead to tissue destruction and disseminated disease. The innate immunity barrier is 2-fold,

a. Tissue macrophages facilitate phagocytosis of spores,
b. Whereas the spores that escape and germinate to hyphae lead to chemotaxis of neutrophils, neutrophils exert oxidative cytotoxic effect on the hyphae. The neutrophils directly damage and phagocytose both the spores and hypae through production and release of reactive oxygen metabolites, cationic peptides, perforins and other antimicrobial enzymes. Neutrophils also produce

proinflammatory cytokines like TNF-alpha, INF-gamma, IL-1b, which further facilitate the activation and recruitment of other immune cells.

Interferon gamma (INF-gamma) and granulocyte macrophage colony stimulating factor (GM-CSF) alone or in combination stimulate the neutrophils to release the TNF-alpha leading to hyphal damage and eradication of mucormycosis.[13,14]

2. ***T-cells:*** T-cells are the part of adaptive immune system. Mucorales specific T-cells were found only in those who suffered from mucormycosis. Treating T-inactivated cells with IL-2, IL-7, or both the cytokines enhances the production of Mucorales-specific T-cells and their cytokines IL-5, IL-10, IL-13.[14]

3. Natural killer cells

Although natural killer cells are considered as a part of the innate immune system and known to possess direct and indirect cytotoxic abilities, they also secrete chemokines and cytokines such as IFN-gamma, TNF-alpha, and GM-CSF, thus affecting the activity of other immune cells. The hyphae of mucoralean fungi can be damaged either by stimulated or unstimulated natural killer cells, but NK cells do not cause any damage to the dormant spores. The NK cells express certain receptors that recognize infected cells and inhibit major histocompatibility complex calss-1 molecules (MHC class-1 molecules) that inhibit the activation of the receptors. The perforins produced by the NK cells have similar functions and structure as that of the complement system, and they contribute to the hyphal damage of the mucoralean species. The hyphae reduce the release of various immunomodulatory molecules such as RANTES (regulated upon activation, normal T-cells expressed and secreted) and IFN-gamma secreted the NK-cells, this damage is fungal growth dependent and appears to be more effective in early stages of infection.[13,14]

4. Dendritic cells

Dendritic cells are considered as a link between the innate and the adaptive immunity as they are found between the epithelium and the interstitium. Dendritic cells usually move to the site of release of microbial antigens which leads to enhancement of the immune response. The dormant spores and the germ tubes of mucoralean fungi stimulate the maturation of dendritic cells.[14]

5. Platelets

Platelets play a key role not only in the hemostasis but also in recognition and killing of the pathogens. Platelets adhere to the spores and hyphae of mucoralean fungi but they cause damage only to the hyphal structures. The hyphal growth is diminished in response to contact with the platelets.

After exposure of platelets to the invading pathogen, platelets show the following antifungal and antimicrobial functions, a) secretion of granules that contain proinflammatory and anti-inflammatory cytokines and chemokines such as transforming growth factor-beta (TGF-beta), and thrombocidines with fungicidal properties. b) Expression of membrane bond molecules like CD154 and platelet toll-like receptors, which facilitate platelet

Binding and also activation if various cells (i.e., binding to endothelial cells activates the intracellular adhesion molecule-1 and vascular cell adhesion molecule-1 pathways; binding to monocytes cause activation or differentiation of macrophages; binding to dendritic cells induce their maturation; binding to B & T- lymphocytes induce their activation.).

In a study it was observed that, the necrotic areas detected in organs with no apparent fungal growth which suggested the occurrence of thrombotic ischemia due to the systemic platelet activation.[13,14]

Interaction of the pathogen with the endothelium

Endothelial cells make up the internal layer of blood vessels and possess various important roles in the pathogen recognition and maintaining physiologic functions. Endothelial cells have the ability to phagocytose and dame the spores of mucoralean species. Certain spore coat homolog (cot H) proteins are present on the Mucorales, these proteins bind with the host endothelial receptor GRP 78 (glucose regulated protein 78), which leads to the endocytosis of the fungi. In addition, GRP 78 mediates invasion and damage of endothelial cells by mucoralean fungi.

When endothelial cells are exposed to acidosis and elevated levels of glucose & iron, as in case of hyperglycemia and DKA, both GRP 78 endothelial surface expression and cot-H fungal surface expression increases.[13,14]

Iron uptake

The importance of iron for fungal cell development was supported by an observation that the fungus undergoes apoptosis in iron-deprived conditions. In addition, elevated iron concentrations facilitate the fungal growth by impairing the phagocyte function and by decreasing IFN-gamma secretion in the mice models of mucormycosis.

Mucorales acquire iron from the host organism through 3 mechanisms, out of which 1 and 2 are the main mechanisms for acquiring iron. The mechanisms include the following,

i. Siderophores (iron chelators, which may be intrinsic, such as rhizoferrhin or extrinsic and named xenosiderophores)
ii. High affinity iron permeases

iii. Iron uptake from hemoglobin, with the help of heme oxygenase present in R oryzae.

Mucorales use ferrioxamine (the iron-rich form of deferoxamine) as a xenosiderophore to obtain iron. Mucorales carry specific ferrioxamine receptors like Fob1 and Fob2, which are induced only in the presence of ferrioxamine, subsequently facilitating fungal iron uptake from ferrioxamine but not from deferoxamine. There are 2 possible mechanisms for the uptake of iron from ferrioxamine: one is energy dependent through the activity of reductase that liberates ferric iron from deferoxamine extracellularly, converting it into soluble ferrous iron; the other mechanism is through complete intracellular uptake of ferrioxamine.[13]

Pathogenesis in covid-19

Invasive mucormycosis has been observed even in patients with mild to moderate SARS-Cov-2 infections. The strongest predisposing factor appears to be hyperglycemia in undiagnosed or uncontrolled diabetics. Hyperglycemia leads to increased expression of the endothelial receptor GRP78, resulting in polymorphonuclear dysfunction, impaired chemotaxis and defective intracellular killing. An important virulence trait of Mucorales is the ability to acquire iron from the host which is an essential element for its growth. In conditions of ketoacidosis, free iron becomes readily available in the serum. This excess endogenous iron is efficiently taken up by the Mucorales through siderophores or iron permeases, further enhancing their virulence. These effects are greatly amplified by the use of corticosteroids and immunosuppressants in susceptible hosts. Corticosteroids themselves cause impairment in the neutrophil migration, ingestion, and phagolysosome fusion. Coupled with the potential implications of steroid-induced hyperglycemia, the diabetic COVID 19 patients receiving corticosteroids or other immunosuppressants are exceptionally vulnerable to the development of mucormycosis.[15]

It might be speculated that lymphopenia could increase the risk of developing invasive mucormycosis, while the recovery of lymphocyte count could.

Improve the adaptive immune system and induce the production of mucorales-specific t-cells, which might have a role in controlling the invasive infection.[16]

Patients treated with deferoxamine have increased incidence of invasive mucormycosis.[17]

Clinical presentation

The clinically important feature of mucormycosis is the thrombosis and tissue necrosis following the angioinvasion. In most cases infection is relentlessly progressive and may lead to death unless the underlying cause is corrected and patient is treated with approprioate antifungal therapy. Based on its clinical presentation and antomical site involved, mucormycosis is categorised as one of the following 6 major clinical forms[18]

- Rhinocerebral (39%)
- Pulmonary (24%)
- Cutaneous (19%)
- Gastrointestinal
- Disseminated
- Uncommon rare forms like endocarditis, osteomyelitis, peritonitis and renal infection.

Rhino cerebral mucormycosis

Along with pulmonary mucormycosis rhiono cerebral involvement is the most common forms effecyting the Covid 19 patients.

Early symptoms are consistent with either sinusitis or periorbital cellulites and include eye or facial pain, sinus pain, soft tissue swelling, periorbital edema, blurred vision, head ache, cranial nerve palsies. If untreated it may extend from sinus into mouth, producing black, necrotic ulcerations into the hard palate. Once if the eye is infected it may progress up the optic nerve then gain access to the CNS and patient may demonstrate an altered mental status.[18] Fever is variable and absent in almost 50% cases.[19,20]

Pulmonary mucormycosis

Clinical presentation of pulmonary mucormycosis is not specific and includes high grade fever unresponsive to antibiotics, dyspnea, cough, chest pain, and haemoptysis. If untreated it may lead to disseminated infection progressing to lung failure and death.[20,21]

Cutaneous mucormycosis

Depending on the extent of infection, cutaneous mucormycosis is classified as localized when it infects only the skin or subcutaneous tissue and disseminated infection when it invades surrounding muscle, bone and tendons. General clinical manifestations include lesions with inflammation and pus, abscess formation, tissue swelling, necrosis and necrotic tissue may produce ulcers. Necrotizing fasciitis may occur as a result of cutaneous and sub cutaneous mucormycosis then it may directly spread into surrounding bones and tendons. Truly disseminated infection may arise from vessel invasion.[19]

Gastrointestinal mucormycosis

Uncommon and results from ingestion of spores. Mostly seen in severely malnourished neonates and children. It can occur in any part of GIT but stomach, colon and ileum are most commonly affected. Most common symptoms include abdominal pain, nausea and vomiting. Fever may be seen in few. Some patients may present with gastric perforation that may be frequently associated with upper GI bleeding.

Disseminated mucormycosis

Mucormycosis may spread hematogenously to other organs away from its origin. The organs that are most

commonly involved are lungs, brain, liver spleen and heart. Patients with iron load, malnourished patients, immunocompromised patients and patients with active leukemia are at higher risk of dissemination. Symptoms of disseminated mucormycosis vary depending on involved organ and extent of invasion.[21]

Other uncommon forms

Mucormycosis may rarely infect heart (endocardium and valves), kidney, bladder and liver. It may directly infect brain without infecting sinus (without rhino cerebral involvement).

Diagnosis

Diagnosis of mucormycosis is one of the complicated process as there is no specific diagnostic tool and no specific predisposing symptoms to conclude mucormycosis

Main characteristic feature of mucormycosis is fast growth and tissue invasion leading to tissue necrosis early detection is very important in determination of patient's mortality and morbidity.

The diagnosis should be performed based on clinical presentation and anatomical site involved. The main warning signs are cranial nerve palsy, diplopia, sinus pain, proptosis, periorbitol swelling, orbital apex syndrome or a palatine ulcer. Any of this signs should prompt immediate further testing.[1]

The suspected patients should be considered for further diagnosis, which include blood or tissue culture, biopsy, endoscopy, and others include CT scan (reveal pulmonary or single lesions and bony destruction), MRI, Advanced molecular techniques include next generation sequencing technique, ITS sequencing analysis provides a breakthrough diagnostic tool.[1,4]

Microscopic examination of tissue or blood is the first step but it doesn't confirm mucormycoses due to chances of contamination of culture media, followed by histopathology which remains standard, but biopsy is not always feasible in most of the cases. So molecular approach is frequently used nowadays to early detection (2). CT scan is further recommend to identify any lesions or Tissue damage.

In tissue or blood culture the sample is tested with koh (10-20%), periodic acid Schiff stain or calcofluor white mount and the microscope examination were done to dectect characteristic broad, sparsely septate, ribbon like hyphae with wide- angle or right- angle branching at irregular intervals[1,3] Fungal culture is done and conventional techniques like lactophenol cotton blue mount were used to identify fungal spores.[3]

Often all the fungal species show same criteria for identification most commonly aspergillus, which on microscopic shows 3-5 wide, septate and form acute-angle branches. Mucorales lack specific antigen markers as in case of galactomannan in aspergillus, Furthermore test like beta -D- glycan can be done detect antigen specific to aspergillus and in differential diagnosis.[4]

Treatment

Early diagnosis and appropriate treatment are important tools in reducing mortality and morbidity. Current guidelines recommend the antifungal therapy, surgery, control of underlying conditions and withdrawal of the offending agent as effective approach for managing mucormycosis.[26]

Because of angioinvasion, thrombosis and tissue necrosis of the disease, there might be poor penetration of anti fungal agents to the site of infection. Therefore even if the causative organism is susceptible to the antifungal agent's invitro, they may be ineffective in vivo. In such cases surgery is necessary to prevent the further spread.[27] Surgery should be considered on a case by case basis, using a multidisciplinary approach and surgery is mostly preferred in case of rhino cerebral infection, soft tissue infection, and localized pulmonary lesion and in disseminated infection.[26] Surgical debridement has to be extensive involving necrotic areas. Repeated surgical procedures are recommended to achieve local control of rhino orbito cerebral mucormycosis.[28]

Antifungal therapy

Center for disease control and prevention suggest the use of amphotericin B, posaconazole and isavuconazole as preferred agents in treating active mucormycosis infection. Among these amphotericin B and isavuconazole are used as first line agents and posaconazole is used as salvage therapy.[26,31]

Amphotericin B and its lipid formulations are considered the drug of choice for primary treatment of mucormycosis. The efficacy of AmB has been reproducibly shown in both laboratory (invitro) and in clinical studies (in vivo)[29,30] Lipid formulation of AmB (liposomal AmB, LAMB and AmB complex, ABLC) are safe and have better therapeutic index than conventional AmB and are considered as the first line therapy of mucormycoses.[32,33] The optimum dosage for AmB and its formulations against mucormycosis is still undetermined but standard daily dose of LAMB and ABLC according to the current guidelines is 5mg/kg/day.[26,36] A study by Lewis et al has shown that efficacy of liposomal AMB was dose dependent and a dose of 10mg/kg/day has been proved to be more effective in reducing fungal burden compared to 5mg/kg/day.[34] A prospective pilot study of high dose (10mg/kg/day) liposomal AMB for initial treatment of mucormycosis was conducted by lanternier et al in which 40 patients were included, the majority of them are with underlying hematological malignancy and or HSCT. Surgery was performed in 71% of patients before initiation of antifungal therapy. Compared to controls

receiving the standard dose of 5mg/kg/day, no improvement was found in mortality and response rate in patients who received higher doses (> 7.5 mg/kg/day) at the end of 12weeks treatment, on the other hand high dose LAMB was associated with increased nephrotoxicity (doubling of baseline serum creatinine was observed in 40% patient) and electrolyte derangement. Although dosages beyond 5mg/kg/day have not been proved to be more efficacious for mucormycosis, higher doses may be considered in individual basis, especially when there is CNS or osteoarticular involvement.[36]

***Isavuconazole*:** Isavuconazole is a broad spectrum triazole and is biologically active agent of prodrug isavuconazonium sulfate. It is available in both intravenous and oral formulations and it is administered with a loading dose of 200mg three times a day for two days and 200 mg daily thereafter.[32] In a single arm open label trial on adult patients, with mucormycosis compared the outcomes in patients receiving isavuconazole 200mg once a day as primary treatment with patients receiving conventional or lipid AMB at a median dose of 70 or 325mg and 250 mg qd respectively as primary treatment. Outcomes in both the groups are similar and they concluded that isavuconazole can be used as alternative to amphotericin B as first line treatment of mucormycosis. The main limitation in this study is small population and many patients are previously exposed to AMB.[38,39]

Isavuconazole has many pharmacokinetic and safety advantages compared to other triazoles including linear pharmacokinetics and thus no need for therapeutic drug monitoring, less drug interactions, less toxicity especially hepatotoxicity, skin and ocular side effects or prolonged QT interval, no nephrotoxicity, no need for dosage adjustment in kidney, liver failure or obesity and excellent oral bioavailability with no food requirement.[40,37]

Isavuconazole has variable species dependent; invitro activity against mucorales and its MIC values against mucorales are 2-4 fold higher compared to posaconazole.[41] Few other case reports have shown that isavuconazole could be used as salvage therapy for mucormycosis in heavily immunosuppressed patients and in patient's intolerance to liposomal amphotericin and posaconazole therapy.[42]

The main concern in use of isavuconazole is breakthrough mucormycosis and other invasive fungal infection. In a retrospective study by rausch et al, nearly 13 patients out of 100 have reported breakthrough infection.[43] There is also a concern on cross tolerance where patients exposed to prolonged prophylaxis with posaconazole might develop a breakthrough mucormycosis which is resistant to subsequent isavuconazole.[44]

***Posaconazole*:** current guidelines support the use of posaconazole as salvage or maintenance therapy. First line treatment with posaconazole is considered only in cases where treatment with AMB is contraindicated.[26] Posaconazole has a variable invitro activity against mucorales, which is species dependent.[45] Clinical studies showing the effectiveness of posaconazole for mucormycosis are scarce. In a retrospective study of oral posaconazole as salvage therapy in 91 patients with refractory mucormycosis, the success at 12 weeks after treatment initiative was 60%; the high success rates reported here provide encouraging data regarding posaconazole as an alternative therapy.

Previously posaconazole was available only as oral suspension, taken 3-4 times a day with food or with acidic carbonated beverages in order to enhance bioavailability. The food requirement makes difficult the use of oral suspension in critically ill patients as they might not be able to eat. To overcome these limitations, gastro resistant tablet and an intravenous solution has been developed.[46] These newer formulations have better bioavailability allowing once daily dosing, no food requirement and absorption is not affected by changes in gastric Ph or motility.

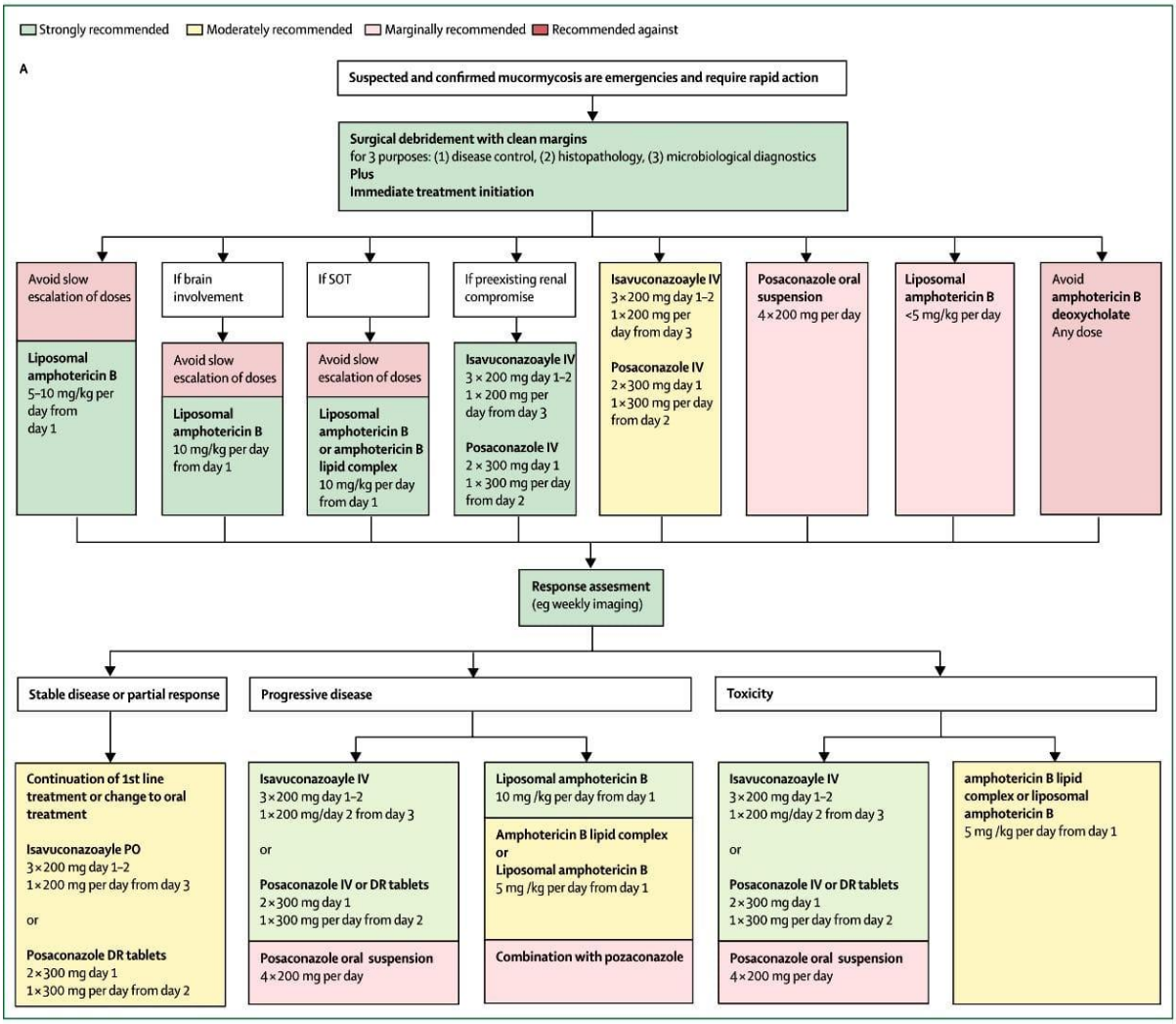
Other antifungal agents like fluconazole, itraconazole and voriconazole have little or no activity against mucorales

Combinational therapy

Any combinational therapy that is considered for treating mucormycosis should use polyenes as back bone. Amphotericin B is the only polyene that is approved for treatment in mucormycosis. Because of high toxic profile conventional AmB should not be used as back bone therapy for combination.[47] Either LAMB or AMLC are appropriate choice for back bone therapy.[48]

Combination of polyenes and echinocandins showed synergism both invitro and invivo. Although echinocandins does not have invitro activity against the mucorales, they are considered to have some in vivo activity. A retrospective clinical study by Caitlin et al has shown that combination therapy with ABLC or LAmB plus capsofungi was associated with significant improvement of survival in patients with rhino orbito cerebral mucormycosis compared with polyene monotherapy.[31]

Combination of AmB + triazole is contradictory. In vivo studies have shown the possible synergism but in-vivo studies have shown no benefits when both the agents are used together.[37] Current guidelines and existing pre clinical and clinical data do not support the use of this combination with possible exception of CNS mucormycosis where a combination of high dose LAMB and posaconazole or isavuconazole might be considered.



Source[52]

Optimal treatment pathway for mucormycosis in adults

Depending on geographical location not all recommended treatments may have regulatory approval for use in clinical settings. Above pathway can be used when all the treatment modalities and antifungal drugs are available. When amphotericin b lipid formulations are not available treatment can be initiated with isavuconazole and posaconazole.

Adjunctive therapy

Reversal of immunosuppression, aggressive glycemic control in patients with uncontrolled diabetes and ketoacidosis is paramount important. Reversal of acidosis especially in patients with diabetic ketoacidosis, by administering of sodium bicarbonate helps in blocking the rhizopus oryzae from invading endothelial cells and also aid in restoring iron chelating and neutrophilic function.[49] Role of iron metabolism in pathogenesis of mucormycosis suggested the possible role of iron chelators as adjunctive therapy. They work by reducing the iron availability and there by inhibiting fungal growth. Preclinical data in a mice model showed improved survival and decreased fungal burden with deferasirox.[50] However in a prospective, randomized clinical study performed on patients with hematologic malignancies showed highest mortality among patients receiving deferasirox.[51] However deferasirox has beneficial role in diabetic patients.

Hyperbaric oxygen helps in increasing oxygen pressure thereby improving neutrophilic functionality. It also increases action of AmB. Other adjunctive therapies include administering of cytokines, granulocyte colony stimulating factor or interferon- γ and nivolumab, a monoclonal antibody that decreases programmed cell death-1 expression on t-cells.[32]

Prophylatic treatment

Primary prophylaxis

There is no evident for primary prophylaxis directed solely towards mucormycosis usually prophylaxis is directed against a broad range of fungal infection, including aspergillosis and candidiasis. Commonly used agent is posaconazole (dose: delayed released tablet 600 mg/day in two divided doses on day one followed by 300mg once daily or suspension 600mg/day in three divided doses) followed by isavuconazole 200mg/day. Other antifungal agents like fluconazole, itraconazole and voriconazole can be used in neutropenic patients. In

patients receiving chemotherapy AmB liposomal 5mg/kg/day can be used.[52]

In some rare conditions breakthrough mucormycosis can be seen in patients receiving posaconazoile prophylaxis.

Secondary prophylaxis: it is either the continued treatment in a patient who had been diagnosed with mucormycosis and responded to treatment or as restarted treatment in patient with successful disease control now immunocompetent, but scheduled for a new period of immunosuppression e.g. : hematopoietic stem cell transplantation. Appropriate intervention to prevent recurrence includes surgical resection and use of last drug effective in the same patient.[52]

CONCLUSION

Mucormycosis is a rare and emerging fatal disease characterized by angio invasion and tissue necrosis. It is mostly seen in immunocompromised patients. Nowadays it became more prevalent among covid-19 patients with diabetes and in patients with long-term steroid usage. Early diagnosis is crucial in reducing the mortality. Direct examination, culture and histopathology remain gold standard but this may result in delay of diagnosis. Newer methods like CT scan, PCR may help in early diagnosis and prompt initiation of treatment. Treatment options include antifungal agents, surgical interventions and various adjunctive therapies and reversal of predisposing factors. Commonly used antifungal agents include amphotericin b lipid formulations, isavuconazole and posaconazole.

REFERENCES

1. Hibbett DS, Binder M, Bischoff JF, Blackwell M, Cannon PF, Eriksson OE, Huhndorf S, James T, Kirk PM, Lücking R, Thorsten Lumbsch H, Lutzoni F, Matheny PB, McLaughlin DJ, Powell MJ, Redhead S, Schoch CL, Spatafora JW, Stalpers JA, Vilgalys R, Aime MC, Aptroot A, Bauer R, Begerow D, Benny GL, Castlebury LA, Crous PW, Dai YC, Gams W, Geiser DM, Griffith GW, Gueidan C, Hawksworth DL, Hestmark G, Hosaka K, Humber RA, Hyde KD, Ironside JE, Kõljalg U, Kurtzman CP, Larsson KH, Lichtwardt R, Longcore J, Miadlikowska J, Miller A, Moncalvo JM, Mozley-Standridge S, Oberwinkler F, Parmasto E, Reeb V, Rogers JD, Roux C, Ryvarden L, Sampaio JP, Schüssler A, Sugiyama J, Thorn RG, Tibell L, Untereiner WA, Walker C, Wang Z, Weir A, Weiss M, White MM, Winka K, Yao YJ, Zhang N. A higher-level phylogenetic classification of the Fungi. Mycol Res, 2007; 111(Pt 5): 509-47. doi: 10.1016/j.mycres.2007.03.004., 2007; 13: PMID: 17572334.
2. Prakash H, Ghosh AK, Rudramurthy SM, Singh P, Xess I, Savio J, Pamidimukkala U, Jillwin J, Varma S, Das A, Panda NK, Singh S, Bal A, Chakrabarti A. A prospective multicenter study on mucormycosis in India: Epidemiology, diagnosis, and treatment. Med Mycol, 2019; 1, 57(4): 395-402. doi: 10.1093/mmy/myy060. PMID: 30085158.
3. 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, 3: e100-3. doi: 10.1016/j.ijid.2009.11.024. Epub 2010 Mar 24. PMID: 20335060.
4. Mehta, Salil, and Abha Pandey. "Rhino-Orbital Mucormycosis Associated With COVID-19." Cureus, 2020; 12(9): e10726. 30. doi:10.7759/cureus.10726
5. Lin E, Moua T, Limper AH. Pulmonary mucormycosis: clinical features and outcomes. Infection, 2017; 45(4): 443-448. doi: 10.1007/s15010-017-0991-6. Epub 2017 Feb 20. PMID: 28220379.
6. Jeong W, Keighley C, Wolfe R, Lee WL, Slavin MA, Kong DCM, Chen SC. The epidemiology and clinical manifestations of mucormycosis: a systematic review and meta-analysis of case reports. Clin Microbiol Infect, 2019; 25(1): 26-34. doi: 10.1016/j.cmi.2018.07.011. Epub 2018 Jul 21. PMID: 30036666.
7. Song, G., Liang, G. & Liu, W. Fungal Co-infections Associated with Global COVID-19 Pandemic: A Clinical and Diagnostic Perspective from China. Mycopathologia, 2020; 185: 599–606. https://doi.org/10.1007/s11046-020-00462-9.
8. Ibrahim AS, Spellberg B, Walsh TJ, Kontoyiannis DP. Pathogenesis of mucormycosis. Clin Infect Dis, 2012; 54 1(1): S16-22. doi: 10.1093/cid/cir865. PMID: 22247441; PMCID: PMC3286196.
9. Spellberg, Brad et al. "Novel perspectives on mucormycosis: pathophysiology, presentation, and management." Clinical microbiology reviews, 2005; 18(3): 556-69. doi:10.1128/CMR.18.3.556-569.2005
10. Arunaloke Chakrabarti, Ashim Das, Jharna Mandal, M. R. Shivaprakash, Varghese K. George, Bansidhar Tarai, Pooja Rao, Naresh Panda, Subhash C. Verma, Vinay Sakhuja, The rising trend of invasive zygomycosis in patients with uncontrolled diabetes mellitus, Medical Mycology, 2006; 44(4): 335–342. https://doi.org/10.1080/13693780500464930
11. Roden MM, Zaoutis TE, Buchanan WL, Knudsen TA, Sarkisova TA, Schaufele RL, Sein M, Sein T, Chiou CC, Chu JH, Kontoyiannis DP, Walsh TJ. Epidemiology and outcome of zygomycosis: a review of 929 reported cases. Clin Infect Dis, 2005; 1, 41(5): 634-53. doi: 10.1086/432579. Epub 2005 Jul 29. PMID: 16080086.
12. Jha VK, Borpujari PJ, Shenoy G, Bhargav S. Empyema with pleuropulmonary mucormycosis. J Assoc Physicians India, 2013; 61(9): 665-7. PMID: 24772711.
13. Petrikkos G, Tsioutis C. Recent Advances in the Pathogenesis of Mucormycoses. Clin Ther, 2018; 40(6): 894-902. doi: 10.1016/j.clinthera.2018.03.009. Epub 2018 Apr 6. PMID: 29631910.

14. Hassan MIA, Voigt K. Pathogenicity patterns of mucormycosis: epidemiology, interaction with immune cells and virulence factors. Med Mycol, 2019; 1, 57(2): S245-S256. doi: 10.1093/mmy/myz011. PMID: 30816980; PMCID: PMC6394756.
15. Rajeev soman, Ayesha sunavala. Post Covid mucormycosis –from the frying pan into the fire, journal of the association of physicians of India.
16. Revannavar SM, P S, Samaga L, et al COVID-19 triggering mucormycosis in a susceptible patient: a new phenomenon in the developing world?BMJ Case Reports CP, 2021; 14: e241663
17. Boelaert JR, Van Cutsem J, de Locht M, Schneider YJ, Crichton RR. Deferoxamine augments growth and pathogenicity of Rhizopus, while hydroxypyridinone chelators have no effect. Kidney Int, 1994; 45(3): 667-71. doi: 10.1038/ki.1994.89. PMID: 8196268.
18. George Petrikkos, Anna Skiada, Olivier Lortholary, Emmanuel Roilides, Thomas J. Walsh, Dimitrios P. Kontoyiannis, Epidemiology and Clinical Manifestations of Mucormycosis, Clinical Infectious Diseases, 2012; 54(1): S23–S34. https://doi.org/10.1093/cid/cir866
19. Talmi YP, Goldschmied-Reouven A, Bakon M, Barshack I, Wolf M, Horowitz Z, Berkowicz M, Keller N, Kronenberg J. Rhino-orbital and rhino-orbito-cerebral mucormycosis. Otolaryngol Head Neck Surg, 2002l; 127(1): 22-31. doi: 10.1067/mhn.2002.126587. PMID: 12161726.
20. Ribes, J a et al. "Zygomycetes in human disease." Clinical microbiology reviews, 2000; 13(2): 236-301. doi:10.1128/cmr.13.2.236-301.2000
21. Spellberg, Brad et al. "Novel perspectives on mucormycosis: pathophysiology, presentation, and management." Clinical microbiology reviews, 2005; 18(3): 556-69. doi:10.1128/CMR.18.3.556-569.2005.
22. Skiada, Anna et al. "Epidemiology and Diagnosis of Mucormycosis: An Update." Journal of fungi (Basel, Switzerland), 2020; 6(4): 265. doi:10.3390/jof6040265
23. Petrikkos G, Tsioutis C. Recent Advances in the Pathogenesis of Mucormycoses. Clin Ther, 2018; 40(6): 894-902. Doi: 10.1016/j.clinthera.2018.03.009. Epub 2018 Apr 6. PMID: 29631910.
24. Kiran Bala, Jagdish Chander, Uma Handa, Rajpal Singh Punia, Ashok Kumar Attri, A prospective study of mucormycosis in north India: Experience from a tertiary care hospital, Medical Mycology, 2015; 53(3): 248–257. https://doi.org/10.1093/mmy/myu086
25. Yinadsawaphan T, Ngamskulrungroj P, Chalermwai W, Dhitinanmuang W, Angkasekwinai N. Gastrointestinal mucormycosis due to Rhizopus microsporus following Streptococcus pyogenes toxic shock syndrome in an HIV patient: a case report. BMC Infect Dis, 2020; 10, 20(1): 817. doi: 10.1186/s12879-020-05548-9. PMID: 33167878; PMCID: PMC7654013.
26. Tissot, Frederic et al. "ECIL-6 guidelines for the treatment of invasive candidiasis, aspergillosis and mucormycosis in leukemia and hematopoietic stem cell transplant patients." Haematologica, 2017; 102(3): 433-444. doi:10.3324/haematol.2016.152900.
27. Spellberg B, Edwards J Jr, Ibrahim A. Novel perspectives on mucormycosis: pathophysiology, presentation, and management. Clin Microbiol Rev, 2005; 18(3): 556-69. doi: 10.1128/CMR.18.3.556-569.2005. PMID: 16020690; PMCID: PMC1195964.
28. Vironneau P, Kania R, Morizot G, Elie C, Garcia-Hermoso D, Herman P, Lortholary O, Lanternier F; French Mycosis Study Group. Local control of rhino-orbito-cerebral mucormycosis dramatically impacts survival. Clin Microbiol Infect, 2014; 20(5): O336-9. doi: 10.1111/1469-0691.12408. Epub 2013 Nov 6. PMID: 24118291.
29. Gamaletsou, M.N., Sipsas, N.V., Roilides, E. et al. Rhino-Orbital-Cerebral Mucormycosis. Curr Infect Dis, 2012; 14: 423–434. https://doi.org/10.1007/s11908-012-0272-6.
30. Antachopoulos C, Meletiadis J, Roilides E, Sein T, Walsh TJ. Rapid susceptibility testing of medically important zygomycetes by XTT assay. J Clin Microbiol, 2006; 44(2): 553-60. doi: 10.1128/JCM.44.2.553-560.2006. PMID: 16455912; PMCID: PMC1392685.
31. Reed C, Bryant R, Ibrahim AS, Edwards J Jr, Filler SG, Goldberg R, Spellberg B. Combination polyene-caspofungin treatment of rhino-orbital-cerebral mucormycosis. Clin Infect Dis, 2008; 1, 47(3): 364-71. doi: 10.1086/589857. PMID: 18558882; PMCID: PMC2793535.
32. Sipsas, Nikolaos V et al. "Therapy of Mucormycosis." Journal of fungi (Basel, Switzerland), 2018; 4(3): 90-31. Jul. doi:10.3390/jof4030090
33. Walsh TJ, Hiemenz JW, Seibel NL, Perfect JR, Horwith G, Lee L, Silber JL, DiNubile MJ, Reboli A, Bow E, Lister J, Anaissie EJ. Amphotericin B lipid complex for invasive fungal infections: analysis of safety and efficacy in 556 cases. Clin Infect Dis, 1998; 26(6): 1383-96. doi: 10.1086/516353. PMID: 9636868..
34. Lewis, Russell E et al. "Comparative pharmacodynamics of amphotericin B lipid complex and liposomal amphotericin B in a murine model of pulmonary mucormycosis." Antimicrobial agents and chemotherapy, 2010; 54(3): 1298-304. doi:10.1128/AAC.01222-09.
35. Lanternier F, Poiree S, Elie C, Garcia-Hermoso D, Bakouboula P, Sitbon K, Herbrecht R, Wolff M, Ribaud P, Lortholary O; French Mycosis Study Group. 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(11): 3116-23. doi: 10.1093/jac/dkv236. Epub 2015 Aug 27. PMID: 26316385.
36. ESCMID and ECMM joint clinical guidelines for the diagnosis and management of mucormycosis, 2013.
37. Kyvernitakis A, Torres HA, Jiang Y, Chamilos G, Lewis RE, Kontoyiannis DP. Initial use of combination treatment does not impact survival of 106 patients with haematologic malignancies and mucormycosis: a propensity score analysis. Clin Microbiol Infect, 2016; 22(9): 811.e1-811.e8. doi: 10.1016/j.cmi.2016.03.029. Epub 2016 Apr 13. PMID: 27085727.
38. A Skiada, C Lass-Floerl, N Klimko, A Ibrahim, E Roilides, G Petrikkos, Challenges in the diagnosis and treatment of mucormycosis, Medical Mycology, 2018; 56(1): S93–S101, https://doi.org/10.1093/mmy/myx101
39. Marty FM, Ostrosky-Zeichner L, Cornely OA, Mullane KM, Perfect JR, Thompson GR 3rd, Alangaden GJ, Brown JM, Fredricks DN, Heinz WJ, Herbrecht R, Klimko N, Klyasova G, Maertens JA, Melinkeri SR, Oren I, Pappas PG, Ráčil Z, Rahav G, Santos R, Schwartz S, Vehreschild JJ, Young JH, Chetchotisakd P, Jaruratanasirikul S, Kanj SS, Engelhardt M, Kaufhold A, Ito M, Lee M, Sasse C, Maher RM, Zeiher B, Vehreschild MJGT; VITAL and FungiScope Mucormycosis Investigators. Isavuconazole treatment for mucormycosis: a single-arm open-label trial and case-control analysis. Lancet Infect Dis, 2016; 16(7): 828-837. Doi: 10.1016/S1473-3099(16)00071-2. Epub 2016 Mar 9. PMID: 26969258.
40. Ananda-Rajah MR, Kontoyiannis D. Isavuconazole: a new extended spectrum triazole for invasive mold diseases. Future Microbiol, 2015; 10(5): 693-708. doi: 10.2217/fmb.15.34. Epub 2015 May 21. PMID: 26000646.
41. Arendrup MC, Jensen RH, Meletiadis J. In Vitro Activity of Isavuconazole and Comparators against Clinical Isolates of the Mucorales Order. Antimicrob Agents Chemother, 2015; 59(12): 7735-42. doi: 10.1128/AAC.01919-15. Epub 2015 Oct 5. PMID: 26438494; PMCID: PMC4649229.
42. Graves B, Morrissey CO, Wei A, Coutsouvelis J, Ellis S, Pham A, Gooi J, Ananda-Rajah M. Isavuconazole as salvage therapy for mucormycosis. Med Mycol Case Rep, 2016; 8, 11: 36-9. doi: 10.1016/j.mmcr.2016.03.002. PMID: 27158585; PMCID: PMC4845387.
43. Rausch CR, DiPippo AJ, Bose P, Kontoyiannis DP. Breakthrough Fungal Infections in Patients with Leukemia Receiving Isavuconazole. Clin Infect Dis, 2018; 30, 67(10): 1610-1613. doi: 10.1093/cid/ciy406. PMID: 29771293; PMCID: PMC6454429.
44. Bellanger AP, Albert ND, Lewis RE, Walsh TJ, Kontoyiannis DP. Effect of Preexposure to Triazoles on Susceptibility and Virulence of Rhizopus oryzae. Antimicrob Agents Chemother, 2015; 59(12): 7830-2. doi: 10.1128/AAC.01583-15. Epub 2015 Sep 21. PMID: 26392499; PMCID: PMC4649224.
45. Dannaoui E, Meletiadis J, Mouton JW, Meis JF, Verweij PE; Eurofung Network. In vitro susceptibilities of zygomycetes to conventional and new antifungals. J Antimicrob Chemother, 2003; 51(1): 45-52. doi: 10.1093/jac/dkg020. PMID: 12493786.
46. Krishna G, Ma L, Martinho M, Preston RA, O'Mara E. A new solid oral tablet formulation of posaconazole: a randomized clinical trial to investigate rising single- and multiple-dose pharmacokinetics and safety in healthy volunteers. J Antimicrob Chemother, 2012; 67(11): 2725-30. Doi: 10.1093/jac/dks268. Epub 2012 Jul 24. PMID: 22833639; PMCID: PMC3468079.
47. Ibrahim AS, Avanessian V, Spellberg B, Edwards JE Jr. Liposomal amphotericin B, and not amphotericin B deoxycholate, improves survival of diabetic mice infected with Rhizopus oryzae. Antimicrob Agents Chemother, 2003; 47(10): 3343-4. doi: 10.1128/aac.47.10.3343-3344.2003. PMID: 14506054; PMCID: PMC201164.
48. Spellberg, Brad et al. "Combination therapy for mucormycosis: why, what, and how?" Clinical infectious diseases: an official publication of the Infectious Diseases Society of America, 2012; 54(1) 1: S73-8. doi:10.1093/cid/cir885
49. Gebremariam T, Lin L, Liu M, Kontoyiannis DP, French S, Edwards JE Jr, Filler SG, Ibrahim AS. Bicarbonate correction of ketoacidosis alters host-pathogen interactions and alleviates mucormycosis. J Clin Invest, 2016; 1, 126(6): 2280-94. doi: 10.1172/JCI82744. Epub 2016 May 9. PMID: 27159390; PMCID: PMC4887168.
50. Ibrahim AS, Gebermariam T, Fu Y, Lin L, Husseiny MI, French SW, Schwartz J, Skory CD, Edwards JE Jr, Spellberg BJ. The iron chelator deferasirox protects mice from mucormycosis through iron starvation. J Clin Invest, 2007; 117(9): 2649-57. doi: 10.1172/JCI32338. PMID: 17786247; PMCID: PMC1957543.
51. Spellberg B, Ibrahim AS, Chin-Hong PV, Kontoyiannis DP, Morris MI, Perfect JR, Fredricks D, Brass EP. The Deferasirox-AmBisome Therapy for Mucormycosis (DEFEAT Mucor) study: a randomized, double-blinded, placebo-controlled trial. J Antimicrob Chemother, 2012; 67(3): 715-22. doi: 10.1093/jac/dkr375. Epub 2011 Sep 20. PMID: 21937481; PMCID: PMC3383100.
52. Global guideline for the diagnosis and management of mucormycosis: an initiative of the European Confederation of Medical Mycology in cooperation with the Mycoses Study Group Education and Research Consortium.