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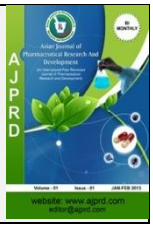

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Review Article

Mucormycosis: Pathogenesis, Diagnosis, and Management

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A B S T R A C T

Mucormycosis (black fungus) is caused by Mucor and Rhizopus. After getting affected such warning signs; pain and redness around the eyes and nose, fever, headache, coughing, shortness of brain, bloody vomit can see. It can suspect in COVID-19 patients, diabetics, or immunosuppressed individuals. Mucormycosis, if not cared it may be turned fatal. Mucormycosis can cause a different types of infections: rhino-cerebral, pulmonary, cutaneous, gastrointestinal, and dissemination mucormycosis. In a study β- hydroxybutyrate (a representative of ketone bodies) and elevated serum iron levels were the major factors that enhanced expression of both CotH and GRP78, whereas lactic acidosis did not affect their expression. In addition,sodium bicarbonate reversed the effect of acidosis and protected β- hydroxybutyrate –treated mice from mucormycosis, implying the significance of correction acidosis as a treatment measure in patients with DKA and mucormycosis.The objective of this paper is screening, different pathogenesis, diagnosis, and management of Mucormycosis. An additional factor that significantly contributes to the poor prognosis of these infections is the inherent resistance of Mucorales to the most available antifungals, with amphotericin-B, posaconazole, and isavuconazole considered the most potent antifungals in vitro.According to the studies Rhizopusarrhizus is present in 85% of rhino-cerebral forms, compared with only 17% of non-rhino cerebral forms. However, recent data enlarge the antifungal armamentarium with the US Food and Drug Administration and European Medicines Agency's approval of the new triazoleisavuconazole, however, comparative clinical data are lacking, and the respective places of polyenes and different azoles need to be discussed.

Keywords: Mucormycosis, DKA, Antifungal, rhino-cerebral, Amphotericin B.

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INTRODUCTION

Zygomycosis or Mucormycosis is an invasive life-threatening fungal infection caused by fungi which are classified under phylum ***Glomeromycota***, subphylum ***Mucormcotina***. Mucormycosis is distinguished by infarction and necrosis in host tissue, a consequence of vasculature invasion due to fungi filament (hyphae) start specific interaction with endothelial cells. [1]

Mucorales are non-septate hyphae and involve the nerves and blood vessels. Mucormycosis or phycomycosis is caused by different types of fungi such as Mucor and Rhizopus. A French RetroZygo study found85% of rhino-cerebral, while only 17% of non-rhino cerebral forms of mucormycosis caused by Rhizopusarrhizus.[2]The lung infection occurs similarly to aspergillosis. Pulmonary lesions are especially common in diabetic ketoacidosis (DKA) patients. They can identify by particular characteristics:Mucor is specified by its broad, non-parallel, non-septate hyphae which branch at an obtuse angle. It is more often angioinvasive, and disseminates; hence it is more destructive than aspergillosis.

The mortality and morbidity rate of mucormycosis varies based onthe organ affected by the infection, the causative species fungi, and the medical status or medical history of the patient.[3]The survival mortality rate is better among patients undergoing stem cell transplantation (8%) than solid organ transplantation (2%).27, 28 Diabetes is the most common clinical risk factor to identify

mucormycosis from Pseudallescheriasis or Rusariosis and other unspecified mold diseases.[4]These insights create a foundation for the development of new immune-based strategies for the prevention or enhanced clearance of fungal diseases. Mainly sinuses or lungs of such individuals get affected after fungal spores are inhaled from the air. Infection can lead to serious disease with a warning sign and symptoms as follows:

- Pain and redness around eyes and/or nose
- Fever
- Headache
- Coughing
- Shortness of breath
- Bloody vomits
- Altered mental status.

Mucormycosis's clinical presentation is also related to underlying conditions (table1)[5]

Table 1: Relationship between predisposing condition and site of infection

Predisposing condition	Pre-dominant site of infection
Diabetic ketoacidosis	Rhinocerebral
Neutropenia	Pulmonary and disseminated
Corticosteroids	Pulmonary, disseminated, or rhino-cerebral
Deferoxamine	Disseminated
Malnutrition	Gastrointestional
Trauma, catheter/injection site, skin maceration	Cutaneous/subcutaneous

It can suspect in COVID-19 patients, diabetics, or immunosuppressed individuals with the help of different screening patterns as following:

- Sinusitis – nasal blockage or congestion, nasal discharge (blackish/bloody), local pain in the cheekbone.
- One side facial pain, numbness, or swelling.
- Blackish discoloration over the bridge of nose/palate
- Blurred or double vision with pain; fever, skin lesion; thrombosis & necrosis (Eschar)
- Chest pain, pleural effusion, hemoptysis, worsening of respiratory symptoms.

In severe acute respiratory syndrome coronavirus2 (SARS-CoV-2) infection can develop coronavirus disease (COVID-19), which can be linked with significant and sustained lymphopenia compromising the immune system, especially in severe cases.[6] Mucormycosis can occur due to respiratory infections and the long-term use of corticosteroids in COVID-19 patients.

Epidemiology and Clinical Manifestation

In 2005, analyze all the available literature regarding mucormycosis was made by Roden et al. In a study, 46% mortality was observed among patients suffering from sinus infections, and a mortality rate of 76% for pulmonary mucormycosis and 96% for disseminated mucormycosis was reported.[3]Epidemiological studies were performed on a large scale either on a national level3 or in patients with selected disease conditions [hematopoietic stem cell transplantation (HSCT)].[1]

The registry (2004) was constructed by the working group on Zygomycosis or Mucormycosis of the European Confederation of Medical Mycology (ECMM) and the International Society of Human and Animal Mycology (ISHAM).4 According tothe French study, mucormycosis incidence expanded in particular conditions, for example, it increased by 7.3% per year, especially in patients with neutropenia.[7]Come to the end of different studies, these kinds of infections are not easily managed due to different reasons.

Firstly, diagnosis is difficult because of similarities with invasive aspergillosis clinical- radiology and shortage of diagnostic tools. However, new tools in serum and tissue, as well as the recognition of highly suggestive radiological signs recently modified diagnostic possibilities. Secondly, treatment is an emergency and combines surgery, which is frequently required owing to the angioinvasive and necrotic character of infection [8] and antifungal treatment. Primary, several antifungal drugs show in-vitro resistance limits in their therapeutic options.[9]

US Food and Drug Administration and European Medicines Agency's approved antifungal armamentarium and new triazole, is avuconazole, however, comparative clinical data are lacking, and the respective places of polyenes and different azoles need to be discussed.

Mucormycosis can cause the following types of diseases (figure 1):

1. Rhino-cerebral mucormycosiscan infect the brain and sinus leading to one side facial swelling, headache fever, sinus congestion black lesions inside the mouth/ outside the face.
2. Pulmonary mucormycosis mainly infect the lung (chest pain), breathlessness, fever, and cough.

Cutaneous mucormycosis causes local skin infection leading to ulcers or blisters, redness, and swelling of the infected skin region.

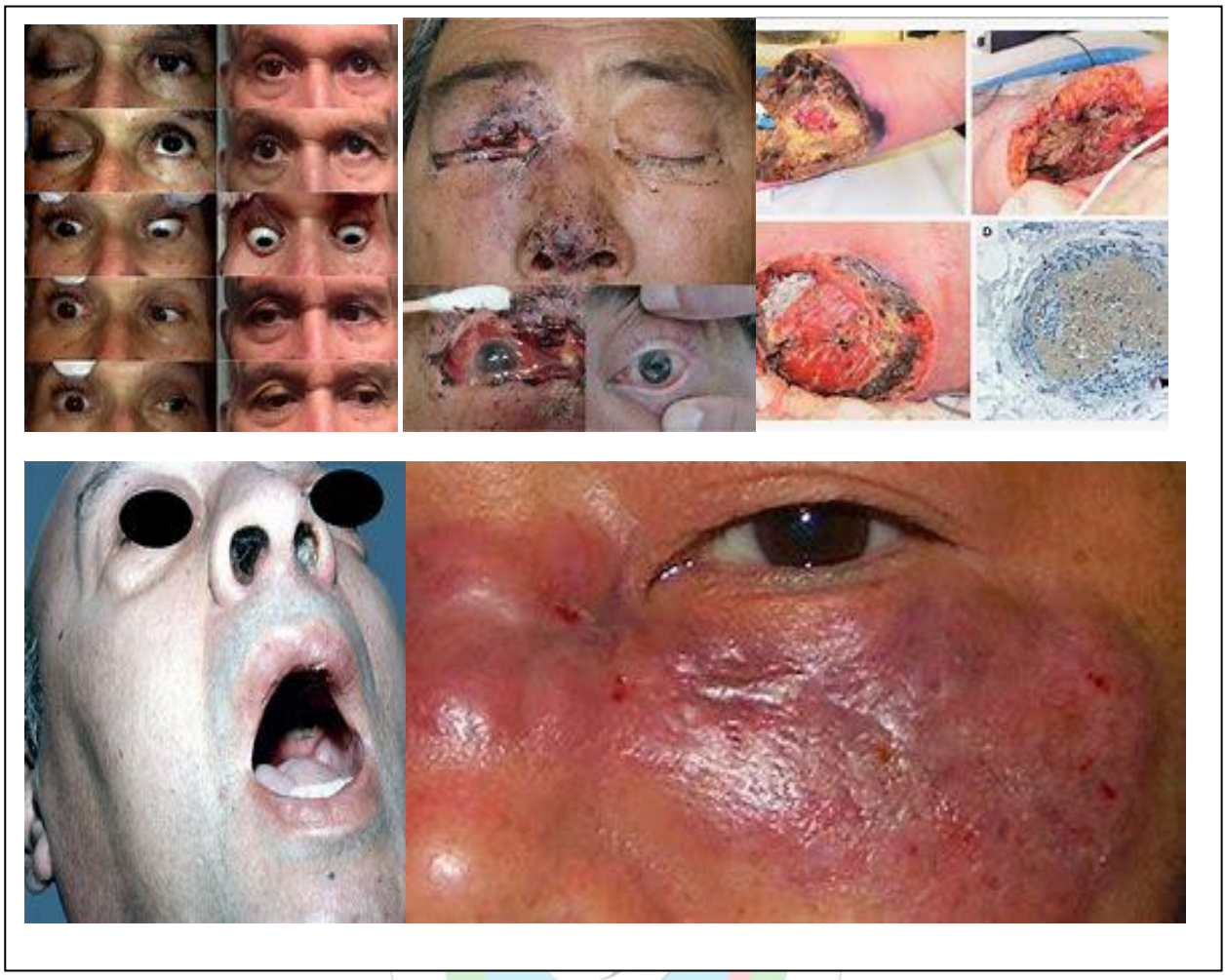

Figure 1*:* Cutaneous and rhino-orbito-cerebral mucormycosis

1. Gastrointestinal mucormycosis is more often in premature neonates leading to vomiting, nausea, gastrointestinal bleeding, and abdominal pain.
2. Disseminated mucormycosis occurs in patients suffering from multiple medical complications impeding the symptomatic discrimination of mucormycosis from other infectious diseases.
3. Uncommon presentation as renal infection. [10-13]

PATHOGENESIS

Mucorales may enter the systemic circulation via ingestion of contaminated food, inhalation, and abraded skin areas. It can cause rhino-orbito-cerebral, pulmonary, gastrointestinal, or cutaneous/wound infections. Various characteristics of Mucorales have been identified (innate thermotolerance, ability to bind on the endothelial cell membrane, rapid growth, ability to obtain iron from the host organism, downregulation of host–defense genes implicated in pathogen recognition, immune defense, and tissue repair) and all these contribute in their aggressive nature of the disease.[11,14]Inhibition of interferon (IFY) -γ expression [15], and an evolutionary duplication of system implicated in energy use and virulence, as revealed in a whole-genome string of Rhizopusoryzae.[16]Predispose factors ketoacidosis and deferoxamine of mucormycosis, reveal the importance of hyperglycemia, iron, and acidifying ketone bodies in Mucorales virulence.

Virulence factors of the Mucorales Human pathogens cause disease in the hostbased on two steps: Firstly capability of infectious microorganisms to evade the immune system and surviving inside the host and secondly, perturbation of the immune system and causing damage to the host cells. Virulence factors of the pathogens play a key role to accomplish the damage process.[17]Inoculation of spores into host tissue (eg, skin or alveoli, depending on the site of entry); evading phagocytosis by macrophages and germinating to hyphae (the angioinvasive from the fungus); increasing their load, attaching to the endothelium through specific unique receptors [spore-coating protein family (CotH) on Rhizopus spp. surface and endothelium glucose regulator protein 78 (GRP78)], subsequently inducing endocytosis and causing finally entering the circulation and dissemination hematogenousand develop systematic disease and multi-organ involvement. [18] (figure2)

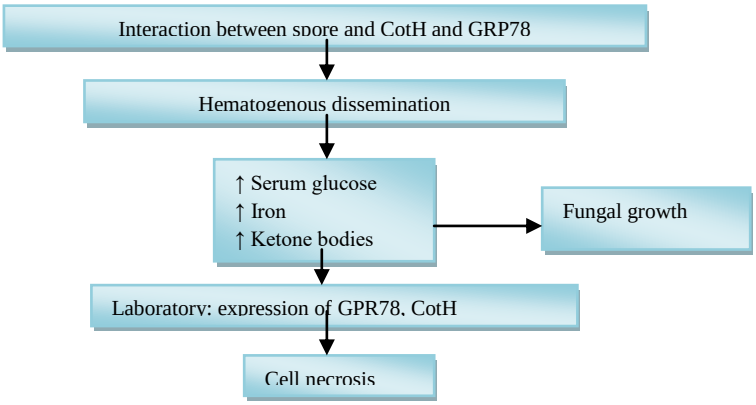

Figure 2: Pathogenesis of mucormycosis

Resulting in increased ability of Rhizopus to invade host tissues and explaining the susceptibility of diabetic and deferoxamine treated patients of mucormycosis. However, it should be noted that the majority of studies on virulence and the association between ketoacidosis and the occurrence of mucormycosis have been conducted with Rhizopus.[19]An additional factor is the inherent resistance of Mucorales to the available antifungals (amphotericin B, posaconazole, and itraconazole, and isavuconazole) which significantly contributes to the poor prognosis.[20]Fungal spores are easily aerosolized, localinoculation (eg, skin lesion), or ingestion through the gastrointestinal tract. Regardless of the point of entry, the establishment of the fungi and the development of mucormycosis require certain critical steps.Decreased number and impaired function of monocytes and neutrophils are known to inhibit Mucorales spore germination. This includes patients with hematological disorders, AIDS, or liver cirrhosis, those who have undergone solid organ transplants, and those being treated with high-dose steroids.[21,20]

Interaction with the Endothelium:

Mucorales adhere to endothelial cells by expressing spore coat homolog (CotH) proteins.[22]Endothelial cells make up the internal layer of blood vessels and possess various important roles in pathogen recognition and maintain physiological functions[23]such as phagocytose and damage the spores of Mucorales. The glucose-regulated protein 78(GRP78) is a receptor present on the surface of endothelial cells and can specifically recognize Mucor spp. But not other fungal pathogens like A. fumigates.[24]In the mice study, increasing the glucose and iron concentration in mice give a result of the enhancement of expression of GRP78 on the endothelial cells surface in the brain, lung, and sinus compared with normal mice.[24]CotH proteins are found exclusively in Mucoralesand bind to the host endothelial receptor GRP78 (a protein found in the endoplasmic reticulum), leading to endocytosis of the fungus after exposure of endothelial cells in acidosis and elevated level of iron and glucose (hyperglycemia and DKA), both GRP78 endothelial surface expression and CotH fungal surface expression increase.[25]When endothelial cells are exposed to acidosis and elevated levels of glucose and iron, as in cases of hyperglycemia and DKA, both GRP78 endothelial surface expression and CotH fungal surface expression increase.

Several recent observations on the interaction of these receptors are of clinical importance and are described. In acidosis due to β- hydroxybutyrate (a representative of ketone bodies) and elevated serum iron levels were the major factors that enhanced expression of both CotH and GRP78, whereas lactic acidosis did not affect their expression. In addition,sodium bicarbonate altered the effect and protected β- hydroxybutyrate–treated mice from mucormycosis, implying the significance of correction acidosis as a treatment measure in patients with DKA and mucormycosis.[26]In another study, the use of anti-GRP78 antibodies or anti-CotH antibodies almost completely blocked endothelial invasion by R. oryzae.However, this action indicates the existence of additional factors incriminate in the interaction between the endothelial cells and fungus.[27] Another possible mechanism of endothelial damage is the production of secondary fungal metabolites that act as toxins.[18,28]

Iron Uptake:

Iron is important for fungal cell development is supported by the observation that fungal cells undergo apoptosis in poor iron conditions.[29] In addition, in a study on mice model of mucormycosis, elevated iron concentration improves the fungal growth by reducing phagocytosis and IFN – ɣ secretion.[30]Two main mechanisms in which Mucoralesacquire iron from the host organism siderophores (iron chelators, which may be intrinsic such as rhizoferrin or extrinsic, and named xenosidero-phores) or high-affinity iron permeases.[31]Heme-oxygenase copies present in R. oryzae or genome sequencing suggest a third mechanism of iron uptake from hemoglobin observed in fungi.[32]

Deferoxamine, an iron chelator used in persons with increased risk of iron overload (eg, patientsreceiving renal replacement therapy and persons receiving multiple transfusions), increases susceptibility to mucormycosis.Subsequent studies have found that iron chelation therapy with deferiprone or deferasirox (which Rhizopus is unable to use as xenosiderophores) protects DKA mice from mucormycosis and improves survival, whereas the use of adjunctive deferasoxinanophen label study of 8 cases of mucormycosis appeared tolerable and beneficial.[33] In addition,deferasirox revered the impairing effect of iron on neutrophil chemotaxis.[34]However, a recent clinical trial using adjunctive deferasirox therapy in patients with mucormycosis failed to find a survival

benefit.[35] Mucorales carry specific ferrioxamine receptors (named Fob1 and Fob2), which are induced only in the presence of ferrioxamine, subsequently facilitating fungal iron uptake from ferrioxamine but not from deferoxamine.(Figure3) Iron uptake from ferrioxamine is energy-dependent through the activity of reductase that liberates ferric iron from deferoxamineextracellularly and converts it into soluble ferrous iron, as well as through complete intracellular uptake of ferrioxamine.[35]

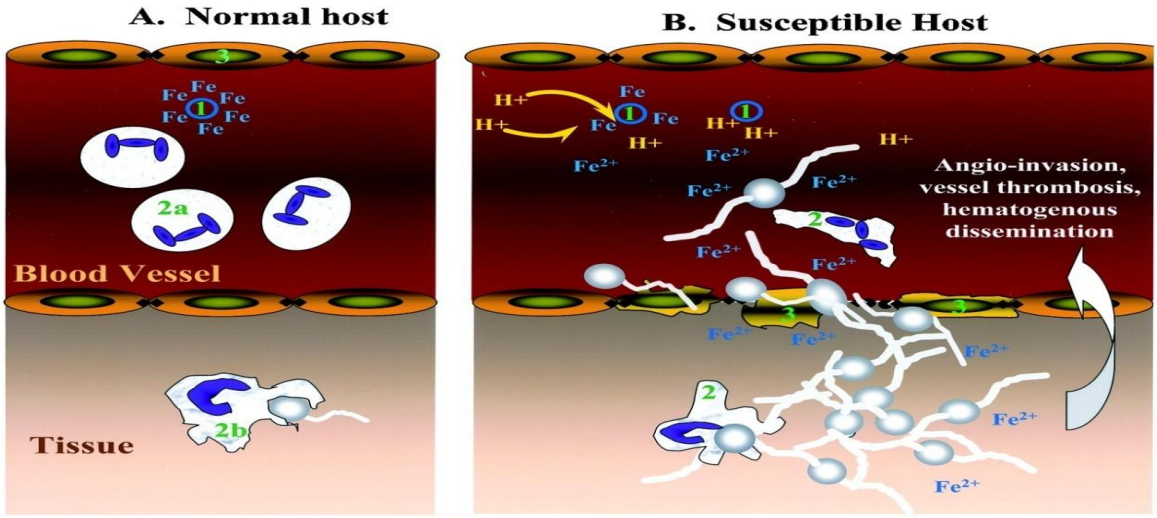

Figure 3: Pathogenetic mechanisms of and host defense mechanisms against mucormycosis**.**

To cause disease, the agents of mucormycosis must scavenge from the host sufficient iron for growth, must evade host phagocytic defense mechanisms, and must access vasculature to disseminate. A)Inanormalhost, primary defense mechanisms against mucormycosis include sequestration of iron in serum by specialized iron-binding proteins (1), phagocytes including circulating neutrophils (2a), and tissue macrophages (2b), and endothelial cells (3), which regulate vascular tone and permeability. Acting in concert, these mechanisms prevent the establishment of infection in the tissue and subsequent endovascular invasion. B) In susceptible hosts, normal defense mechanisms break down. For example, in diabetic ketoacidosis (DKA), the acidic pH of the serum causes dissociation of free iron from sequestering proteins (1). This release of free iron allows rapid fungal growth. Defects in phagocytic defense mechanisms (2), for example, deficiency in cell number (neutropenia) or functional defects caused by corticosteroids or the hyperglycemia and acidosis of diabetic ketoacidosis, allow a proliferation of the fungus. Finally, adherence to and damage of endothelial cells by the fungus (3) allows fungal angioinvasion and vessel thrombosis and subsequent tissue necrosis and dissemination of the fungal infection.

The high-affinity iron permease FTR1 has been suggested to facilitate intracellular transportation of iron from heme or ferrioxamine, and expressed in iron-depleted conditions and suppressed in iron-rich environments. [36] Acidic sera that supported the growth of R. oryzae were found to contain increased available serum iron (69g/dl versus 13g/dl for sera which did not support the growth of R. oryzae). Finally, stimulated acidotic conditions decreased the iron-binding capacity of sera collected from normal volunteers, suggesting that acidosis temporarily disrupts the capacity of transferrin to bind iron. [37]

Interaction of the Mucorales with the immune system:

Several studies investigated the interaction between the most abundant species causing mucormycosis and immune cells summarized as follows:

Platelets

The important role of platelets in host immunity is increasingly recognized. [37] After exposure secretion of granules that contain pro-inflammatory cytokines and chemokines, such as transforming growth factor – β and thrombocidinswith fungicidal properties. [38, 39] Expression of membrane-bound molecules (CD154 and platelet Toll-like receptors, they facilitate platelet binding and activation of various cells and their functions:

Endothelial cells: activates the intracellular adhesion molecules-1 and vascular cell adhesion molecule-1 pathway.

Monocytes: activation or differentiation to macrophages.

Dendritic cells: induce their maturation and B and T lymphocytes induce activation.

Conformity to Mucorales spores and hyphae, conduct platelet activation and increased tendency of aggregation, clot formation, and leads to platelet consumption also caused fungal damage by suppressing hyphal growth. [40]Additionally, platelet aggregation to the fungal wall may prevent the hematogenous dissemination of fungi.As well, necrotic areas in organs without fungal growth suggest thrombotic ischemia which may be due to systematic platelet activation.

Natural killer (NK) cells

Natural killer cells are lymphocytic cells that contribute to the immune defense against infected pathogens.

NK cells convey various receptors that can recognize infected cells and inhibit major histocompatibility complex (MHC) that inhibit the activation of the receptors.[41]

NK cells are considered part of the innate immune system and have the direct and indirect cytotoxic ability. These cells also secretechemokines and cytokines (IFN –γ, TNF-α, and GMCSF).[42] but additionally, in-vitro studies have found the immunosuppressive effect of R. oryzae, which

stops the release of the immune regulatory chemokines from NK cells.[43]

T cells

T cells are part of the adaptive immune system. Antigen-specific T cells count for optimistic diagnostic tools to control infectious diseases. Mucorales-specific T cells were found at most mucormycosis suffered patients as comparedto other patients who produced cytokines IL-4, IL-10, IL-17,and IFN-γ.These cytokines immediate hyphal damage of Mucorales.[44]

Treating T- inactivated cells with IL-2, IL-7 or both cytokines increase the production of Mucorales-specific T cells and their cytokines IL-5, IL-10, IL-13 and also promotes the production of CD4+ T cells that are certain Mucorales antigens.[45]

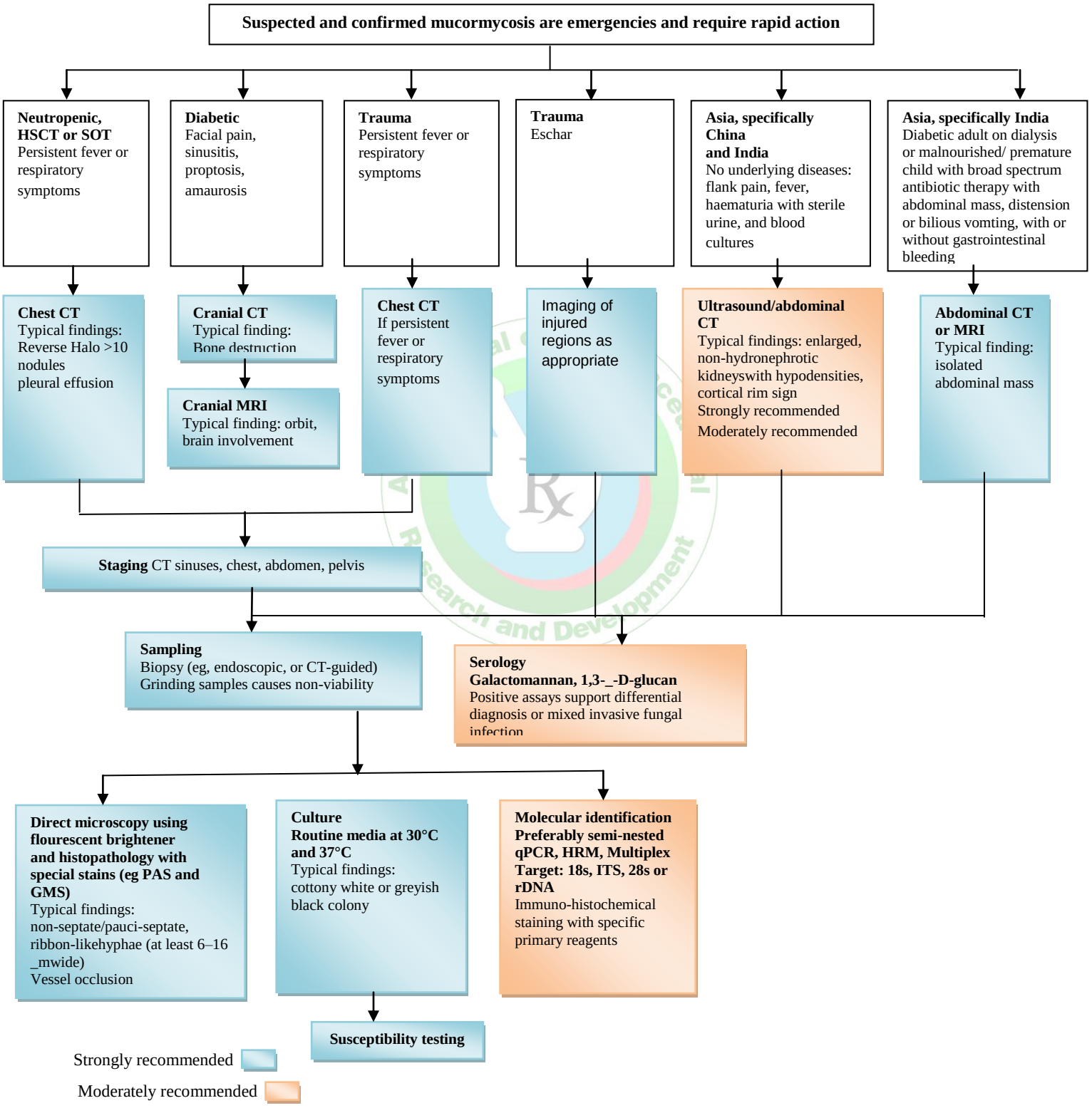

Figure 4: Diagnostic pathway for mucormycosis

Depending on the geographical location not all recommended tests might have regulatory approval for use in clinical settings. HSCT=haematopoietic stem cell transplantation. SOT=solid organtransplantation. PAS=periodic acid Schiff. GMS=Grocott-Gomori'smethenamine-silver strain. qPCR=quantitative PCR. HRM=high resolution melting. ITS=internal transcribed spacer. rDNA=ribosomal DNA.

DIAGNOSIS

The diagnosis and treatment of mucormycosis are challenging. The incidence of the disease seems to be increasing. Hematological malignancies are the most common underlying disease in countries with high income and uncontrolled diabetes in developing countries. The capability of diagnosing mucormycosis depends on the availability of imaging techniques, trained personnel, and mycological and histological investigations. Patients with suspected mucormycosis should be referred immediately to a facility with the highest care level. In case of any delay, management should be initiated following this guidance document. If all diagnostic options are available, one should follow the management pathway depicted in the (figure4).

Microscopic examination and culture:

Microscopy (direct and histopathology) and culture shown hyphae of Mucorales have variable width (6 -25µm) are nonseptate or pauci-septate [46] and show irregular, ribbon-like appearance. The angle of branching is variable and includes wide-angle (90˚) bifurcations. Tissue histology is governed by inflammation which may be neutrophilic or granulomatous, but not seen in few immunosuppressed patients. The histopathological examination may not allow an authentic differentiation between Aspergillus, and Mucorales. For specialization of Mucorales, rapidly grow (3 – 7days) on most fungal culture media, such as sabouraud and potato dextrose agar incubated at 25 - 30˚C. [47]

Imaging: Radiographical signs suggestion for pulmonary mucormycosis (figure5)

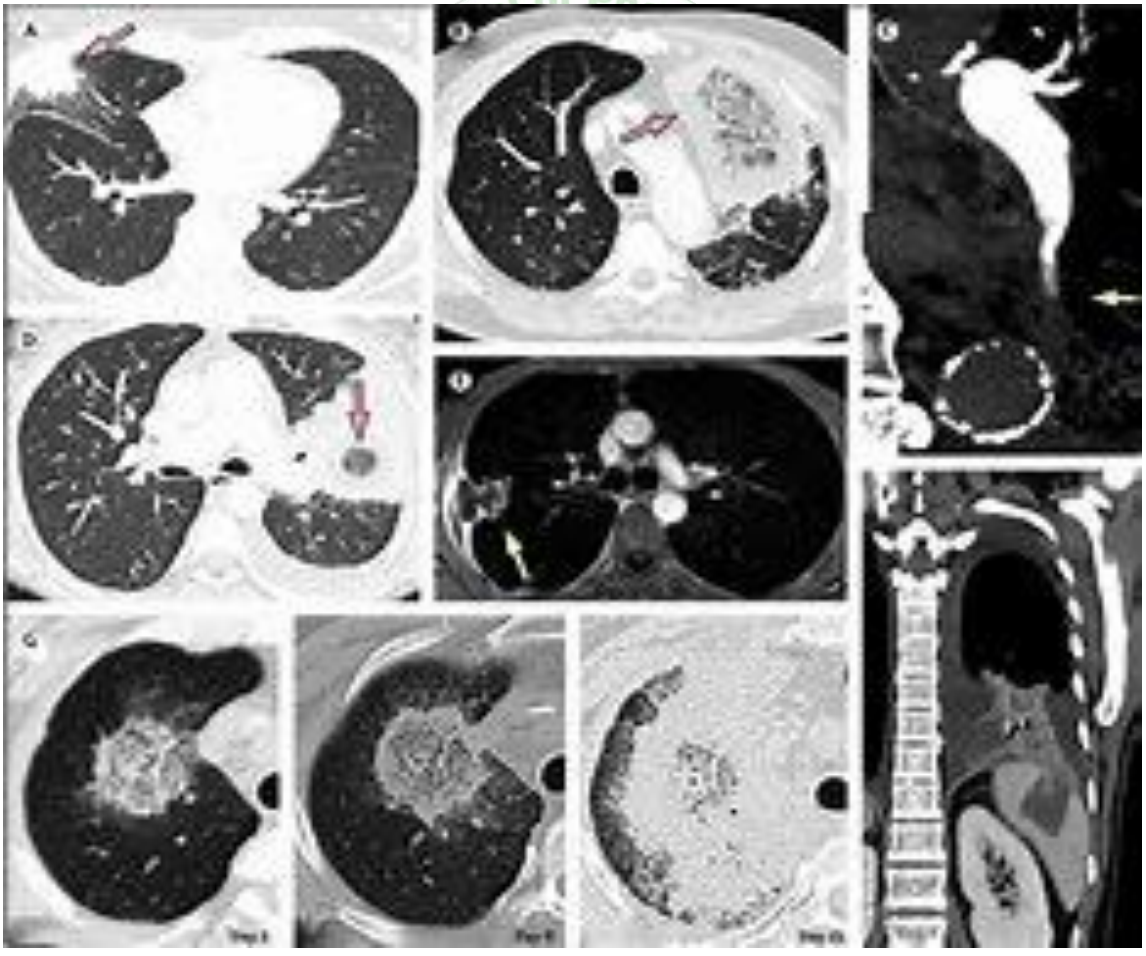

Figure 5: Radiographic signs of mucormycosis Four imaging signs can suggest pulmonary mucormycosis in an appropriate clinical setting.

Molecular assays:

Molecular-based assays include conventional polymerase chain reaction (PCR). [48] Restriction fragment length polymorphism analyses (RFLP), [49] sequencings of defined gene regions. [50] The majority of the molecular assays target either the internal transcribed spacer or the18S r RNA genes. [51]

TREATMENT APPROACH

Mucormycosis: an indication of emergency surgery:

Surgery is necessary due to the massive amount of tissue necrosis occurring during mucormycosis, which may not be prevented by killing the organism. [54] Current guidelines recommend antifungal treatment, surgical debridement, and correction of risk factors. [55]Surgical debridement has to be extensive, involving all necrotic areas for rhino-oculo-cerebral infection, and repeated surgical procedures are recommended to achieve local control and improve outcome 36. For pulmonary mucormycosis, the indication and timing of surgical management outside emergency care (hemoptysis) is still unclear. [56] In a European series of 230 patients, surgical treatment reduced mortality by 79%38, leading to discussion surgery when feasible for any localization, however mandatory for rhino-Cerebro-oculo-cerebral and posttraumatic mucormycosis. [57]

First-line antifungal monotherapy for mucormycosis:

Amphotericin B (Amb) and its lipid formulations are posaconazole were the only antifungal drugs available with in-vitro activity against Mucorales. [58,59] The antifungal armamentarium recently enlarged with the development of isavuconazole.(Table2)

Table2: Recommendations on first-line antifungal monotherapy for mucormycosis by population type

Disease condition	Intention	Interventions	References Study subjects and specific conditions
Any	To cure and to increase survival rates	Amphotericin B, any formulation, escalation to full dose over days	Chamilos1 (N=70, give full daily dose from day 1)
Any	To cure and to increase survival rates	Amphotericin B, liposomal, 5–10 mg/kg per day A	Gleissner144 (N=16, haematology); Pagano109 (N=5); Cornely106 (N=4); Pagano105 (N=44); Rüping67 (N=21); Shoham50 (N=28); Skiada17 (N=130); Lanternier104 (N=34, 18 haematology, six diabetic); Kyvernitakis108 (N=41); Stanzani107 (N=97, increased renal toxicity with cyclosporine)
CNS involvement	To cure	Amphotericin B, liposomal, 10 mg/kg per day, initial 28 days	Ibrahim112 (Animal); Lanternier104 (N=9)
SOT adults	To cure	Amphotericin B, lipid formulation; dose not given	Singh145 (N=25); Sun146 (N=14); Lanternier147 (N=3)
SOT adults	To cure	Amphotericin B, lipid complex; 10 mg/kg per day	Forrest114 (N=6, 3 of 6 died)
Any, without CNS involvement	To cure	Amphotericin B, lipid complex; 5 mg/kg per day	Larkin113 (N=10); Ibrahim112 (animal); Skiada17 (N=7)
Hematological malignancy	To cure	Amphotericin B, liposomal; 1–>5 mg/kg per day ± surgery C Li148 (N=7, 2 of 7 died)	Nosari110 (N=13, 8 of 13 treated, 5/8 died); ; Li148 (N=7, 2 of 7 died)
Any	To cure	Isavuconazole PO or IV; 3 × 200 mg day 1–2, 1 × 200 mg/d from day 3	Marty49 (N=21, 11 hematology, 4 diabetes, overall mortality comparable to amphotericin B formulations)
Any	To cure	Posaconazole DR tablet or intravenously 2 × 300 mg day 1, 1 × 300 mg from day 2 B	Duarte;122 Maertens;124 Cornely;123 Cornely125 (higher trough levels than oral suspension, intravenous bridging when oral dosing not feasible)
Any	To cure	Posaconazole oral suspension; 4× 200 mg/day or 2 ×400 mg/day	Rüping67 (N=8); Skiada17 (N=17); Dannaoui149 (animal, emphasises preference of amphotericin B, liposomal)
Any	To cure	Amphotericin B, deoxycholate, any dose (if alternative therapy available)	Walsh116 (renal toxicity); Pagano109 (N=9); Roden11 (N=532); Ullmann115 (renal toxicity); Chakrabarti66 (N=10); Skiada117 (N=21)
Orbital mucormycosis	To cure	Retrobulbar injection of amphotericin B deoxycholate in addition to systemic therapy	Hirabayashi50 (N=1, post-injection inflammatory response, risk for acute compartment syndrome)
IV=intravenous. PO=per os (taken orally). N=number of individuals. SOT=solid organ transplantation. DR=delayed release.			
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 November 4, 2019, https://doi.org/10.1016/ S1473-3099(19)30312-3			

Immunostimulating drugs:

A case report has recently reported the benefit of treatment with the checkpoint inhibitor nivolumab and interferon-Y for an immunocompetent patient with extensive abdominal mucormycosis unresponsive to conventional therapy.

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