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All You Need To Know About Cutaneous Mucormycosis

M.V. Raghavendra Rao[1], Tina presilla[2], Vishnu Rao.P3, Jahnavi. C[4], ArunaKumari.B[5], S. Jithender Kumar Naik[6], Mahendra Kumar Verma[7]

[1]Scientist-Emeritus and Director, [2,5]Associate Professor, [3]Consultant, [4]Senior Resident,
[6]Professor & Head, [7]Assistant Professor,
[1]Department of Laboratory Medicine, [3]Department of Infectious Diseases,
[4]Department Of General Surgery, [5]Department of Respiratory Medicine,
[6]Department of Zoology, College of Science, Osmania University, Hyderabad, 5500007, TS, India
[7]American University School of Medicine Aruba, Caribbean Islands
[5]ESIC Medical College, Sanathnagar Hyderabad, T India
[1,2,3,4]Apollo institute of Medical Sciences and Research, Hyderabad, TS, India

***Corresponding Author:**
Prof. M.V. Raghavendra Rao
Ph.D, M.D (Medicine) (Hon),D.Sc(Hon), Scientist-Emeritus and Director of Central Research Laboratory, Department of Laboratory Medicine, Apollo Institute of Medical Sciences and Research, Hyderabad, TS, India

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Abstract

Rhizomucor pusillus is an opportunistic fungus that causes infections (mucormycosis) in patients with diabetes mellitus and immunodeficiency.Cutaneous zygomycosis infection caused by zygomycetes that strikes the skin. The fungi are no longer Zygomycetes, they are now currently included in subphylum Mucoromycotina
The natural habitat of Mucoromycotina is soil and mostly colonized in decaying organic matter. Saprophytic Mucoromycotina (e.g., Mucor, Rhizopus) are occasionally found in tissues of compromised hosts, in persons suffering from diabetes mellitus (particularly acidosis), extensive burns, leukemia, lymphoma or other chronic illness or immunosuppression. The organisms are rarely cultured during life but are seen in histologic preparations of tissues as broad nonseptate, irregular hyphae on skin, thrombosed vessels or sinuses with surrounding leukocyte and giant cell response Laceration is paramount to take possession of the disease. It contains primary cutaneous mucor mycotina and secondary cutaneous mucormycotonia clinical forms. Primary cutaneous mucormycotonia is designated by devastating lesions and the fungus is usually injected by trauma. Secondary mucor mycotonia is rhinocerebral variation and penetrates from the cutaneous and subcutaneous tissues into the adjacent fat, muscle, fascia, and bone.
secondary cutaneous mucormycosis can be sec to rhinocerberal mucormycosis or disseminated mucormycosis.The damage or necrosis and the elimination of the competitive influence of a normal bacterial flora by antibiotic may also facilitate fungal infection.

Keywords: Rhizomucor pusillus , Hematologicalmalignancies, Diabetes mellitus, Glucocorticoid, Isavuconazole, posaconazole,(1,3)-β-D-glucan, galactomannan, Amphotericin B

Introduction

Cutaneous Mycormycosis is a rare and lethal fungal infection caused by the family of Mucoraceae, which belongs to the subphylum Mucoromycotina (1) Cutaneous mucormycosis is persistent in unchecked diabetic and individuals with immunosuppression. It is usually acquired by direct inoculation through trauma. (2) Mucormycosis is a rare but severe invasive fungal infection occurring mostly in immunocompromised patients, especially in

individuals diagnosed with uncontrolled diabetes mellitus or hematological malignancies and in previously healthy subjects with open wounds contaminated by Mucorales (3,4). Cutaneous mucormycosis is progressively reported in patients with haematological malignancy, solid organ transplants, and corticosteroid therapy (5). Phenomenon features of cutaneous Mucormycosis skin lesions consist of tender, erythematous, indurated, and necrotic plaques.(6) The possible source of action is amphotericin B, but new azoles, such as posaconazole and isavuconazole, must be considered. (7) Patients with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection might develop coronavirus disease (COVID-19), which can be associated to significant and sustained lymphopenia compromising the immune system, especially in the most severe cases (8). Mucormycosis is an infrequently encountered locally invasive, aggressive fungal infection that frequently occurs in patients with an underlying immunodeficiency. It is usually diagnosed in histopathology and treated with systemic antifungals (9).

COVID-19 patients, especially severely ill or immunocompromised, have a higher probability of suffering from invasive mycoses(12). The infection occurs mainly in immunocompromised patients, especially in individuals diagnosed with uncontrolled diabetes mellitus or haematological malignancies (13). Itraconazole capsule monotherapy (n = 10) was prescribed primarily for cutaneous disease in patients not receiving any immunosuppressive therapy(14). Among the secondary fungal infections in Coronavirus-19 (COVID-19) infection, Aspergillosis has been reported more often than Mucormycosis. Disseminated mucormycosis is almost always a disease of severely immunosuppressed hosts. (15) These skin lesions were infiltrated plaques, ulcers and nodules, which usually remained localized and gradually expanded over months and years (16). The cutaneous type is seen in 10–31% of patients with mucormycosis after trauma following road traffic accidents, burn wounds, intramuscular injection, intravenous catheters, adhesive tapes, and surgical-site infections (17,18).

Chronological record of significant events

First case in humans reported in 1885 by FriedrichKüchenmeister (19). Fürbringer first described the disease in the lungs in 1876 (20). Gregory first observed the rhino-orbital cerebral mycormycosis in 1943. About 250 million years ago, fungi became abundant in many areas, based on the fossil record. (21) Since fungi do not bio mineralize, they do not readily enter the fossil record. (22). One from the Ordovician has been dismissed because it lacks any distinctly fungal features and is held by many to be contaminated (23).

The spectrum of cutaneous mucormycotenia

Cell wall of the fungus contains chitin, a polymer of N-acetylglucosamine, rather than peptidoglycan. Mucormycosis refers to a fungal infection caused by fungi in the order Mucorales. Species in genera Mucor, Rhizopus, Lichtheimia, Mucor, Rhizomucor, Absidia and Cunninghamella are often the cause of infection. Primary cutaneous mucormycosis is usually related to traumatic injuries, but immunocompromised cases are associated with underlying conditions such as diabetes mellitus and malignancies. The cutaneous lesions induced by the mucormycosis affection are often atypical and gangrenous. Cutaneous zygomycosis, which is mainly observed in diabetic and burns patients. The fungus enters through a cut, scrape, and burn. Cutaneous mucormycosis is the third most common form of the disease, after pulmonary and rhino-cerebral. The predisposing factors of this infection are haematological malignancies, diabetes mellitus, and immunocompetent (24).Further progression into deeper tissue affecting muscles, tendons or bone is possible (25). Mucormycosis is rare but serious sequelae of penetrating trauma. In spite of aggressive management, mortality remains high due to dissemination of infection (26). In India, 45–79% of cutaneous mucormycosis patients had trauma. Kaushik et al. reviewed cutaneous mucormycosis cases from India and reported trauma as arisk factor in 59% of the cases, followed by diabetes mellitus (28%) and malignancy (6%) (27). A global study on cutaneous mucormycosis reported that 43–67% of patients were immunocompetent hosts, and other risk factors were diabetes mellitus (10–15%), malignancy (12–23%).

Who is susceptible to cutaneous mucormycosis infections?

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1. Hypo immunity patients are more susceptible to infection.
2. Diabetes reduces immune response.
3. Hyperglycaemia in acidic environment particularly in diabetic ketoacidosis boost up the rapid growth
4. Steroids escalate blood sugar levels and decline the immune response of the body.
5. Patients on immunosuppressants
6. Patients suffering from malignancies
7. Patients with iron overdose
8. Malnourished, trauma, and burn people.

About frontiers of cutaneous mycormycosis

Few among millions of fungal species fulfil four basic conditions necessary to infect humans. High temperature tolerance, ability to invade the human host, lyses and absorption of human tissue, and resistance to human immune system. Fungal infections are among the most difficult diseases to manage in humans. Some fungi cause disease in healthy people, but most fungal infections occur in individuals already experiencing serious illness, and frequently jeopardize the success of newest medical advances in cancer care, solid organ and hematopoietic stem cell transplantation, neonatalmedicine, autoimmune disease therapies, trauma and intensive care and sophisticated surgery.

Animal Models to Study Mucormycosis

Various model hosts, ranging from mammalian species such as laboratory mice over other vertebrates to alternative invertebrate hosts, have been employed to analysepathogenesis andthe impact of potential risk factors on infection, to compare the virulence of mucoralean species and strains, and to determine the efficacy of antifungals. Mucormycosis is a rare but often fatal or debilitating infection caused by a diversgroup of fungi. Animal models have been crucial in advancing our knowledge of mechanisms influencing mucormycosis's pathogenesis and evaluating therapeutic strategies. In general, mammalian species are considered the gold standard for studying human diseases due to similarities in anatomy and physiology. Various animal models have been developed in mice and rats to study type 1 and type 2 diabetes. (28) Indeed, various species, ranging from laboratory mice, rats, guinea pigs, and rabbits, or Asian water buffalo calves can be infected experimentally with pathogenic micromycetes (29). Most studies, however, used mice or rabbits (30).

How can fungus cripple your immune system?

Relatively little is known about the immune response to fungal agents. Cellular immunity appears to be the most important immunological factor in resistance to fungal infections, although humoral antibodies certainly may play a role. Th1-type responses are protective via release of IFN-y . By constant Th2 responses (IL-4 and IL-10) typically correlate with disease exacerbation and pathology. The importance of cellular reactions is directed by the intense mononuclear reactions is indicated by the intense mononuclear infiltrate and granulomatous reactions that occur in tissues infected with fungi and by the fact that fungal infections are frequently associated with depressed immune reactivity of the delayed type (Opportunistic infections). This increase is IL-3 dependent.IL-3 is important for the recruitment of basophil into mediastinal lymph nodes following Nippostrongylus Brasiliensis infection. (31). Life-threatening fungal infections have risen sharply in recent years, owing to advances and intensity of medical care that may blunt immunity in patients. These insights create a foundation for the development of new immune-based strategies for prevention or enhanced clearance of fungal diseases. (32).

The aggressive nature of the mucormycosis, excessive infection and the poor therapeutics and the failure of the human immune system shoot up the high mortality rates (50–100%). The first line of defence against Mucorales is the epithelial cells that are encountered at the initial sites of infection, such as alveoli and skin epithelia (33). Spores are resistant to phagocytic killing. The chief function of macrophages is to engulf, degrade, and present pathogenic antigens. The muckrakes obstructs immune response (34). As a result of excess cortisone treatment, immunity is reduced; macrophage and neutrophils loose the vigor, vitality and physiological efficiency of their original activity against mucormycetes. Macrophages and neutrophils are unable to degrade the swollen spores and hyphae.

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Mucorales confronts platelets and penetrates into the endothelial cells. Neutrophils are the most abundant type of leukocytes found in the blood, and are rapidly recruited to the site of pathogenic infection (35).

The Portrayal of Biomarkers in clinical fungal infection

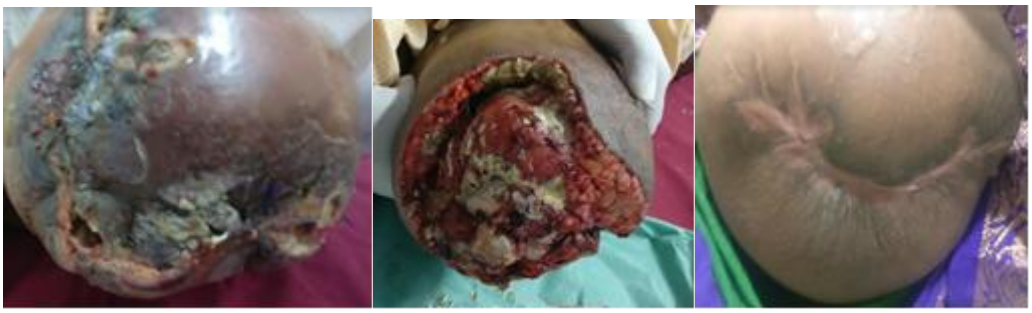
Biomarkers can be specific cells, molecules, orgenes, gene products, enzymes or hormones. Complex organ functions or general characteristic changes in biological structures can also serve as biomarkers. Biomarkers may play a predominant role in the diagnosis of fungal infections. Good research is required to regulate the best game plan for clinical use.(36)

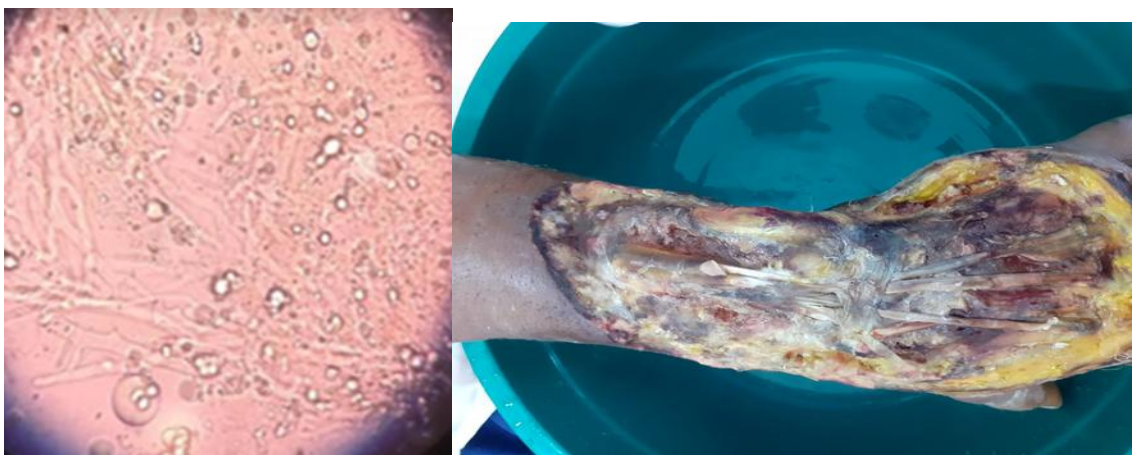
(1,3)-β-D-glucan

The pan fungal β-D-glucan test and *Aspergillus* galactomannan tests do not detect antigen components of the Mucorales cell wall, and a positive test is assumed to provide strong evidence for excluding mucormycetes as causative agents of infection, even though comprehensive evidence-based data supporting this statement are lacking (37). (1,3)-β-D glucan is an important structural component of the majority of fungal cell walls. Fungi that are known to have higher concentrations of BG in their cell walls include *Candida, Saccharomyces, Trichosporon, Spo-rothrix, Penicillium, Fusarium,* and *Aspergills.* In general terms, molds such as *Scedosporium* and the agents of mucormycosis tend to have lower concentrations (38).

Case Report

A 45 year old female presented with non healing wounds with blackish discolouration at the amputedsite. Patient had a road traffic accident with soft tissue injury and fracture of right tibia.She was subjected to multiple debridements and finally with above knee amputation .Multiple Swabs showed growth of klebsiella, enterococcus, Pseudomonas MDR. Patient was put on Meropenam/Forcan/Teicoplanin with not much of improvement. Suspecting Mucormycosis, amputated stump debrided tissue was sent for KOH smear, Culture and Histopathology. All the test results confirmed the diagnosis of Mucormycosis. Patient was subjected to extensive debridement and managed with combination treatments with liposomal Amphotercinb and iv posaconazole for 6 weeks with step down to oral posaconazolefor 3 months. Patient responded well to the treatment with regular follow-ups and no recurrences.





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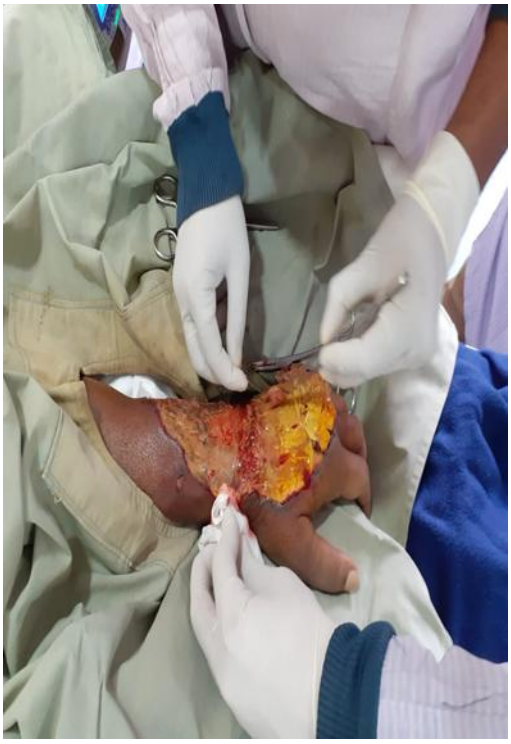

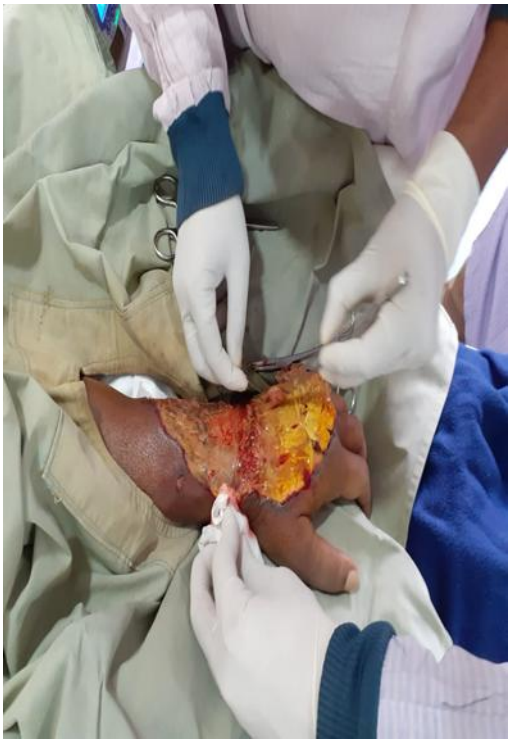

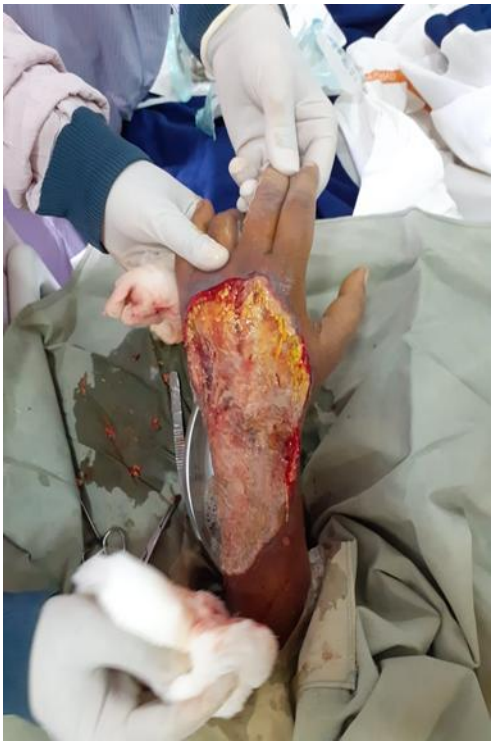

Nosocomial Mucor At Cannula Site Due To? Adhesive Tape Contamination

How is mucormycosis diagnosed?

Accurate diagnosis of mucormycosis, a life-threatening fungal infection, remains a challenge for physicians. Mucormycosis is difficult to diagnose. Mucormycosis infections are quickly advancing and fatal. Though direct microscopy is positive, cultures are often negative. Conventional diagnostic approaches are often unresponsive and undetermined. Molecular assays are encouraging. In the past, various techniques, such as ELISA, immunoblots and immunodiffusion tests, have been designed for the diagnosis of mucormycosis, yet with variable success. Supplements Semi nested PCR targeting 18S rDNA region of Mucorales is useful for

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identification of the causative agents of mucormycosis. Seminested real-time PCR uses mucormycetes-specific primers and is followed by species identification using high-resolution melt (HRM) analysis.A PCR strategy selectively amplifies genomic DNA from molds belonging to the genera Absidia, Mucor, Rhizopus, and Rhizomucor, excluding human DNA and DNA from other filamentous fungi and yeasts. A subsequent digestion step identified the Mucorales at genus and species level. The diagnosis is often difficult and yet a fast, accurate diagnosis is of fundamental importance for treating the infection and planning subsequent management of the fungal disease. One method of evaluation of fungus is sensitivity of computed tomography (CT)-guided percutaneous biopsy in diagnosing fungal infections. CT-guided lung biopsies have high diagnostic accuracy in terms of microscopic examination, and complication rates are low. Molecular-based and antigen tests applied on fungal hyphae-positive specimens showed comparable results. (40)

Serodiagnosis, Biotechnology and Molecular Diagnosis of Mucormycosis.

Wet mount, Gram Stain, BHI broth, Fungal culture, Blood culture Biotechnology and Molecular Diagnosis of Mucormycosis. PCR, RFLP, DNA sequencing that targets the 18S ribosomal DNA of Mucorales, Antigen Detection & Specific T cells. Galactomannan and ß-D Glucan – If negative, likely invasive mucormycosis than IPA. Mucorales-specific T cells - enzyme-linked immunospot (ELISpot) assay, Sequencing of Internal Transcribed Spacer (ITS) of rRNA techniques.

Management of cutaneous mucormycosis

The management protocol includes a multidisciplinary approach for salvaging patients of cutaneous mucormycosis.

Basic principles in the management of mucormycosis

1. High index of suspicion ,
2. Expedating early prompt clinical and laboratory diagnosis, risk stratification for severity of the diseases
3. Timely initiation of an effective antifungal therapy (monotherapy or combination therapy).
4. Aggressive surgical debridement of necrotic lesions along with antifungal therapy
5. Reverse of risk factors and immunosuppression
6. Control of the underlying medical condition

First line therapies

1. 1.Surgical debridement
2. 2.Antifungal therapy
3. 3.Control of underlying conditons
4. 4.Hyperbaric oxygen

Second line therapies

1. Combination therapies

I. Surgical debridement:

i. Surgical debridement is the treatment of choice to halt the progress and control of infection.

ii. Immediate aggressive surgical debridement of necrotic tissue should take place and plays a critical for salvaging patients of cutaneous mucormycosis.

iii. It is usually used in combination with antifungal therapy

II. Antifungal therapies:

A. Amphotercin B

i. It is the drug of choice for cutaneous mucormycosis

ii. Lipid formulations of amphotericin B (liposomal AMB, LAMB; and AMB lipid complex, ABLC) are the preferredfirst line drugs as they have have better therapeutic index and better safety profile than the Conventional amphotericin B deoxycholate

iii. Treatment should be initiated within first 5 days at the earliest

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iv. Recommended dose is intravenous 5mg/kg which could be incremented on an individual basis

v. High dose L-AMB was associated with increased nephrotoxicity and electrolyte derangements.

vi. Topical AmB has been used in the form ofwashes , 5% sulfamylon–amphotericin B (2 μg/ml) dressings], daily topical infusions through dressings (50 mg L-AmB diluted in 1L of sterile water) , soaks or gauze soaked in 0.2 % AmB solution

vii. The duration of treatment varies with the clinical picture and is subjective to the clinical and radiological response

B. Azoles

i. Isavuconazole: It is approved for the treatment of mucormycosis when amphotericin B is not feasible. It is available in both intravenous and oral formulations and it is administered with a loading dose of 200 mg three times a day for two days and 200 mg daily thereafter.

ii. Posaconazole (oral suspension 400 mg × 2/day when taken with meals, or 200 mg × 4/day if not taken with meals) may be considered as salvage treatment of mucormycosis. First–line treatment with posaconazole is considered only in cases when treatment with AMB is absolutely contraindicated

iii. Posaconazole has syrup and tablet formulation. Tablet is preferred

III. Adjunctive therapies

i. Used to reverse immunosuppression

ii. Granulocyte (macrophage) colonystimulating factor or interferon-γ have been tried

iii. Deferasirox,ironchelator have proved to be beneficial in ketoacidosis and ketoacidosis

Hyperbaric oxygen (increased oxygen pressure)treatment improve the functionality of neutrophils which inhibits fungal growth and improves the rate of wound healing especially in diabetics

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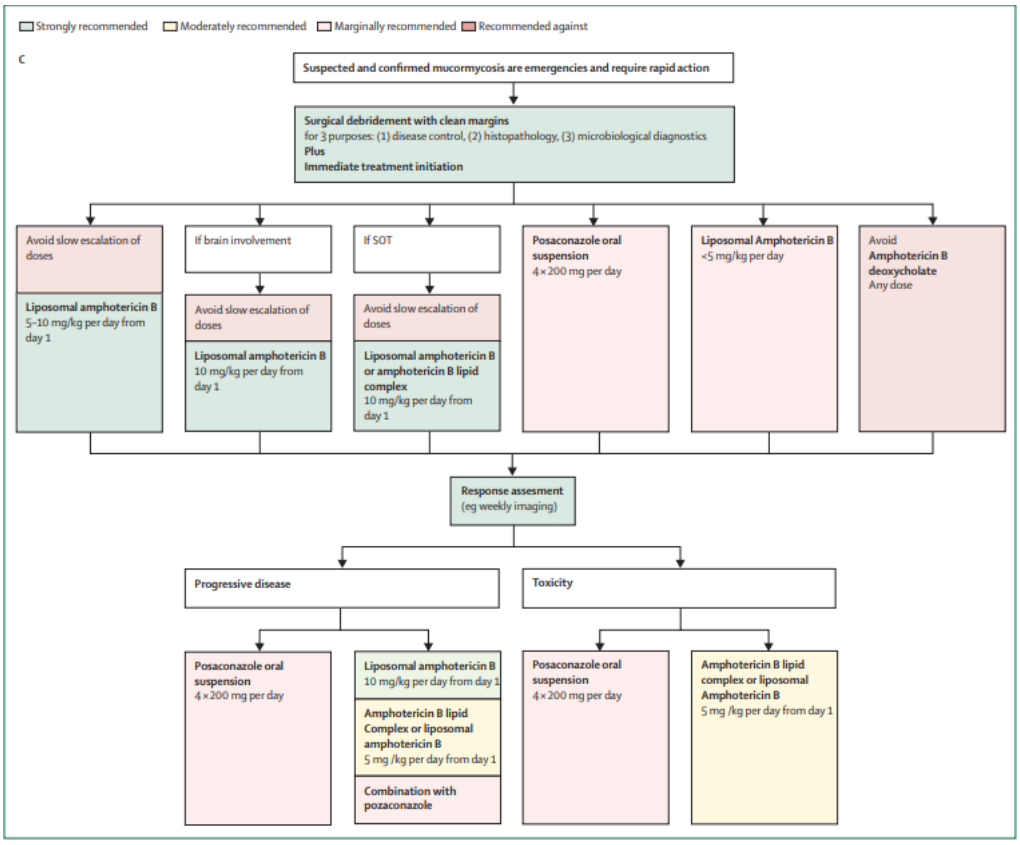

Table 9. ECIL-6 recommendations for first-line therapy of mucormycosis.

	Grade	Comments
Management includes antifungal therapy, surgery and control of underlying conditions	A II	Multidisciplinary approach is required
Antifungal therapy		
Amphotericin B deoxycholate	C II	
Liposomal amphotericin B	B II	Daily dose: 5 mg/kg. Liposomal amphotericin B should be preferred in CNS infection and/or renal failure
Amphotericin B lipid complex	B II	
Amphotericin B colloidal dispersion	C II	
Posaconazole	C III	No data to support its use as first-line treatment. Alternative when amphotericin B formulations are absolutely contraindicated.
Combination therapy	C III	
Control of underlying condition	A II	Includes control of diabetes, hematopoietic growth factor if neutropenia, discontinuation/tapering of steroids, reduction of immunosuppressive therapy
Surgery		
Rhino-orbito-cerebral infection	A II	
Soft tissue infection	A II	
Localized pulmonary lesion	B III	
Disseminated infection	C III	Surgery should be considered on a case by case basis, using a multi-disciplinary approach
Hyperbaric oxygen	C III	
Recommendation against use		
Combination with deferasirox	A II	

CNS: central nervous system.

Table 10. ECIL-6 recommendations for salvage and maintenance therapy of mucormycosis.

	Grade	Comments
Salvage therapy		
Management includes antifungal therapy, control of underlying disease and surgery	A II	
Posaconazole	B II	
Combination of lipid amphotericin B and caspofungin	B III	
Combination of lipid amphotericin B and posaconazole	B III	
Maintenance therapy		
Posaconazole	B III	Overlap of a few days with first-line therapy to obtain appropriate serum levels. Monitoring of serum levels might be indicated[a]

[a]Both comments apply to the oral solution but may not apply to the solid oral formulation.

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Table 4. ECIL-3 recommendations for second-line and maintenance treatment of mucormycosis.

Second-line treatment: first-line treatment intolerance or failure[1]	
Posaconazole 400 mg bid[52,53]	BII
Combination lipid AmB and caspofungin[39]	BII
Combination lipid AmB and posaconazole	CIII
Combination with deferasirox NOT recommended[104]	AI
Maintenance therapy Posaconazole	BIII[2]

Strength of recommendations		
Grade	ECIL-1 to 4	ECIL-5 and 6
A	Strong evidence for efficacy and substantial clinical benefit: strongly recommended	Good evidence to support a recommendation for use
B	Strong or moderate evidence for efficacy, but only limited clinical benefit: generally recommended	Moderate evidence to support a recommendation for use
C	Insufficient evidence for efficacy; or efficacy does not outweigh possible adverse consequences (e.g. drug toxicity or interactions) or cost of chemoprophylaxis or alternative approaches: optional	Poor evidence to support a recommendation for use
D	Moderate evidence against efficacy or for adverse outcome: generally not recommended	Omitted
E	Strong evidence against efficacy or for adverse outcome: never recommended	Omitted
Quality of evidence		
Grade	ECIL-1 to 6 (no change)	
I	Evidence from ≥ 1 properly randomized, controlled trial	
II	Evidence from ≥ 1 well-designed clinical trial, without randomization; from cohort or case-controlled analytical studies (preferably from > 1 center); from multiple time-series; or from dramatic results from uncontrolled experiments	
III	Evidence from opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees	

ECIL: European Conference on Infections in Leukemia.

Discovery without boundaries

Unchecked diabetes makes an appearance as a crucial element in acquiring Cutaneous Mucormycosis infection which flares up in Covid-19 patients after convalescence to further complications. The fungi have potential to flourish and cause damage under filthy conditions, "Moisture in the environment, dirty domains and can be a big source of infection. Covid-19-associated mucormycosis showed 94% of patients had diabetes.

Future directions and challenges

Diabetes may escalate the probability of developing Cutaneous Mucormycosis Infection Post COVID-19. Steroids and tocilizumab drugs decrease immunity. Individuals more susceptible to opportunistic infection like mucormycosis," Professionals suggest that the indiscriminate use of steroids for Covid treatments could be linked to mucormycosis or other fungal infections. Two extensively recommended steroids are dexamethasone and methylprednisolone. These are drugs that reduce the inflammation caused by the body's immune response for Covidpatients. Steroids and IL-6 inhibitors (tocilizumab) decrease immunity.COVID-19 also decreases immunity thus leading to further immune suppression.

An opinion arrived at through a process of reasoning

Mucormycosis is an emerging invasive fungal disease that requires a high level of clinical skill for a prompt clinical diagnosis in order to improve survival. The Covid-19 pandemic harmed our memories. Causalities with diabetic ketoacidosis (DKA) and Covid-19, are exclusively activated to

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Cutaneous mucormycosis, an angioinvasive fungal infection with high mortality. Primary cutaneous zygomycosis is designated by devastating lesions and the fungus is usually injected by trauma. Secondary zygomycosis is rhinocerebral variation and penetrates from the cutaneous and subcutaneous tissues into the adjacent fat, muscle, fascia, and bone. Most fungi encountered by man are harmless saprophytes, but some species may in certain circumstances infect human tissue or promote damaging allergic reactions. Predisposing factors include metabolic disorders, such as diabetes mellitus, toxic states such as chronic alcoholism, diseases such as leukaemia and myelomatosis in which immunological responses are disturbed, treatment with corticosteroids and immunosuppressive drugs and radiotherapy. Local factors such as tissue damage by suppuration or necrosis and the elimination of the competitive influence of normal fungal infections. Mucormycosis can be displayed in distinctive clinical designs and locations. The correct identification is frequently tough, and early recognition is crucial for patients' endurance. Tissue scrutiny by histopathology and culture endorse the fungal infection Current molecular tests should be used to accelerate diagnosis. Amphotericin B is considered as first-line therapy combined with surgery; second generation azoles derivatives can also be used.

Summary

Antifungal therapies associated with surgical debridement are the standard treatments. Antifungal therapies kill fungi or put a stop to growing and thriving. Antifungal drugs are available as creams or ointments. Initial treatment is Amphotericin B from 2-8 weeks based on severity and step down to posaconazole once disease burden is reduced and then continue till complete clinical resolution. A humoral antibody certainly may play a role.Th-1 type responses are protective via release of IFN-y.Cellular immunity comes into view as the most essential immunological factor in resistance to fungal infection.SARS-CoV-2 infection is regarded as a cause of severe immunosuppression that might compromise the host response and increase the risk to develop opportunistic infections, including those caused by moulds, leading to higher risk of negative outcomes in the case of delayed diagnosis and inadequate treatment.

Conclusion

Mucormycosis is an elegant,and aggressive fungal infection affecting the rhino-orbital, respiratory, gastrointestinal or cutaneous systems. Cutaneous mucormycosis , infected area turn black and look like **ulcers or blisters**, .Therapy for cutaneous mucormycosis approved by FDA ,is either amphotericin B deoxycholate at high doses (1.0-1.5mg/kg/day); or lipid formulations of amphotericin B.

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