BMJ Best Practice

Mucormycosis

Straight to the point of care

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Summary

Mucormycosis is predominantly a disease of immunocompromised patients.

Five types are commonly described: rhino-orbito-cerebral (most common), pulmonary, cutaneous, disseminated, and gastrointestinal (rare).

Definitive diagnosis requires positive fungal culture or detection of fungal DNA through molecular testing (where available).

Rhinocerebral mucormycosis commonly occurs in patients with diabetes mellitus and presents with headache, visual changes, sinusitis, and, later, proptosis.

Pulmonary mucormycosis commonly presents as a cough in patients with underlying malignancy or transplant (bone marrow or solid organ). Late diagnosis may result in dissemination, leading to high mortality.

High level of suspicion and early institution of combined medical therapy with amphotericin-B, surgical treatment, and immune restoration is essential for good outcomes.

Definition

Mucormycosis is a group of mold infections caused by fungi in the order Murocales.[1] [2] The most common manifestations are rhino-orbito-cerebral and pulmonary infections, followed by cutaneous, disseminated, and gastrointestinal infections.[3] [4]

Epidemiology

The incidence of mucormycosis is significantly lower than those of invasive *Candida* or *Aspergillus* infections, by about 10- to 50-fold.[3]

There is no national surveillance for mucormycosis in the US, making it difficult to determine exact case numbers and trends.[8] The estimated incidence in the US is about 1.7 cases per million per year, or 500 cases annually.[3] [9] In 2014, 1140 mucormycosis-related hospitalizations occurred in the US.[10]

This disease is more commonly encountered in the immunosuppressed population, but cases in immunocompetent hosts have been described with organisms in the order Entomophthorales.[11] The most vulnerable hosts are those with diabetes mellitus (with or without ketoacidosis), hematologic malignancies, solid organ or bone marrow transplants, history of corticosteroid use, and graft-versus-host disease.[4] [12] [13]

Prematurity is a major underlying factor for acquiring the disease in neonates.[14] Gastrointestinal and cutaneous disease is more common in neonates than in older children and adults. Neonates are also at increased risk for disseminated disease. Overall mortality is 64% in neonates compared with 56% in children more than a month old and less than 18 years of age. Disseminated infection and age less than 12 months are independent risk factors for increased mortality.[15]

In adults, rhino-orbito-cerebral disease is the most common presentation (44% to 49%), followed by cutaneous (10% to 16%), pulmonary (10% to 11%), disseminated (6% to 11.6%), and gastrointestinal (2% to 11%).[16] Rhino-orbito-cerebral is more common in patients with diabetes, whereas pulmonary manifestation is more typical of patients with hematologic malignancies or transplants. The incidence in a study over a 10-year period among transplant recipients, per 1000 patients, was 0.4 to 0.5 in renal transplant recipients, 8 in heart transplant recipients, 4 to 6 in liver transplant recipients, and 13.7 to 14 in lung transplant recipients.[3]

Most cases of mucormycosis are sporadic, though rare outbreaks have occurred in healthcare settings, often linked to nonsterile products such as contaminated bandages, linens, drugs, and food.[4] [17] [18][19] Invasive procedures such as surgery, dental extractions, and tube insertions, as well as medical devices like insulin pumps, finger sticks, and ostomy bags, have also been implicated in transmission.[17] Outbreaks have also been reported following natural disasters, likely due to increased environmental exposure to fungal spores.[4] [20]

Mucormycosis has been increasingly reported in patients with coronavirus disease 2019 (COVID-19), particularly in patients who have diabetes mellitus and have also received corticosteroids.[21] [22] [23][24] [25] [26] [27]

Etiology

Mucormycosis is a group of mold infections caused by fungi in the order Murocales.[1] [2]

Agents of mucormycosis are ubiquitous in soil and can be found on decaying organic matter such as food, hay, and vegetation.[2] Carbohydrate substrates promote rapid growth of hyphae and asexual sporangiospores to help efficient dissemination into the environment. The most common mode of acquiring infection is through inhalation, although infection can also be acquired through cutaneous and subcutaneous inoculation.

The characteristic features of the agents of mucormycosis are broad hyphae.[28]

- In culture: nonseptate hyphae and sporangia containing sporangiospores supported by sporangiophores.
- In tissue: aseptate to minimally septate hyphae branching at 90°.

Pathophysiology

Inhalation of spores is the most common mode of entry. The spores then germinate to produce hyphae, which invade blood vessels, causing thrombosis and subsequent tissue necrosis. Invasion of the vessels also promotes dissemination of the fungus to other organs. Normal mononuclear and polymorphonuclear phagocytes are essential to kill Mucorales by generating oxidative metabolites and cationic peptide defensins.[9] Macrophages inhibit spore germination and neutrophils damage hyphae.

Various factors increase the risk of acquiring mucormycosis by impairing either quantity of neutrophils, as in chemotherapy-induced neutropenia, or quality of neutrophils, as with corticosteroids and acidosis.

Hyperglycemia and acidosis interfere with the oxidative and nonoxidative ability of the phagocytes to move toward and kill the organisms. Macrophage function to prevent germination of spores in vitro and in vivo is affected by corticosteroids in animal models. The exact mechanisms for the above actions are unknown.[3] When applicable, reversal of acidosis in addition to early recognition, with appropriate treatment, results in better outcomes.

Experimental evidence suggests the role of iron in the pathogenesis of mucormycosis. Deferoxamine, an iron chelator (a siderophore), forms a complex with iron that stimulates growth of *Rhizopus* in vitro and pathogenicity in vivo.[29]

Pregerminated spores of *R oryzae* can adhere to the subendothelial matrix. These spores can cause damage after phagocytosis by the endothelial cells. Spore viability is not required to cause cell damage, implying that cidal antifungal agents do not affect the clinical course in established disease.[3]

Classification

Taxonomic classification of clinically significant agents of mucormycosis

Mucormycosis was previously known as zygomycosis, from the phylum Zygomycota. However, molecular studies have led to the taxonomic reclassification of a number of fungal groups. Phylogenetic analysis led to the reclassification of the phylum Zygomycota, which was replaced by two distinct phyla: Zoopagomycota and Mucoromycota. Mucoromycota is further divided into three subphyla: Glomeromycotina, Mortierellomycotina, and Mucoromycotina, with the latter encompassing the orders Mucorales, Umbelopsidales, and Endogenales.[1] The Entomophthoromycetes, now classified under Zoopagomycota, are not included in mucormycosis, but are included in the former term zygomycosis.[5] Infections by Mucorales are called mucormycosis, while those by Entomophthorales are termed entomophthoromycosis.[1] [6] The taxonomic classification of these fungi is an active area of research, a full review of which is out of the scope of this topic.

Order: Mucorales

- Organisms in this group can cause fatal infections in the immunocompromised host.

- Mucorales comprises 55 genera and 261 species, with 11 genera and 39 species known to cause human infections. Clinically significant genera include:[1] [6]
    - *Actinomucor* (species: *A elegans*)
    - *Apophysomyces* (species: *A mexicanus*; *A ossiformis*; *A trapeziformis*; *A variabilis*)
    - *Cokeromyces* (species: *C recurvatus*)
    - *Cunninghamella* (species: *C arunalokei*; *C bertholletiae*; *C blakesleeana*; *C echinulata*; *C elegans*)
    - *Lichtheimia* (species: *L corymbifera*; *L ornata*; *L ramosa*)
    - *Mucor* (species: *M amphibiorum*; *M circinelloides*; *M griseocyanus*; *M indicus*; *M irregularis*; *M janssenii*; *M lusitanicus*; *M plumbeus*; *M racemosus*; *M ramosissimus*; *M variicolumellatus*; *M velutinosus*)
    - *Rhizomucor* (species: *R miehei*; *R pusillus*)
    - *Rhizopus* (species: *R arrhizus* [including var. *arrhizus* and var. *delemar*]; *R homothallicus*; *R microsporus*; *R schipperae*)
    - *Saksenaea* (species: *S erythrospora*; *S loutrophoriformis*; *S trapezispora*; *S vasiformis*)
    - *Syncephalastrum* (species: *S racemosum*)
    - *Thamnostylum* (species: *T lucknowense*)

Order: Entomophthorales

- Infections from these organisms would not be considered mucormycosis, but were included in the former term zygomycosis.
- Organisms in this group usually cause indolent skin, subcutaneous, nasal, and sinus infections in immunocompetent people in tropical and subtropical regions.
- Only two genera are implicated in human infection, including:[5]
    - *Conidiobolus* (species: *C coronatus*; *C incongruus* ; *C lamprauges*)
    - *Basidiobolus* (species: *B ranarum)* .

Case history

Case history #1

A 35-year-old man with a history of type 1 diabetes, illicit drug use, and noncompliance with insulin therapy presents with a 2- to 3-day complaint of left facial and eye pain, blurred vision, proptosis, and purplish discoloration of the periorbital area.

Case history #2

A 25-year-old woman with a recent diagnosis of acute myeloid leukemia undergoes induction chemotherapy resulting in prolonged neutropenia. Her course is complicated with neutropenic fever, for which she is treated with vancomycin and cefepime for 7 days with no definite source identified. Fever resolves in 48 hours and the antibiotics are stopped. She now has a dry cough, occasional hemoptysis, and febrile episodes. Computed tomography scan of the chest reveals nodular pulmonary infiltrates, which do not respond to empiric therapy with voriconazole.

Other presentations

Mucormycosis may present as a primary cutaneous disease involving surgical scars, catheter insertion sites, or burn wounds in immunosuppressed patients. A typical manifestation is necrosis of the involved skin, subcutaneous tissue and, in some cases, the fascia, muscles, and bone. Necrotizing fasciitis may complicate this disease. Cutaneous involvement, as a part of disseminated disease, is rare and is characterized by multiple nodular lesions, which rapidly progress, with development of an ecchymotic center. Gastrointestinal involvement is rare but fatal, often presenting with signs and symptoms of peritonitis due to bowel perforation.[7]

Approach

Mucormycosis infections progress rapidly and can be fatal without early diagnosis and prompt treatment. A high index of suspicion is crucial, particularly in immunosuppressed patients, and should be guided by clinical presentation, radiologic findings, histopathologic exam of the affected tissue, and recognition of presenting signs and symptoms.[38] Definitive diagnosis requires positive fungal culture or detection of fungal DNA through molecular testing (where available).[12] Molecular-based detection techniques are not yet fully standardized or commercially available; however, they show promise for improving the rapid and accurate diagnosis of mucormycosis.[4] Recommended test availability may vary by region.[12]

Clinical presentation

Typical symptoms and signs of mucormycosis in a susceptible patient should be actively pursued. Risk factors include poorly-controlled diabetes mellitus with or without ketoacidosis, bone marrow or solid organ transplant, graft-versus-host disease, hematologic malignancy, corticosteroid therapy, iron overload, iron chelation therapy with deferoxamine, malnourishment, prematurity in newborns, burns, traumatic inoculation, and illicit drug use.

Rhino-orbito-cerebral disease commonly presents with facial pain; sinusitis, which may be accompanied by a viscid, dark brown or black nasal discharge; eye pain; blurred vision; and proptosis.[4] Periorbital cellulitis is also common.[3] Any of these clinical findings in a patient with diabetes mellitus necessitates prompt investigation for mucormycosis since the illness may be aggressive and can be fatal. Involvement of cranial nerves resulting in cranial nerve palsies is an ominous sign and indicates invasion into the central nervous system. Ophthalmoplegia commonly results from the spread of untreated infection from the ethmoid sinuses. Involvement of the contralateral eye signifies cavernous sinus thrombosis. Thrombosis of the internal carotid artery can lead to neurologic deficits and altered mental status. Necrotic eschar on the skin, palate, or nasal turbinates is common in the later stages of the infection.[4] This appearance is due to thrombosis of the vessel by the invading fungus and subsequent tissue infarction.

Typically a dry cough (with or without dyspnea), fever, and chest pain are common symptoms in pulmonary mucormycosis.[4] In patients with hematologic malignancies, initial respiratory symptoms are often attributed to invasive aspergillosis and usually treated with voriconazole or echinocandins, drugs not active against mucormycosis. However, persistence or worsening of symptoms should heighten suspicion of mucormycosis. Another clinical feature that may help differentiate pulmonary mucormycosis from aspergillosis is the higher incidence of accompanying sinus disease in mucormycosis.[39] Hemoptysis can be massive and fatal. Death usually results from dissemination rather than respiratory failure in untreated cases except in hemoptysis. Overall mortality is high, 50% to 70%, and is more than 95% in disseminated disease.[3]

Cutaneous mucormycosis is usually a locally invasive disease, with nodules extending to the soft tissue, fascia, muscles, and even bone. This deep extension into the soft tissues and beyond occurs in about 44% of the patients with cutaneous disease.[40] It usually presents in otherwise immunocompetent patients as a result of traumatic inoculation, dressings, or burns. Skin nodules are more common when skin is involved as a part of disseminated disease. Mortality can be over 80% in very locally invasive disease in an immunocompromised host without extensive surgery.[3] Two types of cutaneous disease have been described: central and peripheral (involving only the extremities). Central cutaneous disease has a mortality of 32% compared with 15.5% in peripheral disease. This difference may be due to

less immunosuppression and better ability to surgically control the disease in the case of peripheral disease.[41]

Gastrointestinal (GI) mucormycosis is a rare condition except in extremely malnourished people and premature neonates.[4] An outbreak of GI mucormycosis was identified due to contamination of wooden tongue depressors used to mix nasogastric feeds.[3] It presents with nonspecific symptoms of abdominal pain and distension, and GI bleeding. GI ulcers and subsequent perforation of the bowel can also occur, resulting in peritonitis.[3] [42] GI mucormycosis is rapidly fatal and most commonly diagnosed post mortem.

Rapid clinical deterioration is a cause for alarm. Even in the presence of a presumptive diagnosis of mucormycosis and appropriate therapy, continued clinical assessment should be done to evaluate for any signs of dissemination of localized disease. Disseminated disease is involvement of 2 or more noncontiguous organ systems and/or positive blood cultures. Disseminated disease could manifest as nodular skin lesions or metastatic brain abscesses. The spleen, heart, skin, and other organs can also be affected.[4]

Laboratory

Routine blood work is rarely diagnostic of mucormycosis but may help in elucidating the underlying risk factor. Patients with diabetes mellitus should have blood chemistry, arterial blood gas, and urinary and serum ketones analyzed to detect the presence of metabolic acidosis. Patients with an underlying malignancy or suspected immunosuppression require a complete blood count to look for neutropenia.

Imaging

In the presence of compatible signs and symptoms in the appropriate susceptible host, imaging can be of great value in evaluating the extent of the disease and determining the accessibility of the lesion for imaging-guided biopsy or open surgical biopsy, and response to therapy. The choice of imaging depends on the site involved. Imaging can help in determining the extent of mucormycosis in a suspect case, but it cannot definitively diagnose the disease.

Patients with diabetes mellitus and sinusitis should have a computed tomography (CT) scan of the sinuses and brain.[12] CT is less sensitive than magnetic resonance imaging (MRI) in detecting invasion into soft tissues but is more readily available and good for evaluating bony erosions. However, absence of bony erosions early in the disease course does not rule out mucormycosis. If the infection is suspected to have spread to the eye or brain, MRI is preferred over CT due to its significantly higher sensitivity.[12] If sinusitis is diagnosed, endoscopy is recommended to diagnose mucormycosis.[12]

Patients with immunosuppression and respiratory symptoms or persistent fever should have a CT chest to assess for possible pulmonary mucormycosis.[12] CT is far superior to plain radiographs in detecting the presence and extent of the disease.[43] Typical findings include:[43]

For neutropenic patients:

- At diagnosis: Nodules with/without halo sign; reversed halo sign
- At 1 week: Hypodense sign; multiple nodules
- At ≥2 weeks: Pleural effusions; cavitation

For other patients, including solid organ transplant recipients, patients under intensive care, and patients with diabetes mellitus:

- At diagnosis: Consolidation, masses, nodules, bronchial wall thickening associated with tree-in-bud nodules
- At 1 week: Hypodense sign
- At ≥2 weeks: Cavitation

In patients with cutaneous mucormycosis, MRI is superior to CT scan in determining the extent of infection.[3] [44]

Patients with abdominal pain and risk factors for mucormycosis should have a CT scan. If there is evidence of colitis on CT scan or active GI bleeding, endoscopy with biopsy is indicated.

Microbiology

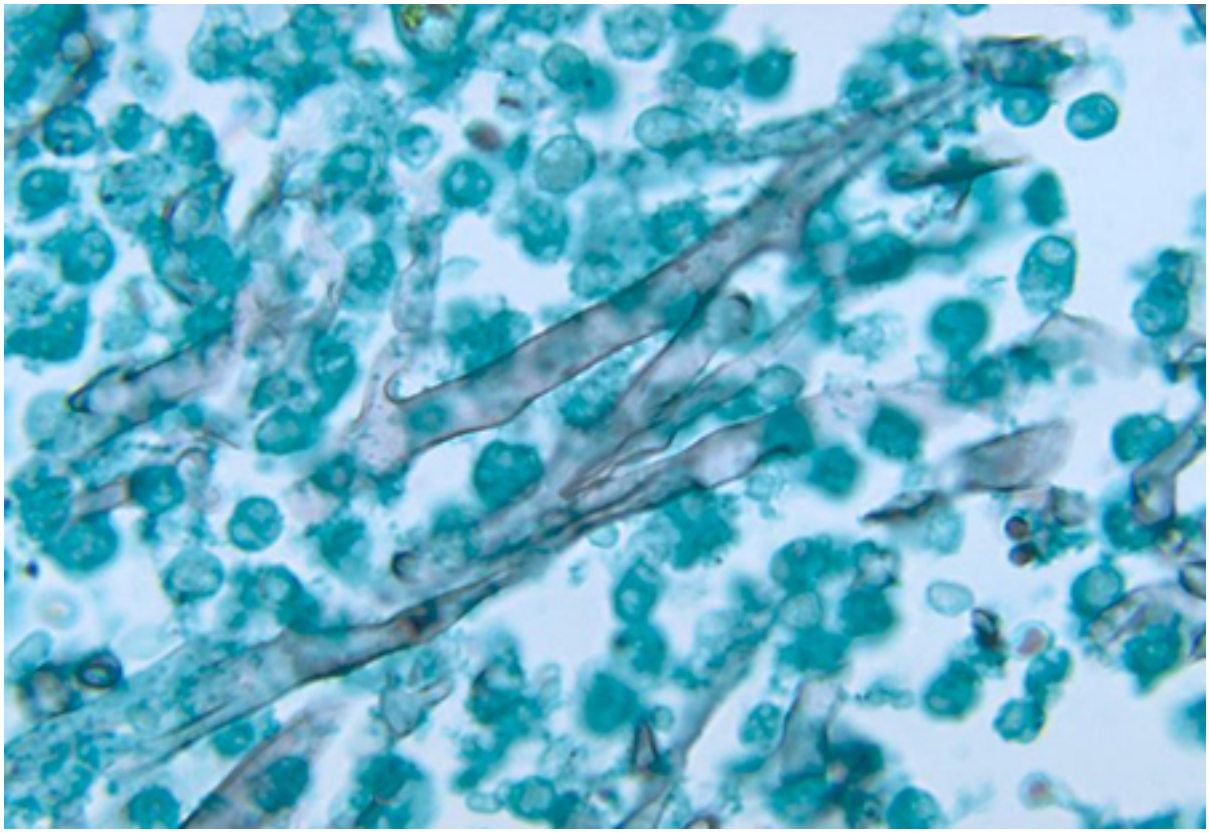
Fungal culture from clinical specimens is recommended, as it is more specific than imaging, can identify the agent at species level, and can inform antifungal susceptibility testing.[12] Results may be affected by several factors:

- Agents of mucormycosis in certain specimens, like sputum, could be laboratory contaminants but should never be dismissed in an immunocompromised patient.
- Recovery of these fungi from blood, cerebrospinal fluid, wound swabs, and bronchoalveolar lavage (BAL) is not always successful, even in the presence of invasive disease.[41]
- The best yield is from tissue cut into small pieces. Grinding of the specimen during certain procedures causes nonviability.[12]

Positive cultures are useful and diagnostic in the appropriate clinical setting. Negative cultures do not rule out infection.[7]

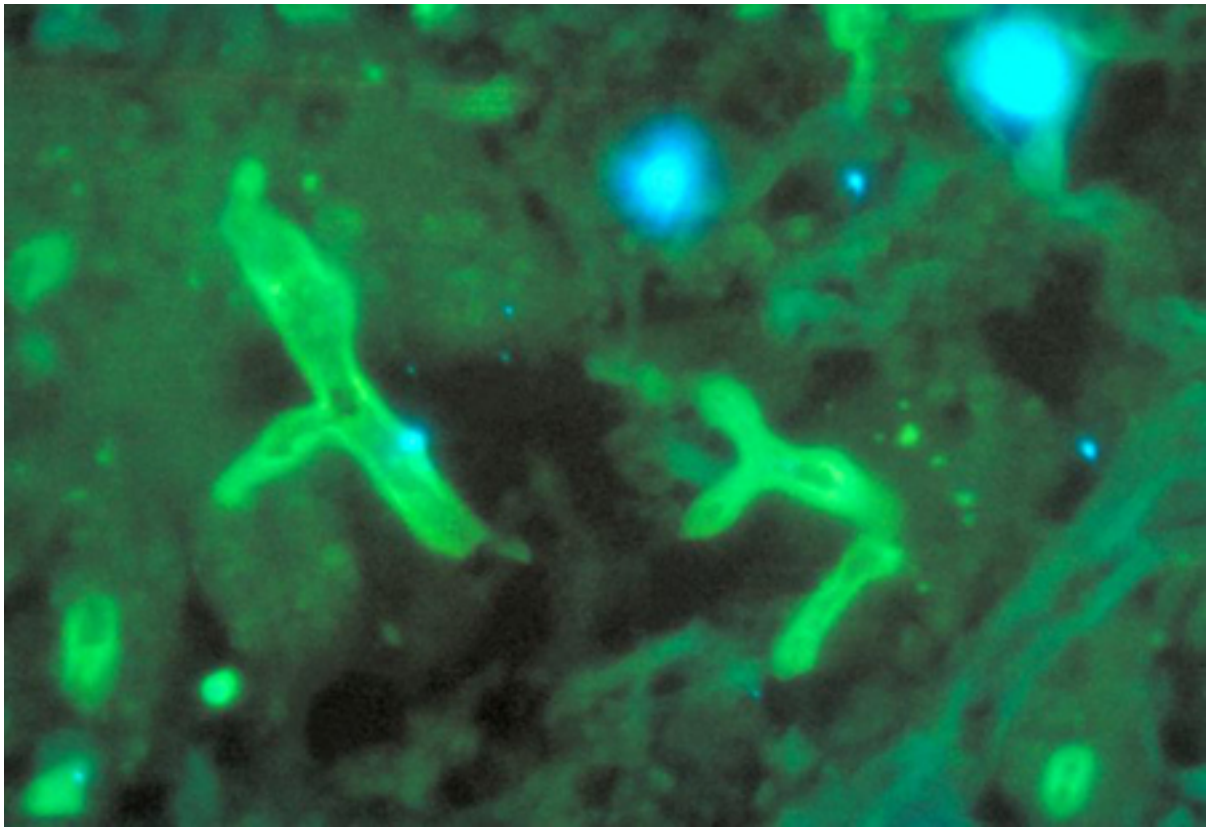
Histopathology

Diagnosing mucormycosis based on histopathology alone is challenging. Definitive diagnosis requires a positive fungal culture or molecular identification (where available).[12] However, mucormycosis is classically suspected based on histopathologic findings.[12] Mucorales species exhibit nonseptate or minimally septate broad, ribbon-like hyphae (6-25 micrometers) that branch at right angles and invade blood vessels in tissue specimens. However, due to tissue pressure and processing artefacts, branching angles can be difficult to assess, making hyphal width and irregular shape more reliable distinguishing features.[12]



Methenamine silver stain demonstrating sparsely septate hyphae of Mucor pusillus

From the CDC Public Health Image Library (PHIL): Dr Libero Ajello



Fluorescent antigen-stained Rhizopus arrhizus

From the CDC Public Health Image Library (PHIL): Dr William Kaplan

All patients should have an appropriate procedure to acquire a histologic diagnosis.[12] However, biopsy may not be possible in patients with underlying hematologic disease due to thrombocytopenia.[45] In such patients, a combination of high clinical suspicion with a positive culture, when obtained, should be sufficient information to treat the mycoses.

Specimens can be obtained by:

- Minimally invasive procedures
    - Imaging-guided biopsy
    - Endoscopy with biopsy of the sinuses or the GI tract
    - BAL
    - Transbronchial biopsy
    - Skin biopsy.
- More invasive procedures
    - Open lung biopsy.

Emerging tests

Diagnostic tools outside of culture and histopathology are improving.

Molecular techniques are useful in diagnosing mucormycosis, particularly in the absence of standardized tests, and are recommended in centers where they are available.[12] Fresh clinical material is preferred due to DNA degradation in formalin-fixed tissues.[1] Molecular assays such as polymerase chain reaction

(PCR) have shown promise for detecting Mucorales DNA in culture-negative specimens. The CotH gene has emerged as a promising PCR target, demonstrating high sensitivity and specificity in animal models.[1] Commercial assays may also offer early diagnosis potential, often preceding culture positivity. However, the diagnostic yield of PCR from serum or whole blood remains variable.[1] Further clinical studies are required to better define the role of PCR in diagnosis of mucormycosis.

Galactomannan and (1-3)-beta-D-glucan are not helpful in diagnosing mucormycosis.[1]

History and exam

Key diagnostic factors

sinus and facial pain (common)

- Common presentation in rhino-orbito-cerebral disease. Usually a manifestation of sinusitis in association with facial pain, facial numbness, and, occasionally, bloody nasal discharge.[3]

eye pain, blurred vision (common)

- Common presentation in rhino-orbito-cerebral disease. Result of involvement of the optic nerve or optic artery.

proptosis (common)

- Common in rhino-orbito-cerebral disease. Accompanied by marked chemosis and ophthalmoplegia. Associated with fungal infiltration of the orbit.[3]

cranial nerve palsies (common)

- Common in rhino-orbito-cerebral disease. Involvement of cranial nerves is an ominous sign and indicates invasion into the central nervous system. Ophthalmoplegia commonly results from the spread of untreated infection from the ethmoid sinuses. Involvement of the contralateral eye signifies cavernous sinus thrombosis.

dry cough, with or without dyspnea (common)

- Typically a dry cough (with or without dyspnea), fever, and chest pain after stem cell transplantation are common in pulmonary mucormycosis.
- However, the more common cause, especially in a hematologic patient, is aspergillosis. But suspect mucormycosis as the cause of the cough, in the event of no improvement, worsening of symptoms, or appearance on imaging studies, and if the patient is receiving appropriate therapy for aspergillosis with a drug not active against agents of mucormycosis.

skin nodules (common)

- Common manifestation of cutaneous and disseminated mucormycosis.
- Skin involvement in the cutaneous form is more commonly a locally invasive disease extending to the soft tissue, fascia, muscles, and even bone, requiring extensive debridement for good outcomes. This deep extension occurs in about 44% of patients with cutaneous disease.[40] Usually presents in otherwise immunocompetent patients as a result of traumatic inoculation, dressings, or burns.
- Nodules are more common when skin is involved as a part of disseminated disease. Mortality can be >80% in very locally invasive disease in an immunocompromised host without extensive surgery.[3]

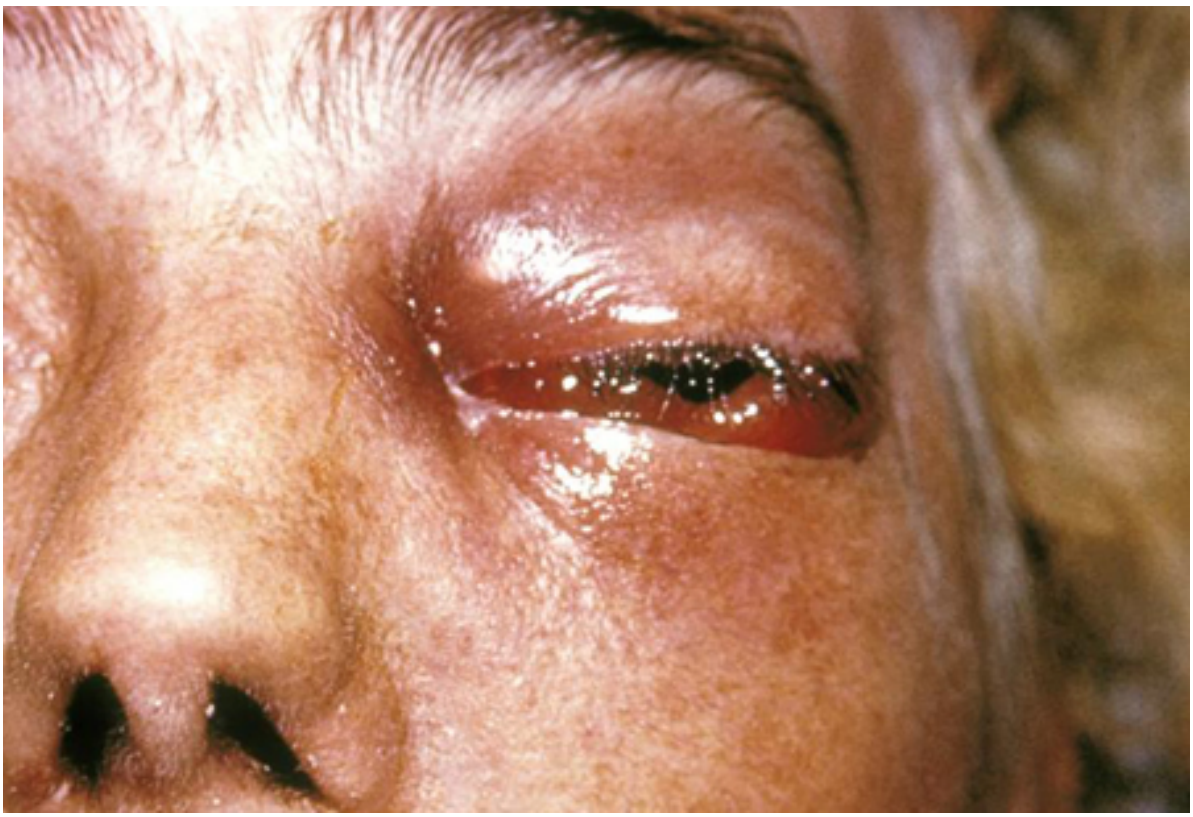
Other diagnostic factors

fever (common)

- Common in pulmonary, gastrointestinal, and disseminated disease. Fever is absent in about one-half the cases of rhino-orbito-cerebral mucormycosis.[3]

periorbital cellulitis (common)

- Common in rhino-orbito-cerebral disease.[3]



Periorbital mucormycosis

From the CDC Public Health Image Library (PHIL): Dr Thomas F. Sellers, Emory University

viscid, dark brown-black nasal discharge (common)

- Common in rhino-orbito-cerebral disease.[46]

focal sensory/motor neurologic deficits and altered mental status (common)

- Thrombosis of the internal carotid artery can lead to neurologic deficits and altered mental status.

necrotic eschar (common)

- Presence on skin, palate, or nasal turbinates is common in the later stages of infection. Due to vessel thrombosis by the invading fungus and subsequent tissue infarction. Absence early in the disease does not rule out mucormycosis.

hemoptysis (uncommon)

- Can be massive and fatal. Death usually results from dissemination rather than respiratory failure in untreated cases except in hemoptysis. Overall mortality is high, 50% to 70%, and is >95% in disseminated disease.[3]

abdominal pain and distension (uncommon)

- Nonspecific to gastrointestinal mucormycosis, which is rare except in extremely malnourished people and premature neonates.

gastrointestinal bleeding (uncommon)

- Mucormycosis may cause ulceration and bleeding.
- Necrotizing enterocolitis occurs in premature neonates.

peritonitis (uncommon)

- Gastrointestinal ulcers and subsequent perforation of the bowel can occur, resulting in peritonitis.[3] [42]

Risk factors

Strong

diabetes mellitus ± diabetic ketoacidosis

- Increased incidence of mucormycosis, especially rhino-orbito-cerebral disease. Mechanism of action is not entirely clear. Absence of ketoacidosis in a diabetic patient with sinusitis does not rule out mucormycosis. At least 50% of diabetic patients with rhino-orbito-cerebral mucormycosis are not ketoacidotic.

hematologic malignancy

- A significant risk factor for mucormycosis due to the immune dysregulation caused by both the disease and its treatment.[30] Patients with leukemia, lymphoma, and myelodysplastic syndromes often have impaired phagocytic function, defects in innate immunity, and disrupted mucosal barriers, all of which facilitate fungal invasion.[30] [31] Chemotherapy increases susceptibility by inducing cytopenias (e.g., prolonged neutropenia) and mucosal damage, providing an entry point for Mucorales. Iron overload from frequent transfusions creates a favorable environment for fungal growth. As a result, mucormycosis is a severe and often fatal complication in this patient population, with mortality rates ranging from 40% to 80%.[32]

neutropenia

- Adequate and functioning neutrophils are essential in killing Mucorales by oxidative and nonoxidative mechanisms. Hence, patients with neutropenia are at an increased risk of developing mucormycosis. The risk increases with the increase in duration of neutropenia. Recovery of the neutrophil count with granulocyte-colony stimulating factor may help improve outcomes, but the role of these hematopoietic growth factors in modifying the clinical course of mucormycosis is understudied.[33]

iron overload or use of deferoxamine

- Iron overload states and the use of deferoxamine, but not hydroxypyridinone iron chelators (e.g., deferiprone, deferasirox), are strong risk factors for the development of mucormycosis. Iron promotes growth of *Rhizopus* . While deferoxamine is an iron chelator, it also acts as a xenosiderophore increases the availability of iron by forming a complex with iron.[29]
- Dialysis patients treated with deferoxamine are at greater risk than patients with normal renal function. This could be explained by the prolonged half-life of deferoxamine in patients with renal failure.[29]

use of corticosteroids

- Corticosteroids have pleiotropic effects on macrophages and neutrophils that impair their phagocytic function and enhance the susceptibility of corticosteroid-treated patients to mucormycosis. Corticosteroids interfere with the ability of *Rhizopus oryzae* hyphae to induce production of toxic phagocytic products and activity of oxidative metabolites.[34] However, the mechanism of action remains unknown.

hematopoietic and solid organ transplantation, graft-versus-host disease

- Induction chemotherapy and corticosteroids cause quantitative and functional impairment of phagocytes, thereby increasing susceptibility to mucormycosis.

breakdown of skin and soft tissue

- Disruption of the skin and/or soft tissue barrier as in catheter insertion, surgical incisions, and burns allows a portal of entry for Mucorales, resulting in invasive local disease, especially in the immunosuppressed host. Traumatic inoculation of spores after motor vehicle accidents or injuries during natural disasters can also cause the disease in immunocompetent patients.[20] [35] The use of illicit drugs also increases the risk of inoculation of spores.

malnutrition

- Association with development of gastrointestinal mucormycosis disease. Exact mechanism is not known.[3][36]

prematurity

- Association with development of gastrointestinal mucormycosis disease. Exact mechanism is not known.[3] [14]

Weak

liver cirrhosis

- Case reports have shown that mucormycosis is associated with high mortality in patients with liver cirrhosis, despite aggressive treatment of the infection.[37]

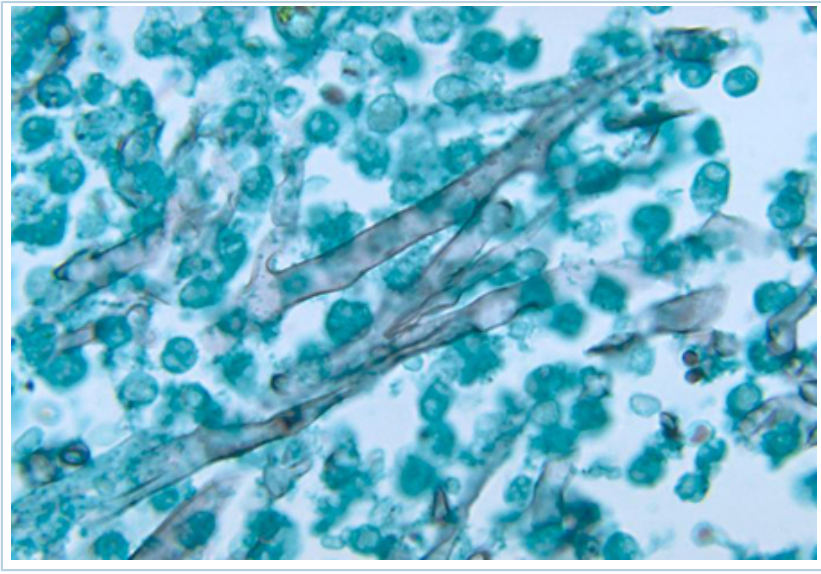
Tests

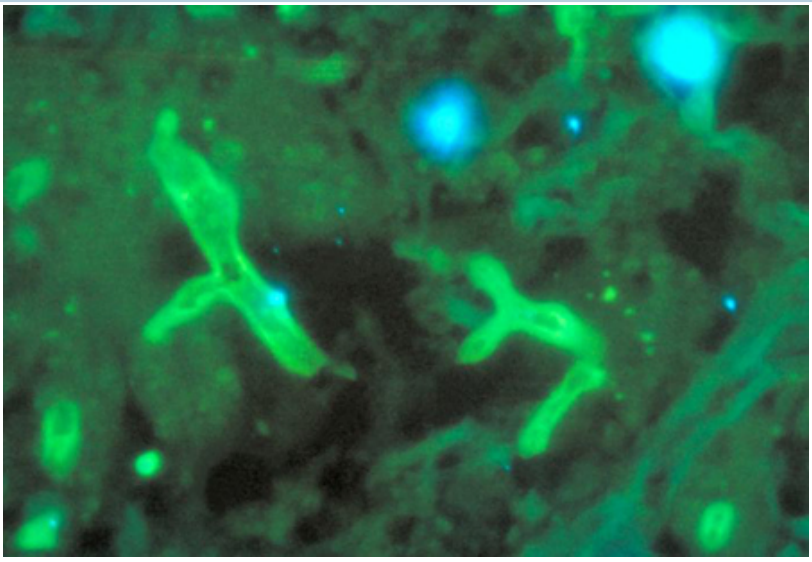
1st test to order

Test	Result
CBC • Test evaluates for presence of underlying immunosuppression. Duration of neutropenia correlates with increase in risk. Lymphopenia may not be as important a risk factor as neutropenia.[47]	**neutropenia, lymphopenia**
basic metabolic profile • Performed in patients with diabetes mellitus to look for metabolic acidosis. These help assess the severity of diabetic ketoacidosis.	**in patients with diabetes mellitus may see increased anion gap acidosis, hyperglycemia**
ABG • Evaluates the severity of acidosis in diabetic ketoacidosis. However, the disease can occur in the absence of acidosis.[48]	**low pH in diabetic ketoacidosis**
urinalysis • Positive dipstick confirms presence of ketones in urine. However, it does not diagnose diabetic ketoacidosis.	**positive for ketones in diabetic ketoacidosis**
serum ketone level • Carried out if urinary ketones are positive.	**positive in diabetic ketoacidosis**
CT sinuses and brain • Diffuse mucosal thickening without air-fluid levels is an early sign in mucormycosis. Bony destruction is usually a late finding.[49] • CT of the sinuses is less sensitive than MRI in demonstrating soft-tissue invasion. CT of the brain may not be able to differentiate between abscesses and early infarcts.[49]	**mucosal thickening, bony erosions, venous sinus thrombosis, abscesses, infarcts**
MRI sinuses and brain • If the infection is suspected to have spread to the eye or brain, MRI is preferred over CT due to its significantly higher sensitivity.[12] MRI delineates soft-tissue invasion into orbital tissues and cavernous sinus thrombosis. Provides better differentiation between abscess and infarcts, and information on posterior fossa involvement.	**soft tissue involvement of the orbital tissues, venous sinus thrombosis, abscesses, infarcts**
CT chest with contrast • CT chest with intravenous contrast is a sensitive test to detect abnormalities in pulmonary mucormycosis.[43] In one study, chest radiographs did not reveal any pathology in 53% of patients, all of whom had abnormalities on CT chest.[44] • Air crescent sign is more commonly seen in aspergillosis on recovery of neutropenia.[43]	**neutropenic patients: nodules with/without halo sign, reversed halo sign (early); hypodense sign, multiple nodules (1 week); pleural effusions, cavitation (≥2 weeks). Other patients (solid organ transplant recipients, intensive care unit patients, patients with diabetes): consolidation, masses, nodules, bronchial wall thickening with tree-in-bud nodules (early);**

Test	Result
	hypodense sign (1 week); cavitation (≥2 weeks)
nasal endoscopy • Essential to establish diagnosis with biopsy on suspicion of rhino-orbito-cerebral disease, because radiologic findings lag behind invasion.[3]	**necrotic mucosa**
gastrointestinal endoscopy • Gastrointestinal mucormycosis is infrequently diagnosed ante mortem owing to its rarity. In one case report, upper endoscopy revealed a plaque-like ulcer with necrotic slough.[52]	**mucosal ulcers, necrotic mucosa**

Other tests to consider

Test	Result
bronchoscopy with bronchoalveolar lavage and/or transbronchial biopsy fungal culture • Literature on utility of bronchoalveolar lavage (BAL) in diagnosing pulmonary mucormycosis is scarce. The disease was diagnosed in 5 of 5 patients, 2 of these by cytology of BAL fluid alone and 3 by transbronchial biopsy.[50] Diagnosis by fungal culture on BAL or transbronchial specimens was poor (20%).[50] • Calcofluor white staining on early biopsy specimens from suspicious lesions can be useful in differentiating mucormycosis from aspergillosis.[51] Because sensitivity of cultures is limited, a specimen must be obtained for biopsy.	**demonstration of wide aseptate hyphae branching at 90° angle**
histopathology of biopsy • Biopsy specimens obtained at endoscopy, CT-guided fine needle aspiration biopsy, transbronchial biopsy, and open surgical methods (skin, lung) are key for suspecting mucormycosis. • Fungi are best observed by using special stains such as periodic acid Schiff or Gomori methenamine silver.[12]  *Methenamine silver stain demonstrating sparsely septate hyphae of Mucor pusillus* *From the CDC Public Health Image Library (PHIL): Dr Libero Ajello*	**nonseptate or minimally septate broad, ribbon-like hyphae (6-25 micrometers), branching at 90°**

Test	Result
 *Fluorescent antigen-stained Rhizopus arrhizus* *From the CDC Public Health Image Library (PHIL): Dr William Kaplan* • Angioinvasion with demonstration of broad, nonseptate hyphae is classically diagnostic; however, definitive diagnosis requires a positive fungal culture or molecular identification (where available).[12]	
microbiology of biopsy • Positive fungal culture can definitively diagnose mucormycosis.[12] Microbiology of specimens, particularly from surgical procedures, helps in identifying the fungus to the species level.[53] This in turn can inform antifungal susceptibility testing.[12]	**positive for Mucorales growth**

Emerging tests

Test	Result
polymerase chain reaction (PCR) • PCR diagnosis, based on amplification of Mucorales-specific fungal genes (usually ribosomal DNA), has shown considerable promise, and is recommended in centers where it is available.[12] The CotH gene has emerged as a promising PCR target, demonstrating high sensitivity and specificity in animal models.[1] Commercial assays may also offer early diagnosis potential, often preceding culture positivity. However, the diagnostic yield of PCR from serum or whole blood remains variable.[1] Further clinical studies are required to better define the role of PCR in diagnosis of mucormycosis. •	**positive for Mucorales**

Differentials

Condition	Differentiating signs / symptoms	Differentiating tests
Aspergillosis	• No differentiating signs or symptoms. Air crescent sign upon CT chest may be more commonly seen in aspergillosis.[43] Presence of accompanying sinus disease makes aspergillosis less likely.	• Histopathology in aspergillosis demonstrates narrow (2.5-4.5 micrometers) septate hyphae, branching at an acute angle of 45°. • Positive serum galactomannan assay may favor the diagnosis of aspergillosis.
Bacterial sinusitis	• Clinically indistinguishable from mucormycosis in the initial stages, but typically responds to antibacterial therapy and lacks necrotic eschar.	• Sinus puncture with culture may be indicated when standard antibiotics have failed; however, this is considered controversial.
Bacterial periorbital cellulitis	• No differentiating signs and symptoms in the initial stages but more commonly lacks risk factors, has history of trauma, and responds to antibacterial therapy.	• Blood/eye swab cultures: positive for bacterial culture.
Sinus lymphomas	• B-cell or T-cell lymphomas may have presence of lymphadenopathy elsewhere in the body.	• Histopathology of biopsy is crucial and demonstrates atypical cells consistent with lymphoma.
Granulomatosis with polyangiitis (formerly known as Wegener granulomatosis)	• May have renal failure and systemic manifestations of vasculitis in addition to sinus symptoms similar to mucormycosis.	• Blood test: positive antineutrophil cytoplasmic antibodies (ANCA) may help in diagnosis of granulomatosis with polyangiitis, but a negative ANCA test does not rule it out. In addition, granulomatosis with polyangiitis and mucormycosis can coexist, especially in a patient treated with immunosuppressants for granulomatosis with polyangiitis.
Bacterial brain abscess	• No differentiating signs and symptoms.	• Aspiration and culture of abscess fluid is positive for bacteria.
Ecthyma gangrenosum	• Necrotic-appearing lesions on the skin, sometimes with surrounding erythema, occurring typically in the	• Culture of lesions is positive for bacteria.

Condition	Differentiating signs / symptoms	Differentiating tests
	presence of pseudomonal sepsis. Similar host populations are vulnerable.	
Fusariosis	• Patients with fusariosis have a high incidence of skin lesions as a manifestation of disseminated disease in >50% to 60%, as opposed to <5% to 10% in mucormycosis.[54] • Lesions are clinically indistinguishable from mucormycosis.	• High incidence of positive blood cultures (>50% of patients) as opposed to rare positive blood cultures in mucormycosis (<5%).[54]
Coronavirus disease 2019 (COVID-19)	• Consider the current COVID-19 epidemiologic situation and any recent outbreaks. May give history of COVID-19 exposure or ill contacts. • Fever, cough, and dyspnea may mimic pulmonary mucormycosis. Patients with COVID-19 may report altered sense of smell or taste.	• Real-time reverse transcription polymerase chain reaction (RT-PCR): positive for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) RNA. Rapid antigen tests may also be used.

Approach

In all susceptible patients with suspected mucormycosis, promptly starting appropriate antifungal therapy and surgical debridement is essential for good outcomes in this otherwise rapidly fatal disease.[4] In appropriate circumstances, immune function should be reconstituted if possible to improve outcome. This may require recovery of neutropenia, tapering of corticosteroids, or reversal of acidosis. Available data suggest that a delay in initiating treatment of 6 days or longer after diagnosis results in a twofold increase in mortality at 12 weeks after diagnosis.[55]

Surgery

Surgery is key to remove necrotic tissue and curb the spread of infection. Necrosis occurs due to vascular thrombosis, which precludes adequate delivery of antifungal agents.[3] Surgery plays a vital role in all forms of mucormycosis whenever feasible; however, some patients may be too unwell to undergo surgery.[12] In patients with rhino-orbito-cerebral mucormycosis, extensive surgical debridement frequently requires removing the paranasal sinuses along with disease from the nose and the orbit, if involved.[56] In patients with isolated cutaneous disease due to burns or in trauma patients, aggressive surgical debridement to remove all necrotic tissue is essential.

Antifungal induction therapy

Antifungal therapy is recommended in addition to surgery, or as a first-line treatment in those who are not suitable for surgery.

Amphotericin-B is recommended first line.[12] Amphotericin-B belongs to the polyene class of antifungals and is the most effective therapy against agents of mucormycosis. Liposomal and lipid formulations are preferred over the deoxycholate formulation as they minimize renal dysfunction, infusion reactions, and toxicity. Amphotericin-B deoxycholate is effective but should be avoided; its use is limited by substantial toxicity in the doses and treatment durations needed for mucormycosis. It should only be used in settings where no other antifungal treatment options are available.[12] Treatment with liposomal amphotericin-B has been reported to result in better survival in cancer patients, compared with amphotericin-B deoxycholate (67% versus 39%).[57] Liposomal amphotericin-B also appears to be more effective in rhinocerebral disease.[57] Liposomal amphotericin-B is more effective than the lipid formulation in treating central nervous system disease, making it the first-line agent in central nervous system mucormycosis, with the lipid formulation a second-line agent.[57]

Posaconazole or isavuconazonium (a prodrug of isavuconazole) are azole antifungals and may be used intravenously as a second-line treatment. They are the preferred treatments in patients with pre-existing renal compromise as amphotericin-B can cause nephrotoxicity, even lipid or liposomal formulations.[12]

Isavuconazonium has been approved by the Food and Drug Administration (FDA) for the treatment of invasive mucormycosis. It has less nephrotoxic potential than other intravenous azoles.[58] No therapeutic drug monitoring is needed.

Breakthrough infection with *Rhizopus oryzae* has been reported in patients on posaconazole prophylaxis.[59] Posaconazole requires about 1 week to reach steady-state serum concentrations and, hence, should not be the initial therapy for a patient with mucormycosis. Consider therapeutic monitoring of posaconazole blood levels in the following:

- No clinical response is noted

- In pediatric patients
- If there is mucositis, malabsorption, or inability to tolerate high fat meals
- With a resistant organism
- There is infection at sanctuary sites
- There is coprescribing with proton-pump inhibitors, anticonvulsants, H2 antagonists, or gastric motility agents.

Trough levels can be measured after 5-7 days of initiating therapy with a goal of >1 mg/L.[1] In a study of patients with graft-versus-host disease following hematopoietic stem cell transplant, the patients who developed invasive fungal infections (IFIs) had median and peak posaconazole levels of 0.611 micrograms/mL and 0.635 micrograms/mL, respectively, while the patients without IFIs had median and peak posaconazole levels of 0.922 micrograms/mL and 1.36 micrograms/mL, respectively.[59] [60]

Amphotericin-B is associated with nephrotoxicity, hypokalemia, anemia, and infusion-related adverse reactions. Azole antifungals are hepatotoxic (monitor liver function during therapy) and undergo a number of potential drug-drug interactions. Data in pregnant women with mucormycosis are not widely available.

The regimens presented in this topic depend on the geographical location as not all recommended treatments have regulatory approval in all regions or are available for use in all clinical settings.[12]

Antifungal maintenance therapy

Further treatment depends on the initial clinical response and whether the patient experiences toxicity from the initial treatment regimens.

Once the patient is stable or has a partial response, either continue the first-line regimen or change to a suitable oral regimen.[12] Oral isavuconazonium or posaconazole are the preferred options for step-down treatment.[12]

Duration of therapy depends on clinical response and resolution of any immune defect; weeks to months of therapy are typically required. Consult an infectious disease specialist for further guidance on when to transition to oral therapy, or taper or stop therapy.[12]

Antifungal therapy: treatment failure

Salvage antifungal therapy is recommended in patients with treatment failure (i.e., due to refractory mucormycosis or toxicity/intolerance to first-line regimens). The choice of drug for salvage therapy depends on the drug used initially. As only two drug classes are recommended for mucormycosis, salvage therapy typically involves switching to the other drug class.[12]

Salvage therapy with isavuconazonium or posaconazole can be considered in patients who do not respond to, or experience toxicity with, initial treatment with amphotericin-B. Liposomal amphotericin-B, and amphotericin-B lipid complex, are suitable salvage options for cases of primary treatment failure with azole antifungals.[12]

Combination antifungal therapy may be used as salvage therapy (and also as initial therapy in immunocompromised patients due to their poor prognosis).[61] [62] Treatment guidelines only marginally recommend combination therapy, largely due to a lack of evidence demonstrating harm rather than evidence indicating clear benefit.[12] There is the potential for an increased risk of toxicity. Consult an infectious disease specialist for further guidance on using combination therapy.

Specific management of underlying medical problem

Patients with diabetes mellitus (rhino-orbito-cerebral disease is the most common)

- Reversal of acidosis is essential.
- Glycemic control is encouraged.

Transplant recipients (solid organ/stem cell) (sinopulmonary disease is the most common)

- Discontinuing or reducing immunosuppressive agents such as corticosteroids and chemotherapy whenever feasible is encouraged.[3]
- Giving granulocyte-colony stimulating factor (G-CSF), granulocyte macrophage-colony stimulating factor (GM-CSF), and interferon gamma may be beneficial by reversing therapy-induced neutropenia.[2] In hematology patients with mucormycosis and ongoing neutropenia, G-CSF has been used as an adjunct to antifungal therapy in several small patient cohorts.[12] Several case reports suggest that interferon gamma may be an effective treatment, including a case of abdominal mucormycosis unresponsive to conventional therapy that improved with nivolumab and interferon gamma.[63] Interferon gamma was also successfully used in an immunocompetent patient with invasive cutaneous mucormycosis after severe burns, leading to rapid clinical improvement and immune recovery.[64] However, adequate controlled trials are lacking.[3]

Patients with iron overload

- Avoiding use of deferoxamine as an iron chelator is recommended. Alternatives include suitable hydroxypyridinone iron chelators (e.g., deferiprone, deferasirox).[65]

Treatment algorithm overview

Please note that formulations/routes and doses may differ between drug names and brands, drug formularies, or locations. Treatment recommendations are specific to patient groups: see disclaimer

Acute (summary)		
suitable for surgery		
	1st	**surgery**
	plus	**intravenous antifungal induction therapy**
	plus	**specific management of underlying medical problem**
	adjunct	**oral antifungal maintenance therapy**
unsuitable for surgery		
	1st	**intravenous antifungal induction therapy**
	plus	**specific management of underlying medical problem**
	adjunct	**oral antifungal maintenance therapy**

Ongoing			(summary)
treatment failure			
	1st	**salvage antifungal therapy**	

Treatment algorithm

Please note that formulations/routes and doses may differ between drug names and brands, drug formularies, or locations. Treatment recommendations are specific to patient groups: see disclaimer

Acute

suitable for surgery

1st **surgery**

» Surgery is key to remove necrotic tissue and curb spread of infection. Necrosis occurs due to vascular thrombosis, which precludes adequate delivery of antifungal agents.[3] Surgery plays a vital role in all forms of mucormycosis whenever feasible.

» In patients with rhino-orbito-cerebral mucormycosis, extensive surgical debridement frequently requires removal of the paranasal sinuses along with disease from the nose and the orbit, if involved.[56]

» In patients with isolated cutaneous disease due to burns or in trauma patients, aggressive surgical debridement to remove all necrotic tissue is essential.

plus **intravenous antifungal induction therapy**

Treatment recommended for ALL patients in selected patient group

Primary options

» amphotericin B liposomal: 5-10 mg/kg intravenously every 24 hours
A dose of 10 mg/kg/day is recommended in patients with central nervous system involvement or solid organ transplant patients.

OR

» amphotericin B lipid complex: 5-10 mg/kg intravenously every 24 hours
A dose of 10 mg/kg/day is recommended in patients with central nervous system involvement or solid organ transplant patients.

Secondary options

» posaconazole: 300 mg intravenously every 12 hours for 2 doses, followed by 300 mg every 24 hours

Acute

OR

» isavuconazonium sulfate: 372 mg intravenously every 8 hours for 6 doses, followed by 372 mg every 24 hours

» Amphotericin-B is recommended first line.[12] Amphotericin-B belongs to the polyene class of antifungals and is the most effective therapy against agents of mucormycosis. Liposomal or lipid formulations are preferred over the deoxycholate formulation as they minimize renal dysfunction, infusion reactions, and toxicity.[12] Amphotericin-B deoxycholate is effective but should be avoided; its use is limited by substantial toxicity in the doses and treatment durations needed for mucormycosis. It should only be used in settings where no other antifungal treatment options are available.[12]

» Posaconazole or isavuconazonium (a prodrug of isavuconazole) are azole antifungals and may be used intravenously as a second-line treatment. They are the preferred treatments in patients with pre-existing renal compromise as amphotericin-B can cause nephrotoxicity, even lipid or liposomal formulations.[12]

» Isavuconazonium has been approved by the Food and Drug Administration (FDA) for the treatment of invasive mucormycosis. It has less nephrotoxic potential than other intravenous azoles.[58] No therapeutic drug monitoring is needed.

» Posaconazole requires about 1 week to reach steady-state serum concentrations and should not be the initial therapy for a patient with mucormycosis.[59] [60] Routine therapeutic drug monitoring is recommended with a trough level of >1 mg/L.[1]

» Amphotericin-B is associated with nephrotoxicity, hypokalemia, anemia, and infusion-related adverse reactions. Azole antifungals are hepatotoxic (monitor liver function during therapy) and undergo a number of potential drug-drug interactions.

» Combination antifungal therapy may be used in select patients (e.g., immunocompromised) under specialist guidance. However, there is a lack of evidence of clear benefit and an increased risk of toxicity.[12]

» Initial treatment regimens are presented here. These regimens depend on the geographical location as not all recommended treatments

Acute

have regulatory approval in all regions or are available for use in all clinical settings.[12]

» Duration of therapy depends on clinical response and resolution of any immune defect; weeks to months of therapy are typically required. Consult an infectious disease specialist for further guidance on when to transition to oral therapy, or taper or stop therapy.[12]

» Consult an infectious disease specialist if disease is progressive.[12]

plus **specific management of underlying medical problem**

Treatment recommended for ALL patients in selected patient group

» In patients with diabetes mellitus reversal of acidosis is essential.

» In transplant recipients (solid organ/ stem cell), discontinuing or reducing immunosuppressive agents such as corticosteroids and chemotherapy whenever feasible is encouraged.[3] Granulocyte-colony stimulating factor (G-CSF), granulocyte macrophage-colony stimulating factor (GM-CSF), and interferon gamma may be beneficial by reversing therapy-induced neutropenia.[2] In hematology patients with mucormycosis and ongoing neutropenia, G-CSF has been used as an adjunct to antifungal therapy in several small patient cohorts.[12] Several case reports suggest that interferon gamma may be an effective treatment, including a case of abdominal mucormycosis unresponsive to conventional therapy that improved with nivolumab and interferon gamma.[63] Interferon gamma was also successfully used in an immunocompetent patient with invasive cutaneous mucormycosis after severe burns, leading to rapid clinical improvement and immune recovery.[64] However, adequate controlled trials are lacking.[3]

» Patients with iron overload who are treated with deferoxamine as an iron chelator should be switched to a suitable alternative iron chelator (e.g., deferiprone, deferasirox).[65]

adjunct **oral antifungal maintenance therapy**

Treatment recommended for SOME patients in selected patient group

Primary options

Acute

» posaconazole: 300 mg orally (delayed-release tablet) twice daily for 2 doses, followed by 300 mg once daily
Loading dose is not required if intravenous posaconazole was used for induction therapy.

OR

» isavuconazonium sulfate: 372 mg orally every 8 hours for 6 doses, followed by 372 mg every 24 hours
Loading dose is not required if intravenous isavuconazonium was used for induction therapy.

» Further antifungal therapy depends on the initial clinical response and whether the patient experiences toxicity from the initial treatment regimens.

» Once the patient is stable or has a partial response, either continue the first-line regimen or change to a suitable oral regimen.[12]

» Oral isavuconazonium or posaconazole are the preferred options for step-down treatment. The delayed-release tablet formulation of posaconazole is preferred to the suspension due to suboptimal bioavailability of the suspension.[12]

» Azole antifungals are hepatotoxic (monitor liver function during therapy) and undergo a number of potential drug-drug interactions.

» Duration of therapy depends on clinical response and resolution of any immune defect; weeks to months of therapy are typically required. Consult an infectious disease specialist for further guidance on when to taper or stop therapy.[12]

unsuitable for surgery

1st **intravenous antifungal induction therapy**

Primary options

» amphotericin B liposomal: 5-10 mg/kg intravenously every 24 hours
A dose of 10 mg/kg/day is recommended in patients with central nervous system involvement or solid organ transplant patients.

OR

Acute

» amphotericin B lipid complex: 5-10 mg/kg intravenously every 24 hours
A dose of 10 mg/kg/day is recommended in patients with central nervous system involvement or solid organ transplant patients.

Secondary options

» posaconazole: 300 mg intravenously every 12 hours for 2 doses, followed by 300 mg every 24 hours

OR

» isavuconazonium sulfate: 372 mg intravenously every 8 hours for 6 doses, followed by 372 mg every 24 hours

» Some patients may be too unwell to undergo surgery and these patients should receive antifungal therapy first line.[12]

» Amphotericin-B is recommended first line.[12] Amphotericin-B belongs to the polyene class of antifungals and is the most effective therapy against agents of mucormycosis. Liposomal or lipid formulations are preferred over the deoxycholate formulation as they minimize renal dysfunction, infusion reactions, and toxicity.[12] Amphotericin-B deoxycholate is effective but should be avoided; its use is limited by substantial toxicity in the doses and treatment durations needed for mucormycosis. It should only be used in settings where no other antifungal treatment options are available.[12]

» Posaconazole or isavuconazonium (a prodrug of isavuconazole) are azole antifungals and may be used intravenously as a second-line treatment. They are the preferred treatments in patients with pre-existing renal compromise as amphotericin-B can cause nephrotoxicity, even lipid or liposomal formulations.[12]

» Isavuconazonium has been approved by the Food and Drug Administration (FDA) for the treatment of invasive mucormycosis. It has less nephrotoxic potential than other intravenous azoles.[58] No therapeutic drug monitoring is needed.

» Posaconazole requires about 1 week to reach steady-state serum concentrations and should not be the initial therapy for a patient with mucormycosis.[59] [60] Routine therapeutic drug

Acute

monitoring is recommended with a trough level of >1 mg/L.[1]

» Amphotericin-B is associated with nephrotoxicity, hypokalemia, anemia, and infusion-related adverse reactions. Azole antifungals are hepatotoxic (monitor liver function during therapy) and undergo a number of potential drug-drug interactions.

» Combination antifungal therapy may be used in select patients (e.g., immunocompromised) under specialist guidance. However, there is a lack of evidence of clear benefit and an increased risk of toxicity.[12]

» Initial treatment regimens are presented here. These regimens depend on the geographical location as not all recommended treatments have regulatory approval in all regions or are available for use in all clinical settings.[12] Duration of therapy depends on clinical response.

» Duration of therapy depends on clinical response and resolution of any immune defect; weeks to months of therapy are typically required. Consult an infectious disease specialist for further guidance on when to transition to oral therapy, or taper or stop therapy.[12]

» Consult an infectious disease specialist if disease is progressive.[12]

plus **specific management of underlying medical problem**

Treatment recommended for ALL patients in selected patient group

» In patients with diabetes mellitus reversal of acidosis is essential.

» In transplant recipients (solid organ/stem cell), discontinuing or reducing immunosuppressive agents such as corticosteroids and chemotherapy whenever feasible is encouraged.[3] Granulocyte-colony stimulating factor (G-CSF), granulocyte macrophage-colony stimulating factor (GM-CSF), and interferon gamma may be beneficial by reversing therapy-induced neutropenia.[2] In hematology patients with mucormycosis and ongoing neutropenia, G-CSF has been used as an adjunct to antifungal therapy in several small patient cohorts.[12] Several case reports suggest that interferon gamma may be an effective treatment, including a case of abdominal mucormycosis unresponsive

Acute

to conventional therapy that improved with nivolumab and interferon gamma.[63] Interferon gamma was also successfully used in an immunocompetent patient with invasive cutaneous mucormycosis after severe burns, leading to rapid clinical improvement and immune recovery.[64] However, adequate controlled trials are lacking.[3]

» Patients with iron overload who are treated with deferoxamine as an iron chelator should be switched to a suitable alternative iron chelator (e.g., deferiprone, deferasirox).[65]

adjunct **oral antifungal maintenance therapy**

Treatment recommended for SOME patients in selected patient group

Primary options

» posaconazole: 300 mg orally (delayed-release tablet) twice daily for 2 doses, followed by 300 mg once daily
Loading dose is not required if intravenous posaconazole was used for induction therapy.

OR

» isavuconazonium sulfate: 372 mg orally every 8 hours for 6 doses, followed by 372 mg every 24 hours
Loading dose is not required if intravenous isavuconazonium was used for induction therapy.

» Further antifungal therapy depends on the initial clinical response and whether the patient experiences toxicity from the initial treatment regimens.

» Once the patient is stable or has a partial response, either continue the first-line regimen or change to a suitable oral regimen.[12]

» Oral isavuconazonium or posaconazole are the preferred options for step-down treatment. The delayed-release tablet formulation of posaconazole is preferred to the suspension due to suboptimal bioavailability of the suspension.[12]

» Azole antifungals are hepatotoxic (monitor liver function during therapy) and undergo a number of potential drug-drug interactions.

» Duration of therapy depends on clinical response and resolution of any immune defect;

Acute

weeks to months of therapy are typically required. Consult an infectious disease specialist for further guidance on when to taper or stop therapy.[12]

Ongoing

treatment failure

1st **salvage antifungal therapy**

Primary options

» amphotericin B liposomal: 5-10 mg/kg intravenously every 24 hours
A dose of 10 mg/kg/day is recommended in patients with central nervous system involvement or solid organ transplant patients.

OR

» amphotericin B lipid complex: 5-10 mg/kg intravenously every 24 hours
A dose of 10 mg/kg/day is recommended in patients with central nervous system involvement or solid organ transplant patients.

OR

» posaconazole: 300 mg intravenously/orally (delayed-release tablet) every 12 hours for 2 doses, followed by 300 mg every 24 hours

OR

» isavuconazonium sulfate: 372 mg intravenously/orally every 8 hours for 6 doses, followed by 372 mg every 24 hours

» Salvage antifungal therapy is recommended in patients with treatment failure (i.e., due to refractory mucormycosis or toxicity/intolerance to first-line regimens). The choice of drug for salvage therapy depends on the drug used initially. As only two drug classes are recommended for mucormycosis, salvage therapy typically involves switching to the other drug class.[12]

» Salvage therapy with isavuconazonium or posaconazole can be considered in patients who do not respond to, or experience toxicity with, initial treatment with amphotericin-B. Liposomal amphotericin-B, and amphotericin-B lipid, complex are suitable salvage options for cases of primary treatment failure with azole antifungals.[12]

» Amphotericin-B is associated with nephrotoxicity, hypokalemia, anemia, and

Ongoing

infusion-related adverse reactions. Azole antifungals are hepatotoxic (monitor liver function during therapy) and undergo a number of potential drug-drug interactions.

» Combination antifungal therapy may be used in select patients under specialist guidance. However, there is a lack of evidence of clear benefit and an increased risk of toxicity.[12]

» Duration of therapy depends on clinical response and resolution of any immune defect; weeks to months of therapy are typically required. Consult an infectious disease specialist for further guidance on when to transition to oral therapy, or taper or stop therapy.[12]

Emerging

Amphotericin-B plus caspofungin combination therapy

Some mouse models and small clinical studies have described improved outcomes with amphotericin-B and caspofungin (an echinocandin antifungal), particularly in patients with diabetes with rhino-orbital cerebral disease.[66] [67] However, larger retrospective studies, particularly patients with hematologic malignancy and transplant recipients with pulmonary mucormycosis, did not show improved outcomes.[68] [69] [70] Further research is needed to clarify the role of this combination.[71]

Localized administration of amphotericin-B

Case reports have described endobronchial instillation of amphotericin-B for the treatment of pulmonary mucormycosis.[72] [73] Use of oral amphotericin-B suspension (which acts locally in the gastrointestinal tract) as part of combination therapy has also been described in one case report in the treatment of localized gastrointestinal infection.[74] Amphotericin-B beads have been used successfully in one case report of rhizopus osteomyelitis.[75] More research is needed on these novel ways of administering amphotericin-B.

Hyperbaric oxygen therapy

Hyperbaric oxygen therapy has been beneficial in certain case reports, but data are not adequate in the absence of control groups for comparison.[12][76]

Primary prevention

Certain preventive strategies, such as judicious use of immunosuppressants like corticosteroids, and adequate glycemic control in diabetes mellitus, may help in decreasing the risk of infection with agents of mucormycosis. Using rooms equipped with high-efficiency particulate air (HEPA) filtration and using masks for patients with severe immunosuppression may also be useful. Individuals at high risk can minimize exposure by avoiding dusty environments like construction sites, wearing N95 respirators when exposure is unavoidable, and avoiding water-damaged buildings and floodwaters. Protective measures such as wearing long clothing, gloves, and closed-toe shoes during outdoor activities can further reduce risk, along with promptly cleaning any skin injuries with soap and water to prevent infection.[18]

Secondary prevention

The global guideline for diagnosis and management of mucormycosis recommends surgical resection and continuation, or restart, of the last effective drug in immunosuppressed patients with a previous diagnosis of mucormycosis.[12] Consult an infectious disease specialist.

Patient discussions

Patients should be advised to seek medical care immediately if their symptoms worsen or recur.

FOLLOW UP

Monitoring

Monitoring

Close follow-up for worsening of symptoms is required. Weekly computed tomography (CT) scans are strongly recommended to evaluate for disease progression.[12]

Monitoring for adverse effects of amphotericin-B is essential. Serial measurement of electrolytes and renal function is advised.

Close follow-up for recurrence is warranted after stopping antifungal therapy.

Complications

Complications	Timeframe	Likelihood
blindness	**short term**	**medium**
Caused by occlusion of the central retinal artery by fungal invasion. The damage is irreversible. If the orbit is involved, treatment includes enucleation.		
amphotericin-B-related renal failure	**variable**	**high**
Tubular toxicity leads to electrolyte imbalance such as hypokalemia, hypomagnesemia, and hypocalcemia. Use of liposomal or lipid formulations minimize renal dysfunction and toxicity.[12]		
cerebral infarction	**variable**	**medium**
Proliferation of the spores after invasion of the vasculature produces hyphae. These hyphae subsequently erode the vascular endothelium, leading to thrombosis and tissue infarction.[79] These inflammatory events cause thrombosis of cavernous sinus and internal carotid artery.		
cerebral abscess	**variable**	**medium**
Thrombosis of cerebral vessels causes tissue necrosis resulting in abscess formation. Usual symptoms include focal deficits and seizures. Treatment is surgical drainage and prolonged medical therapy.		
cavernous sinus thrombosis	**variable**	**low**
Ophthalmoplegia associated with significant eye pain, proptosis, chemosis, and headache signifies likely presence of cavernous sinus thrombosis. Early medical and adequate surgical therapy is essential. Role of anticoagulation is controversial.		
intracranial hemorrhage	**variable**	**low**
Occurs due to development of mycotic aneurysm or fungal abscess. These can lead to subarachnoid hemorrhage and intracranial hematoma.[80]		

Prognosis

Mortality depends on the host and clinical presentation (e.g., disseminated disease in a transplant patient versus cutaneous disease in an immunocompetent host after inoculation trauma). Mortality is 97% in untreated disease. Mortality is reduced to 30% in patients treated with a combination of medical and surgical therapy. Infection with *Cunninghamella* species and disseminated disease are associated with poor outcomes.[40]

Outlook based on disease type

- Localized sinus disease has the best outlook with mortality <10%.
- Primary cutaneous disease in transplant recipients has a mortality of about 30%.[77]
- Pulmonary disease has a mortality of 55% with medical therapy alone and 27% with surgery. Of note, the diagnosis was made at autopsy in nearly 30% of the patients.[78]
- Rhino-orbito-cerebral disease has a mortality >50% in the presence of central nervous system extension.[56]
- Disseminated disease has the worst outlook with mortality of nearly 100%.[3]

Diagnostic guidelines

International

Global guideline for the diagnosis and management of mucormycosis (https://www.ecmm.info/guidelines/mucormycoses-2019/) [12]

Published by: European Confederation of Medical Mycology; Mycoses Study Group Education and Research Consortium **Last published:** 2019

Treatment guidelines

International

Global guideline for the diagnosis and management of mucormycosis (https://www.ecmm.info/guidelines/mucormycoses-2019) [12]

Published by: European Confederation of Medical Mycology; Mycoses Study Group Education and Research Consortium **Last published:** 2019

Key articles

- Pham D, Howard-Jones AR, Sparks R, et al. Epidemiology, modern diagnostics, and the management of mucorales infections. J Fungi (Basel). 2023 Jun 12;9(6):659. Full text (https://pmc.ncbi.nlm.nih.gov/articles/PMC10304757) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/37367595?tool=bestpractice.bmj.com)
- Spellberg B, Edwards J Jr, Ibrahim A. Novel perspectives on mucormycosis: pathophysiology, presentation, and management. Clin Microbiol Rev. 2005 Jul;18(3):556-69. Full text (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1195964) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/16020690?tool=bestpractice.bmj.com)
- Centers for Disease Control and Prevention. Mucormycosis: clinical overview of mucormycosis. Apr 2024 [internet publication]. Full text (https://www.cdc.gov/mucormycosis/hcp/clinical-overview/index.html)
- Cornely OA, Alastruey-Izquierdo A, Arenz D, et al. 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. Lancet Infect Dis. 2019 Dec;19(12):e405-21. Full text (https://pmc.ncbi.nlm.nih.gov/articles/PMC8559573) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/31699664?tool=bestpractice.bmj.com)

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Images

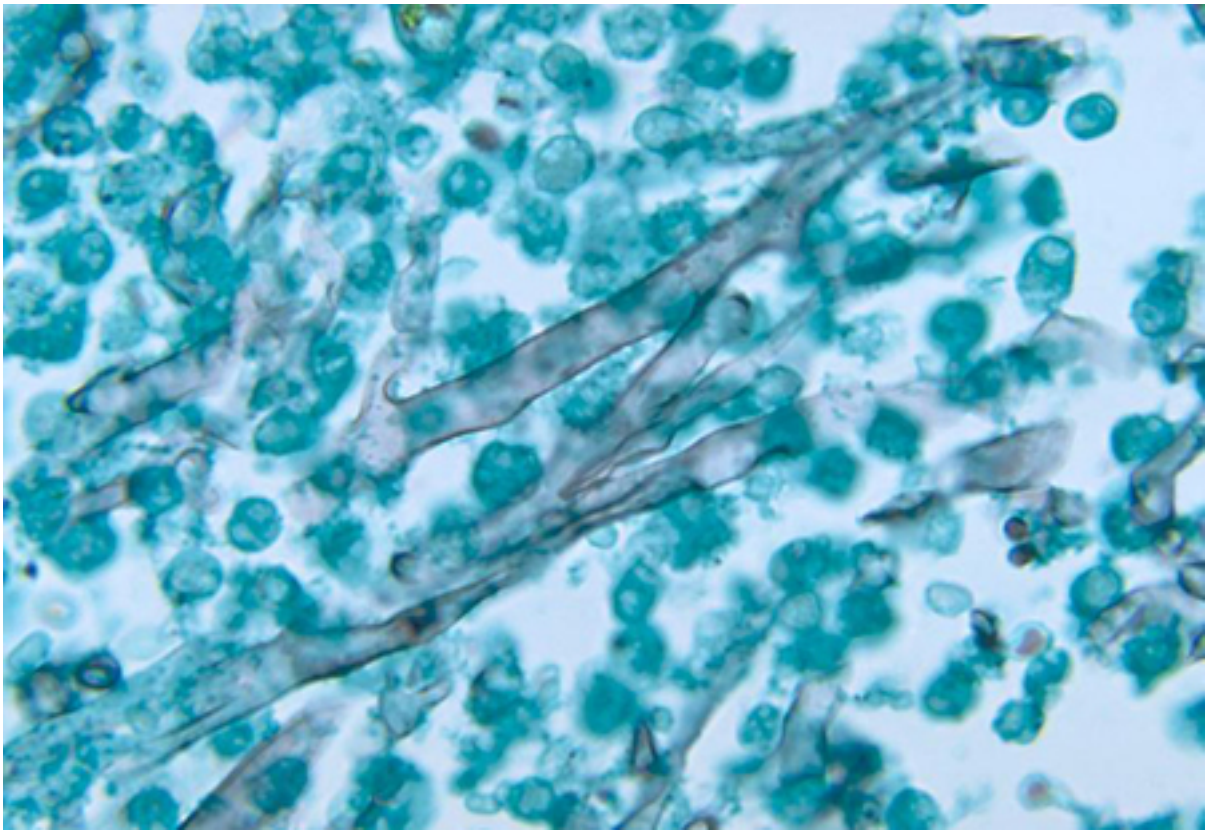

Figure 1: Methenamine silver stain demonstrating sparsely septate hyphae of Mucor pusillus

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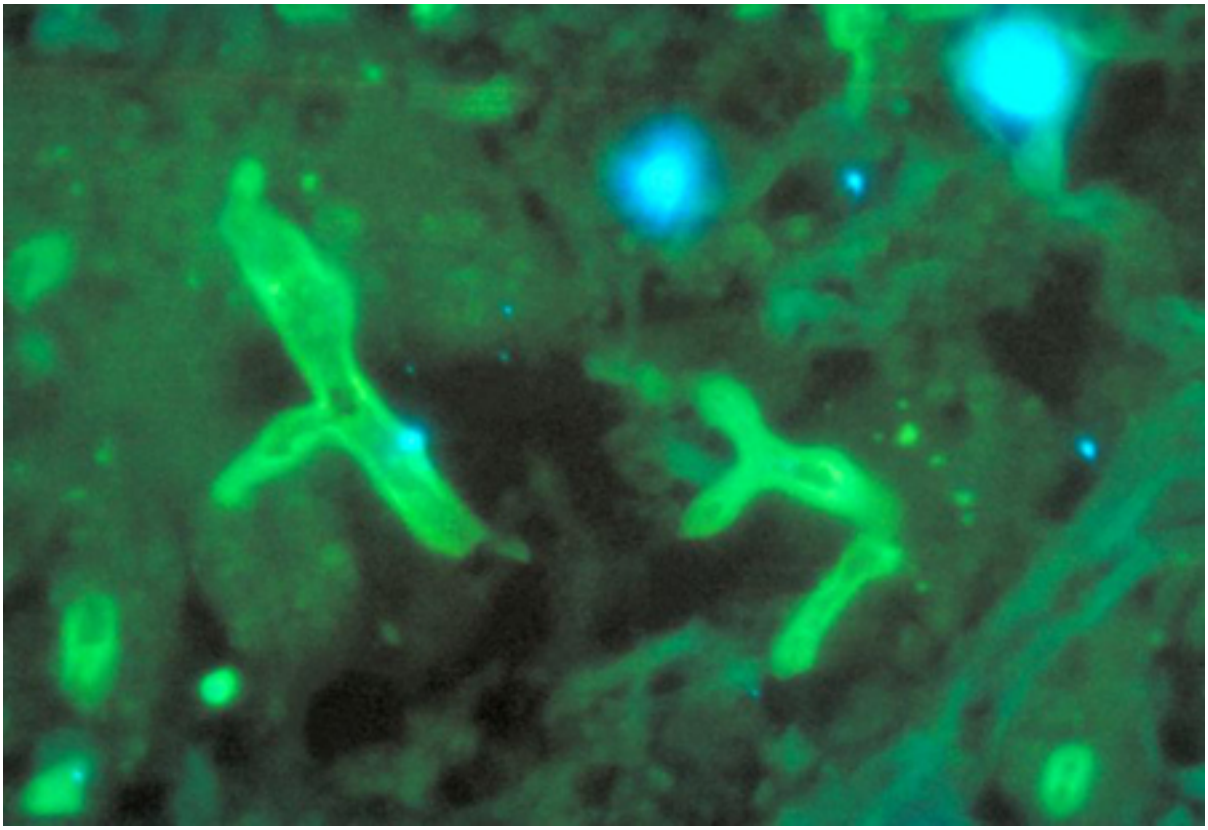

Figure 2: Fluorescent antigen-stained Rhizopus arrhizus

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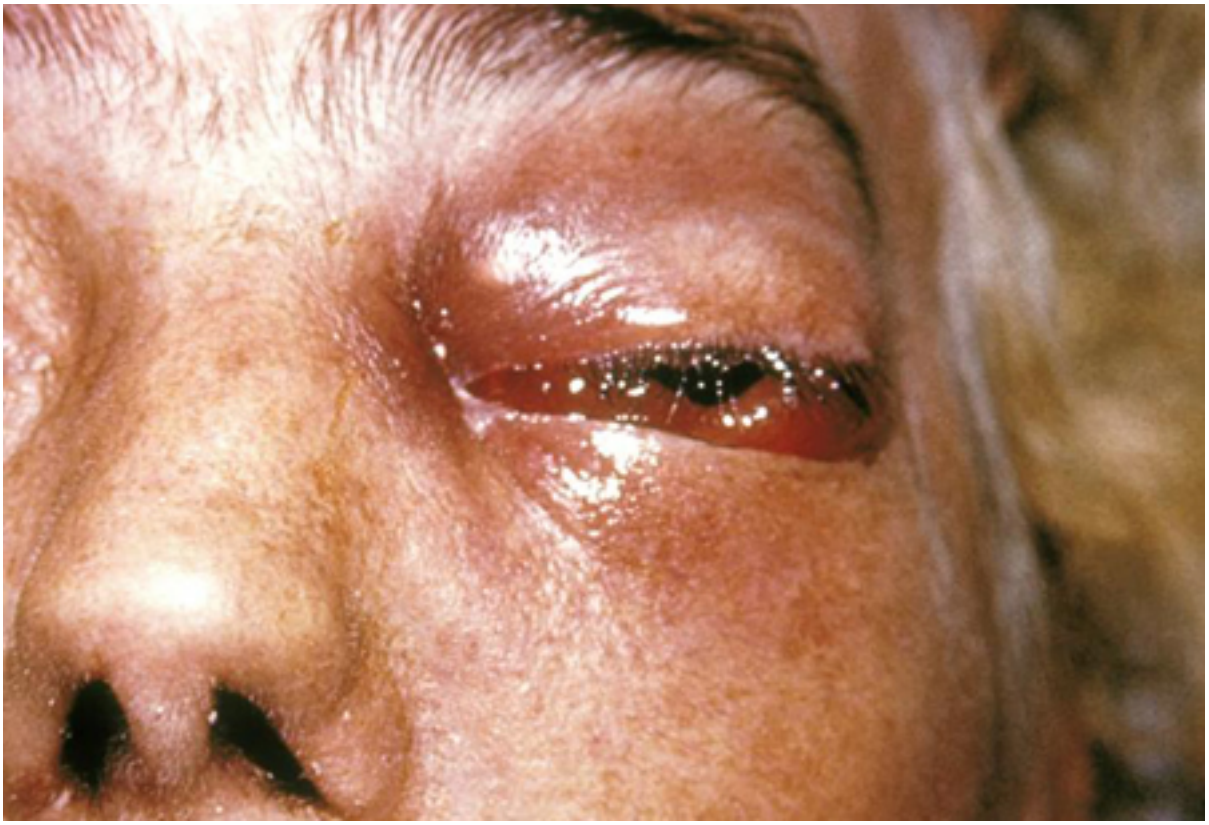

Figure 3: Periorbital mucormycosis

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Figure 1 – BMJ Best Practice Numeral Style

5-digit numerals: 10,000

4-digit numerals: 1000

numerals < 1: 0.25

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