MMTN
MEDICAL MYCOLOGY TRAINING NETWORK

How do I diagnose and manage mucormycosis?

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How I Diagnose and Manage Mucormycosis

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Background: Mucormycosis

- Life threatening angio-invasive fungal infection predominantly occurs in immunocompromised host
- Associated with very high mortality despite aggressive therapy, (surgical and antifungal therapy)
- The most frequently reported pathogens in mucormycosis are *Rhizopus* spp., *Mucor* spp. and *Lichtheimia* spp. (formerly of the genera *Absidia* and *Mycocladus*), followed by *Rhizomucor* spp., *Cunninghamella* spp., *Apophysomyces* spp. and *Saksenaea* spp
- Cunninghamella species is more virulent in experimental models and may be associated with a higher mortality rate in patients.

Skiada A, et al. Clin Microbiol Infect 2011; 17: 1859–1867.
Roden MM, et al. Clin Infect Dis 2005; 41:634.
Patraitis V et al. Med Mycol. 2013;51(1):72-82.

Risk Factors: Mucormycosis

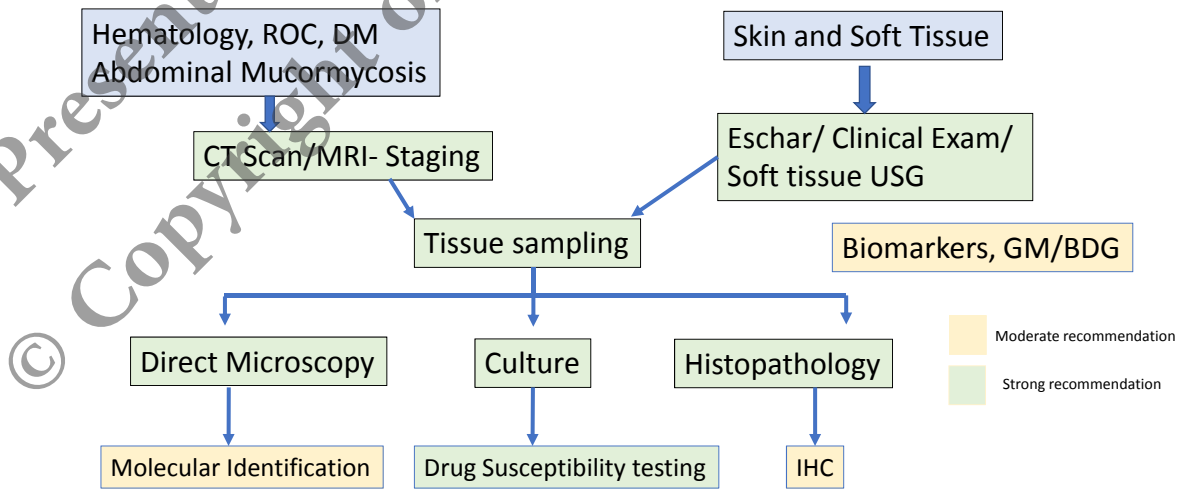
- Diabetes and hyperglycemia
- Hematological malignancies
- Solid organ Transplant
- Steroids & Immunosuppressive
- Road Traffic accidents, Natural disasters (Tornado, Tsunami victims)
- Nosocomial; surgical site infection, Adhesive taps, ECG lead, Wooden tongue depressor
- Prior Voriconazole exposure (scant data)
- Iron Overload, deferoxamine therapy

Kontoyiannis D P & Lewis R E. Blood 2011, Future Microbiol 2013, U. Binder,et al. Clin Microbiol Infect 2014; 20 (Suppl. 6): 60–66G. N. Pongas et al. Clinical Microbiology and Infectious Diseases, 2009, Andresen D, et al. Lancet 2005

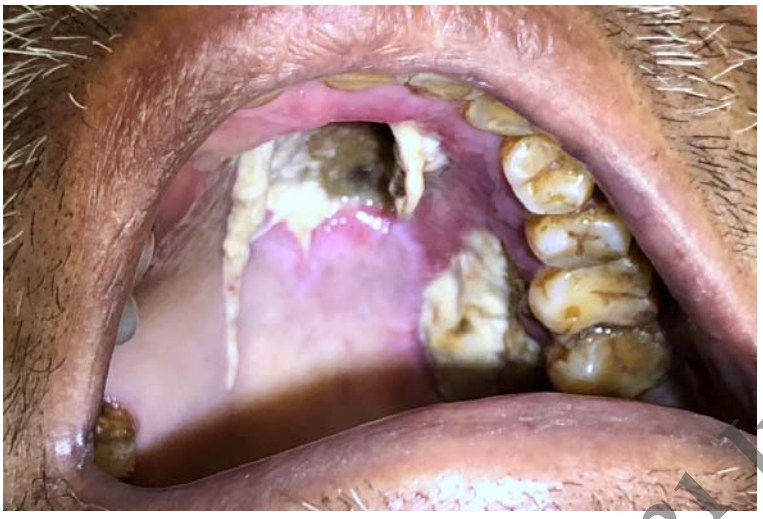
Site of Infection

- Rhino-orbito-cerebral (ROC)
- Pulmonary
- Skin and soft structure
- Gastrointestinal
- Isolated Renal
- Disseminated

Diagnostic Modalities: Suspected mucormycosis

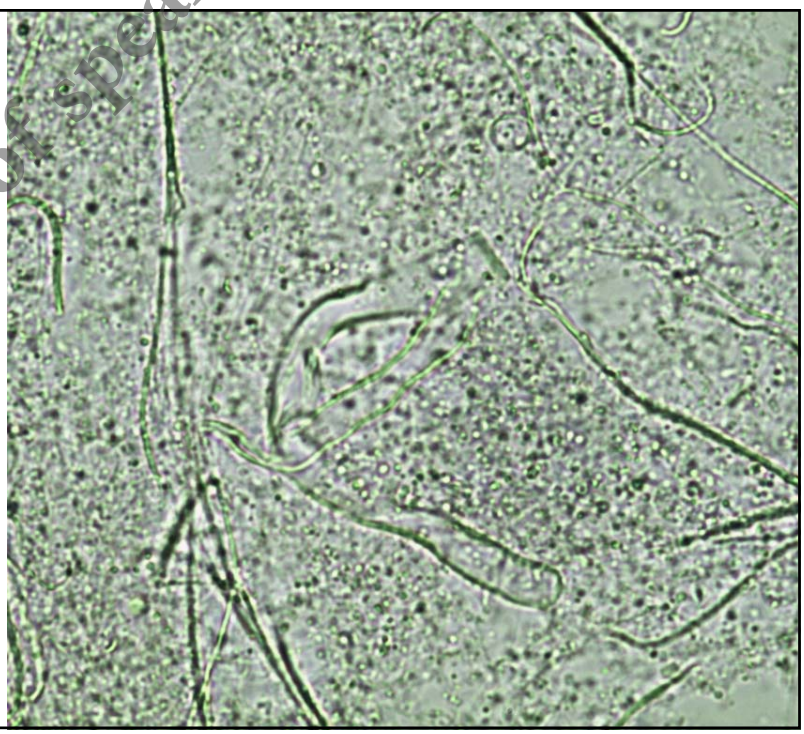


Adapted from Global guideline on mucormycosis: Under review; The Lancet ID



If mucormycosis is a potential diagnosis, biopsy is strongly recommended

- Direct Microscopy
- Calcofluor white stain

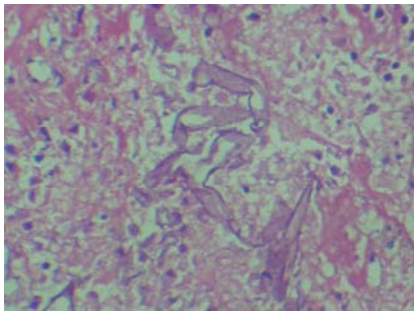


Culture and Species Identification

- Don't have enough evidence to recommend identification of mucormycosis to the genus and/or species level helps guide antifungal treatment
- Species identification is important for outbreak investigations and epidemiology
-

Histopathology

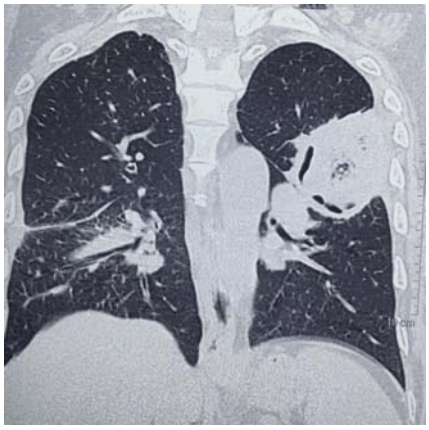
- Mucormycosis diagnosis on histo-morphological basis is challenging
- Frequently misidentified Mucorales as *Aspergillus* spp and vice versa
- Immunohistochemistry with commercially available monoclonal antibodies or PCR

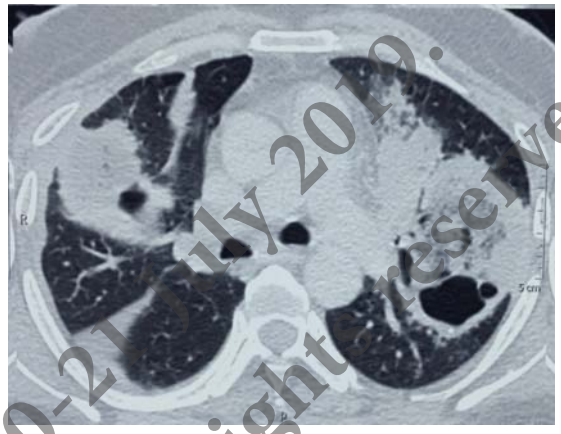


Broad (3-25 µm in diameter), ribbon like, folded, thin-walled, primarily aseptate hyphae that have irregular diameters; with nondichotomous irregular branching and accompanying tissue necrosis and fungal angioinvasion

Radiology

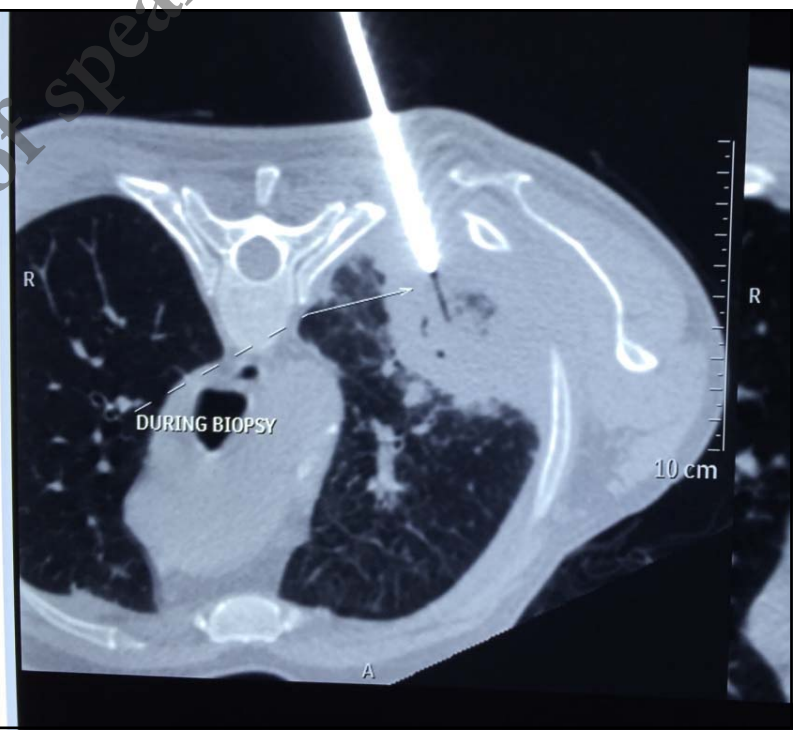
The lesions of mucormycosis are characteristic, but nonspecific

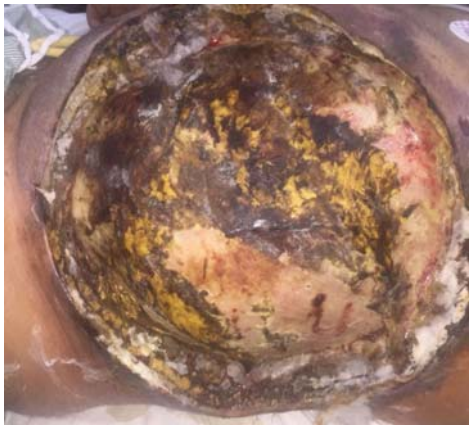


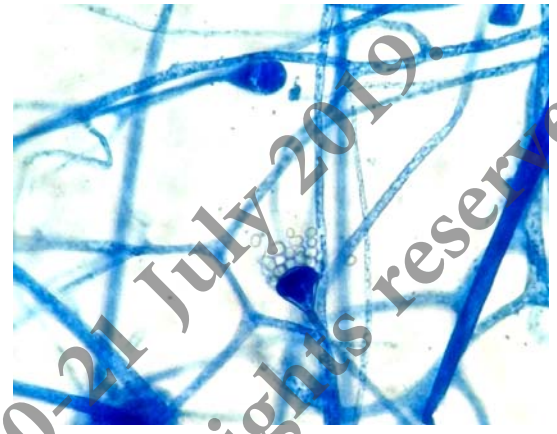


Radiological Features

- Vessel occlusion detected by CT pulmonary angiography is a more sensitive and possibly more specific radiographic sign than other common CT findings of invasive mould disease in patients with haematological malignancies
- CT guided needle biopsy was found to be superior in diagnosing pulmonary mucormycosis over BAL







Laboratory based testing: Under development

- Specific serological markers to detect Mucorales are currently not available.
- Use of galactomannan to exclude mucormycosis is moderately recommended, although mixed infections do occur
- Certain *Rhizopus* spp. could yield positive BDG results
- ELISA and lateral-flow immunoassay (LFIA) that is able to detect several fungal pathogens including *Mucor* spp. and *Rhizopus arrhizus*
- Detection of a serum disaccharide by mass spectrometry (MS) has been useful for the diagnosis of nine out of 10 patients with mucormycosis

Angebault C et al. *Open Forum Infect Dis* 2016; **3**(3): ofw128.
Ostrosky-Zeichner L, et al. *Clin Infect Dis* 2005; **41**(5): 654-9
Mery A, et al. *J Clin Microbiol* 2016; **54**(11): 2786-97

Principles

- Suspected mucormycosis requires urgent intervention: often rapidly progressive and destructive infection
- Delay in initiation of therapy: Increases mortality
- Team approach: For making early diagnosis and management (Medicine, Microbiology, Radiology, Surgeon and Histopathology)

Approach to treatment:

- Effective treatment of mucormycosis requires both surgical and antifungal drugs
- Early complete surgical treatment for mucormycosis whenever possible (Strong Recommendation)
- Resection or debridement should be repeated as required

Systemic antifungal treatment

- Amphotericin B deoxycholate has been the drug of choice for decades
- Liposomal Amphotericin B is preferred
- No definitive data to guide the utilization of antifungal combination therapy
- The downsides of combination therapy are unclear aside from potential added toxicity, drug interactions and cost

Kyvernitakis A, et al *Clin Microbiol Infect* 2016; **22**(9): 811 e1- e8

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	

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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

Isavuconazole is strongly supported as salvage treatment.
Posaconazole delayed release tablets or infusions are strongly supported for salvage treatment,
It should be preferred over posaconazole oral suspension

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Mortality

- All-cause mortality rates range from 40% to 80%
- Depending on underlying conditions and sites of infection.
- Better prognosis is described in patients with a healthy immune status and those without co-morbidities
- The poorest prognosis is observed in patients with haematological malignancies and HSCT recipients and in patients with extensive burns
- Disseminated disease, especially to the central nervous system (CNS), is often associated with mortality rates above 80%
- Mortality is also high in neonates and other immunocompromised patients with gastrointestinal mucormycosis, possibly related to delay in diagnosis and polymicrobial sepsis
- Prognosis is also good in patients with skin and soft tissue and Sinus involvement with Mucormycosis: early diagnosis and surgical debridement

Roden MM, *Clin Infect Dis* 2005; **41**(5): 634-53, Guinea J, et al. *PLoS One* 2017; **12**(6): e0179136
Shoham S, et al. *Med Mycol* 2010; **48**(3): 511-7

How long should be the treatment continued?

- The duration of therapy necessary to treat mucormycosis is unknown
- No definite answer
- Factors affecting treatment duration
  - Reversibility of underlying condition: DKA, control of DM, reducing immunosuppression, neutropenia
  - Surgical debridement: Complete surgical debridement shortens duration of antifungal
- In general, weeks to months of therapy are given
- Therapy can be continued until resolution of signs and symptoms of infection, and marked radiographic improvement

Greenberg RN, et al. *Antimicrob Agents Chemother* 2006; **50**(1): 126-33
van Burik JA, *Clin Infect Dis* 2006; **42**(7): e61-5.
Kim JH, *Mycoses* 2016; **59**(11): 726-33 Marty FM, *Lancet Infect Dis* 2016; **16**(7): 828-37

Adjunctive treatment

- Iron Chelator:
  - Adjunctive deferasirox use should be avoided in patients with haematological malignancy
  - Its use in patients with diabetes as a predominant risk factor merits further exploration in clinical trials
- Augmentation of host response:
  - G-CSF to augment host response against mucormycosis in patients with ongoing neutropenia
- Hyperbaric Oxygen:

My take on Mucormycosis

- Difficult to treat:
  - Medical factors: Late diagnosis (Not suspected and late biopsy) Immunosuppressions, Disseminated disease is not uncommon, Fungal virulence, Angioinvasive, unpredicted complications during the course of treatment especially CV stroke, fatal hemoptysis, lack of team work, Antifungal resistance, Antifungal toxicity
  - Social factors: Cost (hospitalization, surgery, antifungal), high expectations, prolonged and uncertain duration treatment, poor prognosis with 50% mortality
- Antifungal: L AmB (preferred)/D AmB (alternative) for 3-6 weeks for localized disease along with surgical debridement
- Disseminated/deep organ/Surgery is not possible: L AmB/D AmB for 6 weeks followed by prolonged oral Posaconazole
- Control of DKA/DM, reduction of immunosuppressives (Steroids ASAP), Deferasirox, HBO in selected patients