Review

How to understand and manage Mucormycosis infections during Covid-19/ SARS-CoV-2/ novel coronavirus pandemic era in India & developing countries?

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Abstract

This time last year in May 2020 India was under lockdown phase, many theories invented and discovered without any scientific evidence about India's surprisingly low rates of Sars-CoV-2 infection, included variety of factors such as hot weather, natural immunity, heard immunity, robust health system, highly qualified doctors, natural healers and the India's big proportion of young healthy people; as well as also due to the complete lockdown[i]. India was doing so well that in biggest cities like Mumbai and Delhi, officials had begun dismantling temporary COVID-19 facilities. Comparing it to current scenario in ***May 2021, covid-19 & Mucormycosis*** (new epidemic[ii] &notifiable[iii] disease declared by several states of India) cases and deaths are a big problem faced by healthcare department and system of India. There are chances of emergence of other diseases which can become epidemic in India due to several factors like improper techniques applied for disposing dead bodies of covid-19 patients etc in rivers[iv] low burials to be digged by animals and improper immunization and care of pregnant women.[v] The shortage of medicine for treatment of Mucormycosis is so acute that people are dying daily[vi] waiting to get medicine and proper treatment at hospitals. Daily rates of covid-19 cases are currently about 200,000, but now the main concern in India is Mucormycosis death rate. Several theories are again being invented and discovered on daily basis coming through news media and other channels again misguiding peoples and creating panic. It seems that the Indian scientific bodies are not able to understand and formulate a proper protocol for treatment and management of pandemic and epidemic. Cases of Mucormycosis, or black fungus, a potentially serious condition that causes blurred or defective vision, severe chest pain and little or severe breathing difficulties, have increased in India, mostly among COVID-19 patients. More than 8,848 cases of Mucormycosis have been found across the various states of India as of May 21, according to the govt[vii]. The covid-19 pandemic have not subsided yet in India from which the healthcare system is struggling since2020 January .Mucormycosis represents a group of life-threatening infections caused by fungi of the order Mucorales which are difficult-to-manage owing to limited as well as less number of diagnostic tools and therapeutic options available till date particularly in developing countries like India having a large portion of population dwelling in villages with poor infrastructure and limited resources in healthcare (both private and public). Fungi of order Mucorales divided into six families, all of which have capacity to cause Mucormycosis. *Rhizopus oryzae is the most common cause of infection usually*. Others are Rhizopus microspores, Rhizomucor pucillus, Mycoclaudus corymbifier, Apophysomyces elegans, etc. Reclassification have abolished class zygomycetes and placed the order Mucorales in the subphylum Mucoromycotina. Mucormycosis is very invasive and progressive disease with greater than 40% morbidity and mortalities. For diagnosis a very high index of suspicion and history of patient is necessary to initiate early therapy to achieve better outcome. I review here advances in pathological understanding, modern diagnostic tools including computed tomography (CT), and serum polymerase chain reaction and therapeutic options with different available medicines.

Keywords

Mucormycosis, fungal, patient, treatment, covid-19 Reverse Halo sign, PCR, Isavuconazole, Liposomal amphotericin B,

Background

Mucormycosis represents a group of life-threatening fungal infections mostly occurring in(***epidemiology***) patients with diabetes mellitus, chemotherapy, AIDS, solid organ or hematopoietic stem cell transplantation (HSCT), prolonged neutropaneia of various etiologies, defects in phagocytic functions, malignancies, elevated level of free iron(supports fungal growth), treatment with deferoxamine in patients of renal failure, diabetic ketoacidosis(DKA-rhino cerebral Mucormycosis), hyperglycemias etc. It may also affect immune-competent patients following a traumatic implantation of soil or vegetation, after maceration of skin by moist surface, burn, prolonged glucocorticoids/steroids therapy. Nosocomial or community outbreaks have been occurred via direct access

through intravenous catheters or subcutaneous injections. The Mucorales are ubiquitous environmental fungi hence human beings are constantly exposed to it. Mucormycosis is usually divided into six clinical categories based on presentation and involvement of anatomical sites viz. rhino-cerebro-orbital, pulmonary (lungs), cutaneous (skin), gastrointestinal (abdominal), disseminated (widespread) and miscellaneous or other anatomical sites. Rhino-cerebral-orbital Mucormycosis is the ***most common*** presenting form of disease. Several news-reports[viii] [ix]& studies[x] have reported an increasing incidence & prevalence of Mucormycosis in India probably due to an increase in the at-risk population and improved diagnostic tools and several factors related to covid-19 infection and its management.

In a study by **Hariprasath Prakash and Arunaloke Chakrabarti- Epidemiology of Mucormycosis in India**[xi] they found regarding Mucormycosis **Prevalence and Incidence in India** an increase in trend of Mucormycosis from a single centre at successive periods, with an annual incidence of 12.9 cases per year during1990–1999, 35.6 cases per year during 2000–2004, and 50 cases per year during 2006–2007. The total numbers increased from 25 cases per year (1990–2007) to 89 cases per year (2013–2015). This rise in incidence over the years at that centre may be due to improved awareness and expertise in diagnosing the disease, though there is possibility of an actual rise in incidence cannot be ruled out. Another 10-year study from South India (Tamilnadu) showed an annual incidence of 18.4 cases per year during 2005–2015. Another study from Tamilnadu state in south India reported 9.5 cases/year during 2015–2019. A multicentre study in India reported 465 cases from 12 centers over 21 months; the study reported an annual incidence of 22 cases/ year, and an average of 38.8 cases/ participating centre. Invasive aspergillosis is usually given more importance among invasive mould infections in intensive-care units (ICUs) but a multicentre study in Indian ICUs reported Mucormycosis in a considerable (14%) number of patients. Sindhu et al. reported Mucormycosis present at rate of 12% in ICU patients at a single centre in North India. As there is lack of **population**-based estimates, it is difficult to determine the exact incidence and prevalence of Mucormycosis in the Indian population. A computational-model-based method estimated a prevalence of 14 cases per 100,000 individuals in India. The cumulative burden ranged between 137,807 and 208,177 cases, with a mean of 171,504 (SD: 12,365.6; 95% CI: 195,777–147,688) and mean attributable mortality at 65,500 (38.2%) deaths per year. ***The data indicates that the estimated prevalence of Mucormycosis in India is nearly 70 times higher than the global data, which were estimated to be at 0.02 to 9.5 cases (with a median of 0.2 cases) per 100,000 persons.***

Mucormycosis (***pathogenesis***) infection leads to host tissue infarction and necrosis resulting from invasion of vasculature by hyphae (long, branching filamentous structure of a fungus) starting with a specific interaction with endothelial cells. These infections are very difficult to manage due to many reasons such as difficulty and delay in diagnosis, lack of diagnostic tools and pathologist. However with the introduction of new tools such as radiographic (CT/MRI) evidence, culture, biopsy with histo-pathological examinations(most sensitive and specific).Secondly, treatment is an uncalled emergency and combines medicine with surgery, which is frequently required owing to the angio-invasiveness and necrotic character of infection, and antifungal treatment.

Primary *in vitro* resistance to several antifungal drugs had limited therapeutic options which may have aroused due to injudicious use of antifungal by quacks and natural healers. However, the antifungal armamentarium increased with the US Food and Drug Administration's and European Medicines Agency's approval of the new triazole Isavuconazole[xii]. Isavuconazole is water-soluble triazole prodrug with wide-spectrum of antifungal activity. It is absorbed easily and can be given either orally or intravenously. It is hydrolyzed to its active moiety BAL4815 by enzymatic action of plasma esterases. BAL4815 inhibits fungal cytochrome P450 lanosterol 14-alpha-demethylase (CYP51) which catalyzes the conversion of lanosterol to ergo sterol, an important component of the fungal cell membrane. Enzymatic inhibition by this agent leads to a decrease in ergo sterol pool and therefore disturbs synthesis of fungal cell membrane, thereby increasing cell membrane permeability and promoting loss of essential intracellular elements which ultimately causes fungal cell lysis and death. Isavuconazole is a triazole antifungal with broad spectrum of activity and good safety profile. It is approved by the FDA and EMA for the treatment of invasive

aspergillosis and Mucormycosis. It works by inhibiting fungal cell membrane synthesis. Invasive fungal infections are significant clinical challenges for patients and clinicians treating them, especially those who are immunocompromised. In vitro, most of the *Candida* species, most *Aspergillus* species, *Fusarium* species, dermatophytes, Mucorales, *Cryptococcus* spp., and dimorphic fungi displayed susceptibility to Isavuconazole. Resistance to Isavuconazole occurs due to mutation in the target gene CYP51. Cross-resistance between Isavuconazole and other azoles may be possible although the clinical relevance is unclear. As Isavuconazole displays low water solubility, it is found as an active ingredient of its prodrug, [DB06636]. The prodrug formulation of Isavuconazole is FDA- EMA-approved and is marketed under the trade name Cresemba for the treatment of invasive aspergillosis and Mucormycosis as oral or intravenous administration. The intravenous formulation is cyclodextrin-free which gives Isavuconazole an advantage over other azoles antifungal which requires cyclodextrin for facilitating drug solubility because cyclodextrin has a potential for nephrotoxicity. The intravenous and oral dosing can be used interchangeably, without the need for a repeat loading dose when transitioning from an IV to an oral formulation. Isavuconazonium have excellent water solubility for intravenous formulations, good absorption, and enhanced oral bioavailability. After administration, Isavuconazonium undergoes biotransformation to form the active moiety, Isavuconazole, for the antifungal actions[xiii].

Mucormycosis Understanding

Human Mucormycosis infections are caused by (***etiology***) a wide range of pathogenic species. *Rhizopus oryzae* (Figure 1[xiv]) is present in 85% of rhino-cerebral forms, compared with only 17% of non-rhino-cerebral forms. This finding is due to virulence differences between *Mucorales* species. Mucormycosis' clinical presentation is also related to underlying conditions. Rhino-cerebral Mucormycosis is the most common form in patients with uncontrolled diabetes mellitus, while pulmonary Mucormycosis occurs most often in patients with hematological malignancies. Radiological findings in patients with pulmonary Mucormycosis are also related to decreased immunological status. Although its unusual, but there have been diagnosis made in the gastrointestinal system. The stomach is more involved then the colon. Usual symptoms are abdominal pain and gastro-intestinal bleeding, upset, discomfort, indigestion etc. Diagnosis can be suspected on endoscopic findings with necrotic lesions that can lead to perforation and peritonitis.

Mucorales can gain entry to a susceptible host through inhalation, ingestion of contaminated food, or abraded skin(*during covid-19 era some people are taking excessive steam inhalations as well as repeated excessive cleaning can remove protective layer too*). These routes result in rhino-orbito-cerebral, pulmonary, gastrointestinal, cutaneous/wound infections. One of the characteristic features of Mucormycosis is its angioinvasive property, resulting in vascular thromboses and ultimately tissue necrosis & destruction. Ketoacidosis and deferoxamine are known factors to predispose to Mucormycosis, revealing the importance of hyperglycemia, iron, and acidifying ketone bodies in *Mucorales* virulence. Angioinvasive property (pathogenesis) is due to the interaction between a spore-coating protein family (CotH) on *Rhizopus* species surface and endothelium glucose regulator protein 78 (GRP78) expressed at the surface of endothelial cells. The interaction between CotH and GRP78 triggers host cell injury and subsequently fungus hematogenous dissemination to different parts of the human body. Increased levels of serum glucose, iron, and ketone bodies in the body than the normal values increase fungal growth and induce the expression of GRP78 and CotH, resulting in increased ability of *Rhizopus* to invade host tissues and explaining the vulnerability of diabetic and deferoxamine treated patients to Mucormycosis. It must be noted that the majority of studies on virulence and the association between ketoacidosis and the occurrence of Mucormycosis is conducted with *Rhizopus* species. Continuously decreasing counts and derailed or improper function of monocytes cells and neutrophils cells are important Mucormycosis risk factors, because these cells can inhibit *Mucorales* spore germination. Patients with hematological disorders, AIDS, or liver cirrhosis, those who have undergone solid organ transplant, and those being treated with high-dose steroids have generally a decreased count or impaired function of neutrophils and monocytes cells. Finally, victims of natural disaster are also produce risk owing to wounds contaminated with water, soil, or debris, such as after the 2004 Indian tsunami disaster.

Clinical Findings

The initial symptoms complained by majority of patients in rhino-cerebral Mucormycosis are no specific and includes eye pain , facial pain and numbness followed by conjunctiva suffusions, unclear vision and swelling. Fever is present in more than fifty percent with elevated WBC count in patients having normal bone marrow functioning. The infection gradually spread ethmoid sinus to orbit, with compromised extra ocular muscle functions and proptosis typically added with chemosis. If not treated properly and timely the contra lateral eye involvement with resulting bilateral proptosis, chemosis, vision loss and opthalmoplegia is imminent with cavernous sinus thrombosis. Infection sometimes also spread to mouth and produces painful ulcerations of hard palate (late finding).

Pulmonary Mucormycosis is next to most common rhino-orbito-cerebral form. Symptoms of lung involvement are similar to covid-19 in many ways such as dyspnoea, chest pain, cough, sometimes fever. Angioinvasion is suggested by necrosis, cavitations (CT), and or hemoptysis. HRCT and chest x-ray is very useful to determine extent of involvement by finding consolidations, masses, nodules, cavities, wedge shaped infarcts. For differential diagnosis from aspergillosis the presence of >or = 10 pulmonary nodules, pleural effusion, and concomitant sinusitis suggest Mucormycosis more likely. It's very important to differentiate two as voriconazole used as first line treatment for aspergillosis can exacerbate Mucormycosis seen in mouse and fly models.

Cutaneous Mucormycosis resulting from external implantation can be highly invasive penetrating muscles, fascia and bones. It may result due to contamination during endotracheal intubation (covid-19 cases on ventilators), infected surgical, trauma. In Mucormycosis necrotizing fasciitis carries a mortality rate of 80 %. Prompt surgical methods of debridement are life saving in such cases.

Gastrointestinal Mucormycosis seen in premature neonates in association with disseminated disease and necrotizing enterocolitis. Abdominal pain, distension, nausea vomiting are usually seen. Hematogenous dissemination can occur from primary site of infection due to angio-invasion. The most common site of dissemination is brain with mortality near 100%.

Computed tomography

The most common radiological pattern of pulmonary Mucormycosis on initial computed tomography (CT) scan is a halo sign and then nodule or mass. However, when studied very early and on serial follow-up, sequential morphologic changes could be observed as (a) reversed halo sign (Figure 2) followed by (b) consolidation or nodule or mass with halo sign and, finally, (c) central necrosis and air-crescent sign. For pulmonary Mucormycosis, a study[xv] showed that there was a significant increase in the prevalence of reversed halo sign in neutropaneia (79%) and non-neutropaneia (31%) patients (P <0.05).

Diagnosis of Mucormycosis (Figure 3)

Mucormycosis diagnosis is difficult in early stage & it is associated with high mortality, especially in immuno-compromised patients. Differential diagnosis from invasive aspergillosis is very important, as antifungal treatment may differ, because underlying co-morbid conditions and clinical presentation are often similar. Mucormycosis diagnostic tools are based on limited basic microbiology in most rural areas and frequently led to diagnosis delay. Unlike invasive aspergillosis, the detection of circulating anti-gen such as galactomannan and β-D-1, 3-glucan provides no help in Mucormycosis diagnosis. Therefore, samples from the anatomical site of infection are most often required to diagnose Mucormycosis beside culture and clinical features.

The latest techniques of molecular biology tools have allowed non-invasive diagnosis of Mucormycosis. Million *et al.* developed a quantitative multiplex polymerase chain reaction (qPCR)-based 18S rRNA targeting *Mucor/Rhizopus*, *Lichtheimia*, and *Rhizomucor*[xvi]. The purpose of PCR assay was to detect *Mucorales* DNA early in the course of the infection in the blood (serum). The authors in a study were able to detect *Mucorales* DNA in serum samples from 90% of patients up to three days before Mucormycosis diagnosis[xvii]. Negative serum PCR have also shown better outcome as compared to patients with persistently positive PCR results. Another study performed among severely ill burn patients found that circulating *Mucorales* DNA was

detected 11 (4.5-15) days before standard diagnosis for invasive wound Mucormycosis[xviii]. Another study has evaluated the use of real-time PCR targeting *Mucorales* on tissue & respiratory samples in patients with hematological malignancy suffering from proven and probable Mucormycosis. Consequently, it is currently necessary in patients with covid-19 infections to include the value of reverse halo sign on Computed tomography scan combined with serum qPCR targeting *Mucorales* for the early diagnosis of pulmonary Mucormycosis.

Mucormycosis: indications for emergency surgery

Latest guidelines recommend antifungal treatment, surgical debridement, and correction of underlying risk factors and co-morbidities. Surgical debridement should be extensive, involving all necrotic areas for rhino-oculo-cerebral infection, and repeated surgical procedures required to achieve local control and better outcome. For pulmonary Mucormycosis, the indication and timing of surgical management outside emergency care (hemoptysis) is difficult and lung transplantation may be considered[xix]. In a European study on 230 patients, surgical treatment reduced mortality by 79%[xx], leading to discuss surgery when feasible for any localization, and if mandatory for rhino-cerebro-oculo-cerebral and post-traumatic Mucormycosis.

Antifungal treatment

Several antifungals now available for Mucormycosis treatment, the two main classes of antifungal medications used to treat Mucormycosis are the polyene (amphotericin formulations) and triazole (isavuconazole and posaconazole). Amphotericin B and isavuconazole are the two agents currently FDA approved for the primary therapy of Mucormycosis.[xxi]

Amphotericin B deoxycholate (Amb) with its lipid formulations ***liposomal Amb*** (LAmB- less nephrotoxic, better CNS penetration than ABLC & Amb, better results in murine models, expensive) as well as Amb lipid complex (ABLC) and posaconazole[xxii] were the only antifungal drugs available with *in vitro* activity against *Mucorales*. The antifungal medical management recently enlarged with the development of isavuconazole.

The first-line recommended antifungal agent is Amb (5 decades of clinical relevance, inexpensive, high toxicity, and poor CNS penetration) in dosage of 1.0-1.5mg/kg body weight qd, liposomal Amb (L-Amb) 5-10mg/kg qd (costly) or Amb lipid complex (ABLC) 5-7.5 mg/kg qd. Primary combination therapy used in some places include (caspofungin, Micafungin, Deferasirox) + lipid polyene.

The duration of the first-line antifungal treatment usually 2-4 weeks is still a matter of debate and should be determined on an individual basis and adjusted on the underlying conditions. When there is clinical and radiological improvement, a consolidation by posaconazole can be considered. However, it must be guided by negative PCR and therefore shortened for some patients. Isavuconazonium sulfate compound is a water-soluble pro-drug, which is quickly hydrolyzed to the triazole isavuconazole after oral or intravenous administration. Isavuconazole has shown high oral bioavailability, linear pharmacokinetics, and a broad antifungal spectrum of coverage. The *in vitro* activity of isavuconazole, minimum inhibitory concentration (MIC), ranges from 0.125 to 4 mg/L, across *L. corymbifera*, *L. ramosa*, *Rhizomucor pucillus*, *Rhizomucor microspores*, and *R. arrhizus* but greater against *Mucor circinelloides* (1 to 16 mg/L).The minimum inhibitory concentration found to be one- to three-fold higher than posaconazole. In the Lancet infectious disease published vital study, 21 patients were treated with isavuconazole as first-line of treatment; 42-day response rate was only 14% and week 12 response was 10% compared to 45% of the AmBizygo study which found 43% deaths[xxiii]. The results found through this study a mortality rate at day 42 comparable to that observed in the AmBizygo study. In this study, isavuconazole was well tolerated and toxic effects were an uncommon cause of discontinuation. The place of isavuconazole has not yet been specified in the most recent guidelines and textbooks. At last but not least, a cost-effectiveness study demonstrated positive economic impact of the use of isavuconazole compared over Amb for the treatment of Mucormycosis[xxiv].Posaconazole shown to have *in vitro* and *in vivo* activity against *Mucorales*, but there are no data for the use of first-line posaconazole therapy in Mucormycosis. Here it is very important to

know that there are currently no validated MIC breakpoints for any of the available medicine used as antifungals. Thus the determinations of susceptibility categories are not possible for the agents of Mucormycosis.

Immunostimulating drugs

A study recently reported the beneficial role of a treatment with the checkpoint inhibitor nivolumab and interferon-Y[xxv] for Immuno-competent patient with extensive abdominal Mucormycosis unresponsive to conventional therapy.

Conclusion

Mucormycosis infection can be a life-threatening fungal infection if not treated timely and properly. The infection is characterized by host tissue infarction and necrosis that occurs mostly in immunocompromised patients and is associated with an increasing incidence and mortality in covid-19 patients in India despite the availability of therapeutic tools. Determining whether the patient has invasive aspergillosis or Mucormycosis could be challenging at the bedside. The latest development of new tools in molecular biology helps us to obtain earlier diagnosis for starting optimal medico-surgical treatment. Comparative studies are needed to better optimize induction and consolidation treatment. The optimal dosage for antifungal treatment of Mucormycosis is not well established and mainly guided by patient's conditions and laboratory findings. Echinocandin – lipid polyene combinations improved survival rate among mice with disseminated Mucormycosis. The antifungal treatment should be continued until resolution of clinical signs and symptoms with resolution or stabilization of radiological signs and resolution of underlying immuno-suppression.

Prophylaxis: Patients receiving antifungal prophylaxis or injudicious use of with either itraconazole or voriconazole may be at increased risk of Mucormycosis.[xxvi] These patients typically presents with disseminated Mucormycosis, the most lethal form of disease. Breakthrough Mucormycosis has been described repeatedly in patients receiving posaconazole or echinocandin prophylaxis. For patients who are receiving immunosuppressant's infected with Mucorales secondary antifungal prophylaxis is given as long as immunosuppressive drugs are given.

'Declarations':

-This paper has not been previously published and is not currently under consideration by another journal. The document is Microsoft word with English (United States) language & 4036 words Total.

- Ethics approval and consent to participate: Not applicable. This study has not involved any human or animals in real or for experiments.

-**Consent for publication:** Not applicable

-**Availability of data and materials:** The data & materials for study are available as reference.

-Conflicts of Interest/ Competing Interest: There are no conflicts / competing of interest

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Figures

Figure1. Morphological features of Rhizopus oryzae separated from soft rot lesions on apple (Malus pumila var. dulcissima Koidz.). A, Colony growth seen on potato dextrose agar after a 7 day incubation; B, Sporangium and sporangiophore;C, Columella; D, Sporangiospores; E, Rhizoids.

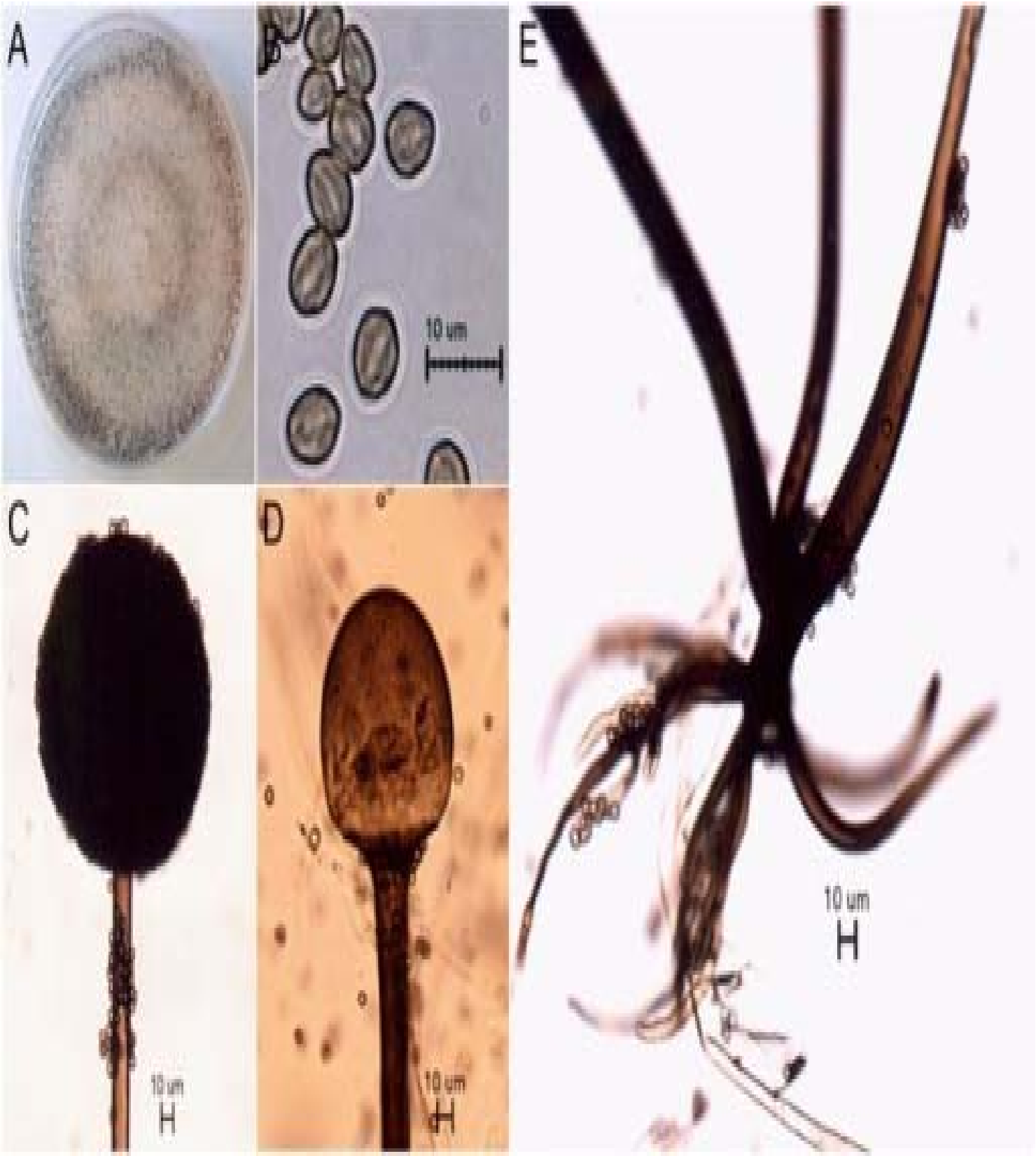


Figure 2[xxvii] the reversed halo sign in pulmonary Mucormycosis seen in a renal allograft recipient

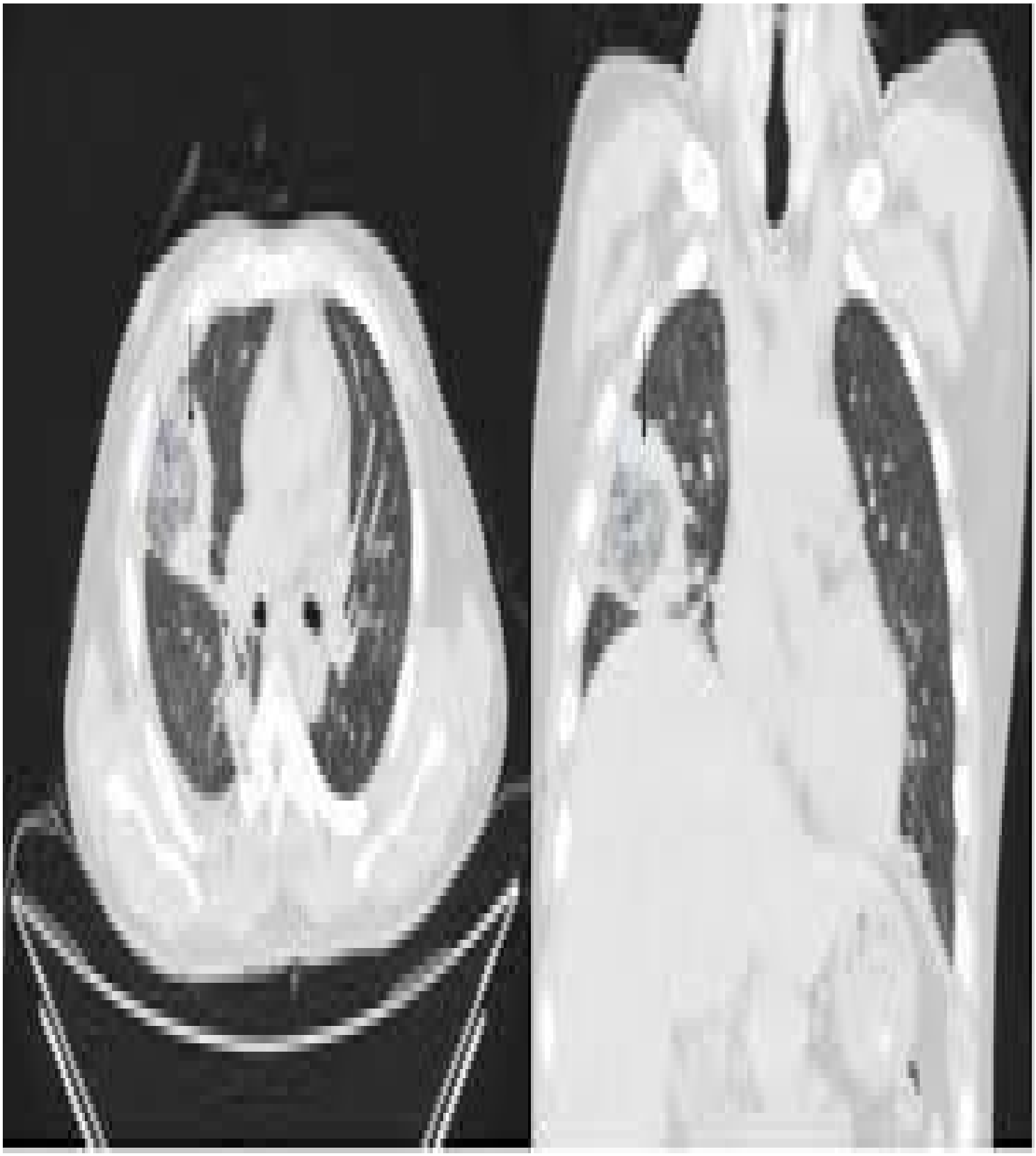
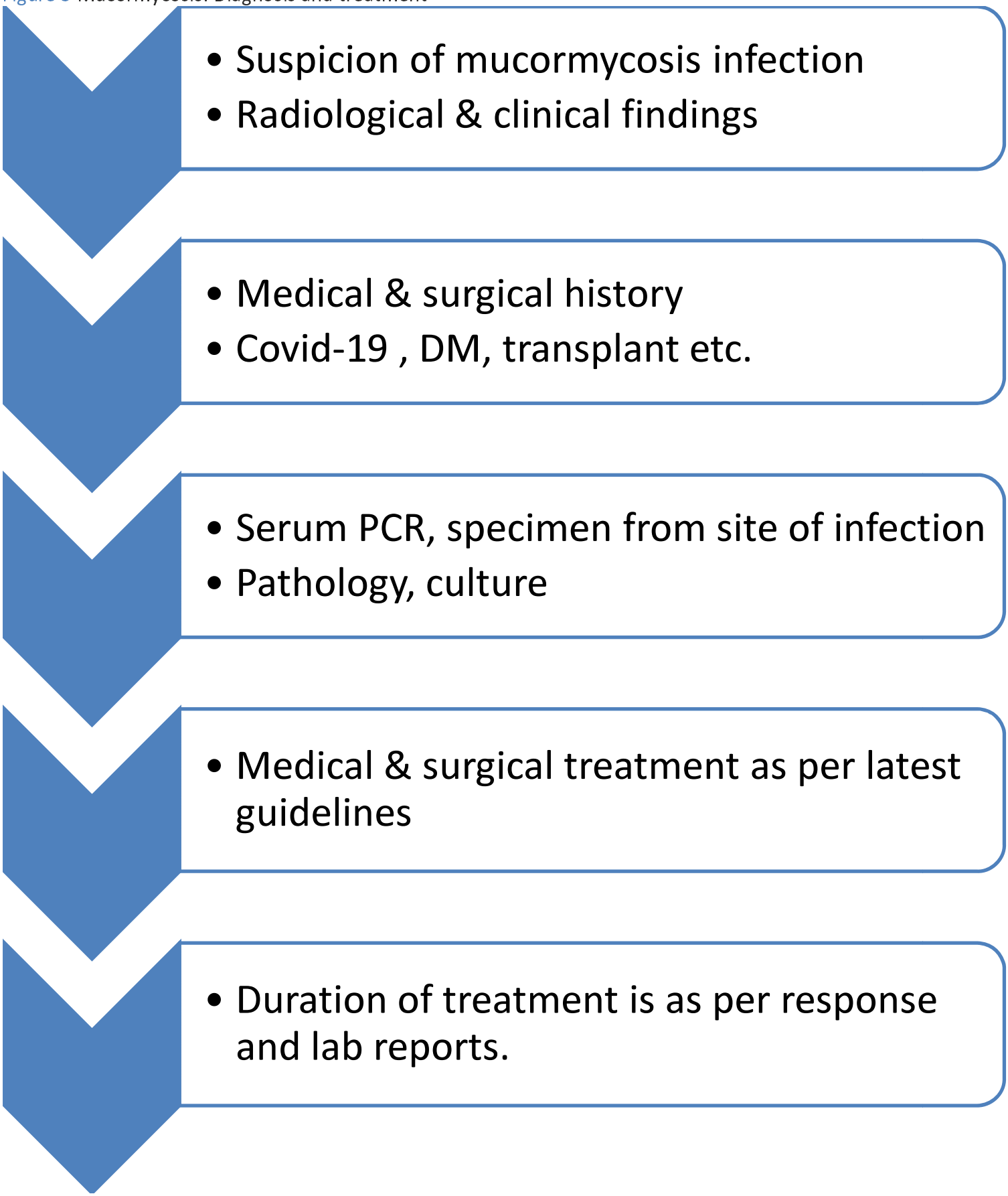


Figure 3 Mucormycosis: Diagnosis and treatment



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