REVIEW

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In recent times, numerous reports of systemic fungal infections have been a major concern. The angioinvasive fungal infection, mucormycosis has surged in patients with COVID-19 due to various factors, mainly uncontrolled diabetes and inappropriate corticosteroid use. The prevalence of this acute and fatal fungal infection caused by Mucorales-related fungal species has been highest in the Indian population. COVID-associated mucormycosis (CAM) has a propensity for contiguous spread, and exhibits high morbidity as well as mortality. Unless promptly detected and treated, it is associated with a poor prognosis. A high index of suspicion, aggressive surgical debridement and use of systemic antifungal agents continue to be the standard of care for CAM. Moreover, there is an imperative need to address this public health issue by increasing public awareness and education. This article provides a comprehensive overview on the emergence of CAM during the pandemic, the current burden, pathophysiology, diagnostic interventions and management of CAM in Indian clinical practice.

Key words: Mucormycosis, COVID-19, antifungal

INTRODUCTION

SARS Coronavirus disease-2019 (SARS CoV-19) shows a correlation with various opportunistic bacterial and fungal infections (Singh *et al.,* 2021). In recent times, several cases of mucormycosis, also incorrectly referred to as black fungus infection, have been widely reported globally, and especially from India (Singh *et al.,*2021; Rahman *et al.,*2021).It is a life threatening invasive fungal infection, which is increasing among patients affected with or recovering from COVID 19(Rahman *et al.,*2021; Devnath *et al.,*2021).Dissemination of mucormycosis in the human body can occur extremely fast, and a delay of even a few hours could be fatal (Rahman *et al.,* 2021) Mucormycosis is often associated with extremely severe complications in immuno-compromised patients. Such infections are caused by opportunist and ubiquitous fungi belonging to the order Mucorales, family Mucoraceae. Solid organ transplantations and neutropenia, haematological malignancies, stem cell transplantation, use of steroids, and uncontrolled diabetes mellitus serve as critical risk factors for development of mucormycosis(Devnath *et al.*2021).Rapid progression of mucormycosis might occur without early diagnosis and treatment. Mortality rates of 50–80%from intra-orbital and intracranial complications have been reported.Management is often challenging even after early diagnosis, treatment of underlying diseases along with aggressive medical and surgical measures. There could be possible extension of infection and ultimately death (Sharma *et al.* 2021).The current review aims at providing a comprehensive review on available evidence on COVID-associated mucormycosis (CAM).

EPIDEMIOLOGY

The prevalence of mucormycosis varied from 0.005 to 1.7 per million population worldwide. However, according to a recent estimate of year 2019-2020, prevalence of mucormycosis is almost 80 times higher (0.14 per 1000) in India in comparison to developed countries (Singh *et al.,* 2021).The incidence of mucormycosis has increased more rapidly during the second wave of COVID-19 with over 45,432 cases and 4,252 deaths

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reported as on 15th July 2021(Raut *et al.,* 2021; Kumar *et al.* 2021).India contributed to nearly 71% of the global cases of mucormycosis in patients with COVID-19 (Raut and Huy, 2021).India continues to have the second largest population with diabetes mellitus (DM) and importantly, DM has been the most frequently associated risk factor for mucormycosis in India (Singh *et al.* 2021).

The first case of mucormycosis was reported in a 15-year-old boy from Gujarat, who recovered successfully from Covid-19 and got discharged. Subsequently, the first death caused by mucormycosis was reported from Auraiya district in Uttar Pradesh. The highest death rate was recorded in the state of Rajasthan. Most of the cases were reported from the states of Gujarat, Maharashtra, Rajasthan, Karnataka, Andhra Pradesh, Haryana and Telangana according to government reports (Bhogireddy *et al.* 2021).A multicenter epidemiologic Indian study conducted by Patel *et al.,*(2021) demonstrated that among 287 mucormycosis patients, 65.2% had CAM and the CAM prevalence was 0.27% among hospitalized COVID-19 patients. In 32.6% of CAM patients, COVID-19 was the only underlying disease.

CLINICAL FEATURES OF CAM

On the basis of clinical presentation and the anatomical site infected, mucormycosis is classified into rhino-orbito-cerebral (ROC), pulmonary, gastrointestinal, cutaneous, and disseminated types. The ROC form usually occurs in patients with uncontrolled diabetes and diabetic ketoacidosis. On the other hand, pulmonary, gastrointestinal, and cutaneous infections are frequently reported from patients with hematological malignancies or neutropenia, severe malnutrition, and trauma or burns, respectively (Singh *et al.* 2021). Clinical features of CAM include certain symptoms which are illustrated in Fig. 1 (Rocha *et al.* 2021).

Mucormycosis might affect the lungs, however, nose and sinuses are the most commonly infected sites. The disease can then spread to the eyes, leading to blindness, or to the brain, initiating headaches and seizures. The most common form is ROC mucormycosis, followed by pulmonary mucormycosis (Rocha *et al.* 2021).

PATHOPHYSIOLOGICAL ASPECTS

The main characteristics of COVID-19 create an ideal environment for the growth and development of Mucorales inside the human body (Fig. 2) [Mahalaxmi *et al.* 2021]. COVID-19 leads to atrophy of lymphoid tissue, weakens defence system reserve pool, and prevents further proliferation of protective lymphocytes. Furthermore, occurrence of lactic acidosis destroys the regenerative type II alveolar cells causing respiratory compromise, which exacerbates acid-base levels. Ultimately, this results in hypoxemia and hypoperfusion (Almas *et al.* 2021).

Also, potential mechanisms by which diabetes increases COVID-19 morbidity and mortality include decreased viral clearance, reduced T-cell function, high cytokine storm and immune-suppression.Hyperglycaemia worsens the cytokine storm by disturbing endothelial cells resulting in multi-organ damage in COVID-19 patients. During diabetic ketoacidosis, the growth and invasion of Mucorales is supported by the acidic environment and increased levels of free ferric ions(Mahalaxmi *et al.* 2021).As mucormycosis invades blood vessels, insulin resistance and high glucose levels lead to proliferation of fungus and progressive deterioration of an already weakened immune system (Almas *et al.* 2021).

Additionally, steroids decrease inflammation and activity ofthe immune system, where the production of white blood cells and T-helper cells are reduced, easily enabling microorganisms to invade and entirely corrode the host immune system. Also, these steroids could trigger the uncontrolled release of sugar,which also enables Mucorales to grow, multiply and invade at arapid rate (Mahalaxmi *et al.*2021).

RISK FACTORS FOR CAM

Diabetes mellitus continues to be the major risk factor associated with mucormycosis globally, with a mortality rate of 46% (Singh *et al.* 2021).In COVID-19 patients with diabetes, mucormycosis could result in adverse clinical outcomes and prolonged hospital stay (Mishra *et al.,* 2021).A study by Ravani *et al.* reported that the major risk factors associated with CAM were uncontrolled diabetes (96.7%) and COVID-19 positivity (61.2%), along with concomitant steroid use (61.2%).Other

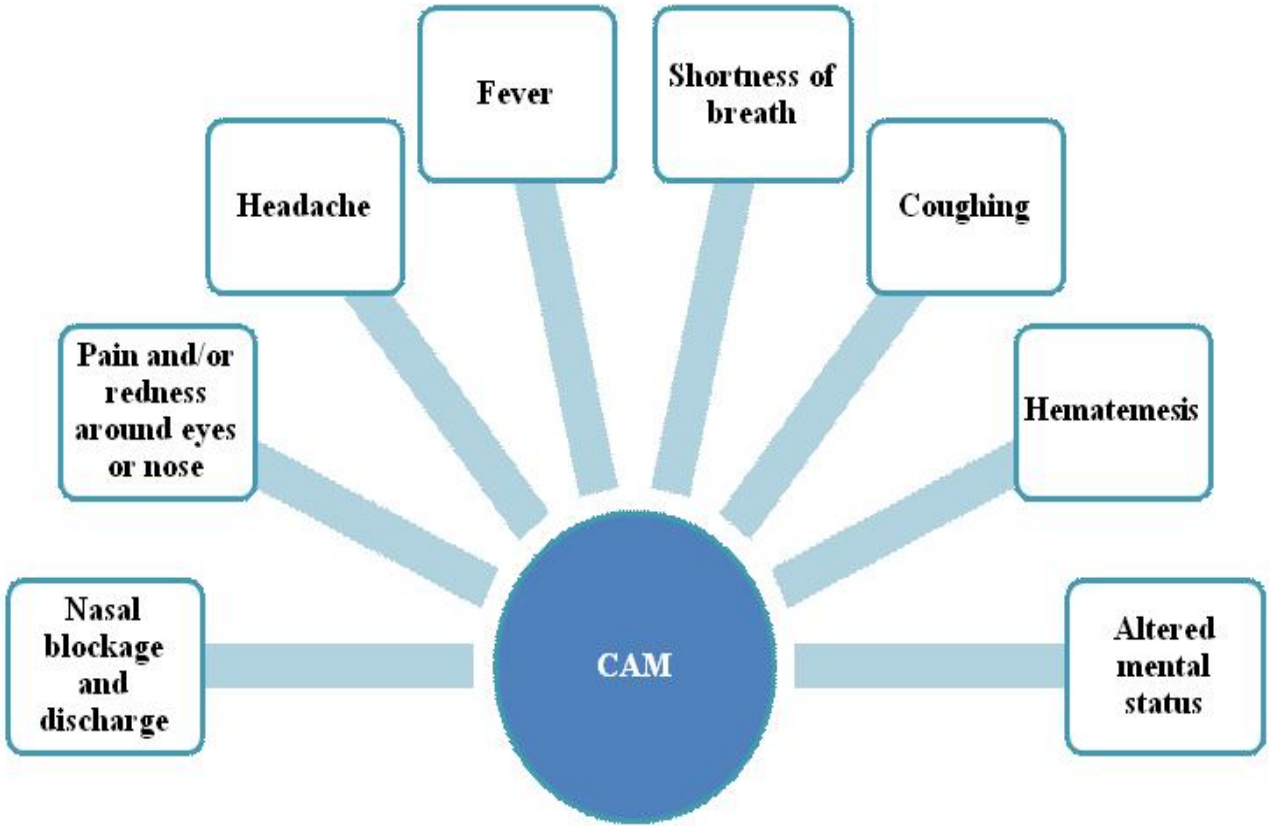

Fig.1: Clinical features of CAM

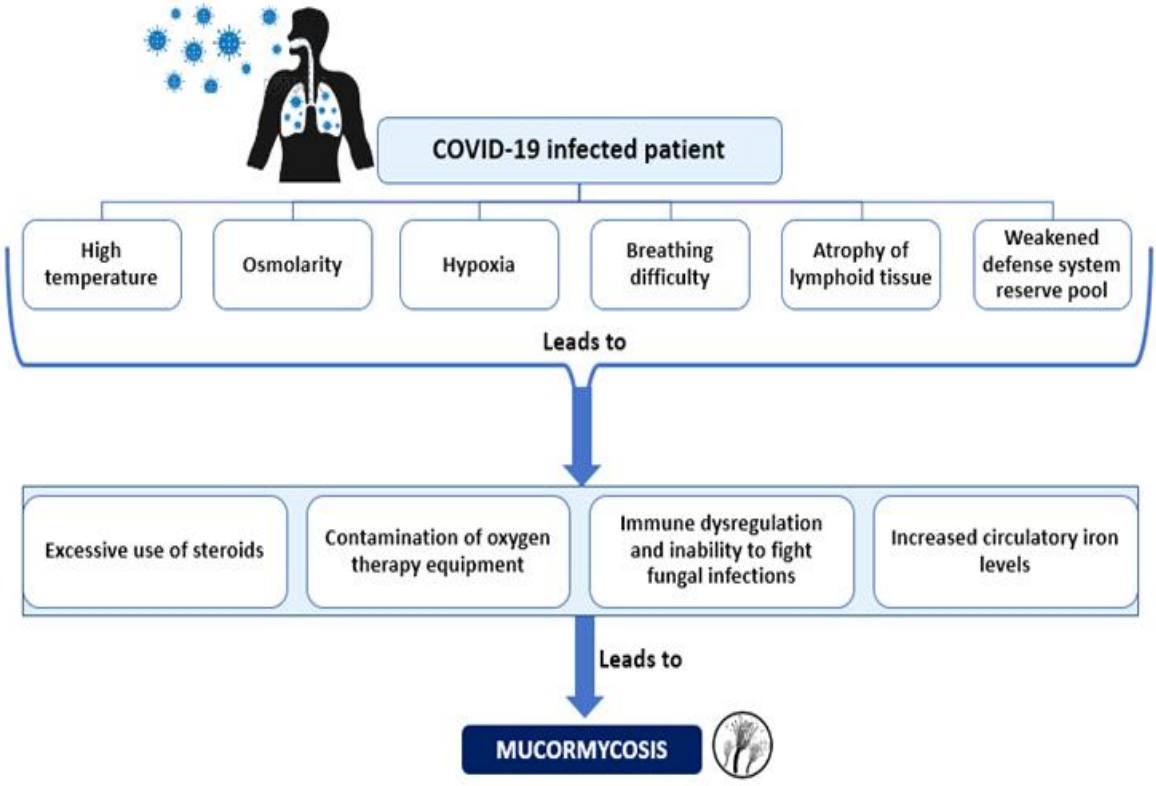

Fig. 2: Possible correlation of COVID-19 and mucormycosis

well-known major risk factors include iron overload, deferoxamine therapy, malignancy, organ transplantation, inappropriate corticosteroid use and environmental mucoralean spore count (Patel *et al.* 2021; Mishra *et al.* 2021; Rudramurthy *et al.* 2021).Additionally, COVID-19 associated glycaemic imbalance, hypoxemia, elevated iron levels, vascular endothelial injury, immunosuppression and diabetic ketoacidosis are also considered as crucial risk factors (Patel *et al.* 2021; Gandra *et al.* 2021; Pal *et al.* 2021). The rampant usage of glucocorticoids in COVID-19 patients is undoubtedly responsible for an upsurge in cases of CAM. Moreover, evidence suggests that lack of phagocytes or impaired phagocytic function increases risk of mucormycosis (Pal *et al.* 2021).

Interestingly, many cases have presented with no risk factors, apart from a history of COVID-19 and its recommended steroid therapy, thereby making it more challenging (Suvvari *et al.* 2021).Also, prolonged hospital stay with mechanical ventilation, indiscriminate and prolonged use of antibiotics as well as oxygen therapy could predispose to mucormycosis (Dasand Dhar, 2021).

DIAGNOSIS

Early detection of infection is a key aspect in the management and subsequent outcome of patients suffering from mucormycosis (Banerjee *et al.* 2021). According to literature, the mean duration between diagnosis of COVID-19 and onset of mucormycosis symptoms is 15.6 ± 9.6 days. A delay of even 6 days in starting treatment doubles the 30-day mortality from 35% to 66%, which signifies the importance of early diagnosis (Rocha *et al.* 2021).Certain unique characteristics and key distinguishing factors could aid early suspicion of infection and subsequently confirm the diagnosis. The two common manifestations of CAM are rhino-orbital-cerebral and pulmonary. Tissue necrosis manifested as a necrotic lesion, eschar or black discharge in the nasal or oral cavity is the clinical hallmark. Orbital, ocular and cranial nerve involvement are warning signs (Fig. 1). Pulmonary mucormycosis has specific radiologic findings which enable distinguishing it from aspergillosis (Soman *et al.* 2021).The most frequent CT findings are consolidation and cavitation. Pleural effusion, pneumothorax and nodules have also been observed (Garg *et al.* 2021a,b).

Negative galactomannan and Beta-D-Glucan (BDG) assays are useful for ruling out other mould infections. Biopsy, KOH mount and Calcofluor stains are rapid diagnostic approaches. Biopsy is the mainstay of diagnosis with benefits out weighing the risks, even in a 'difficult to access' location or in cases of coagulopathy (Soman and Sunawala, 2021).T cells specific for Mucorales, such as CD4+ and CD8+, produce cytokines like IFN-ã and IL-4, IL-10, IL-17, and fungal filaments that cause damage. These unique T cells are only present in patients with invasive mycosis. Thus, they may be useful surrogate diagnostic markers for invasive mycosis (Gupta *et al.* 2021).

MANAGEMENT

For minimizing mortality associated with CAM, reversal of underlying immunosuppression is essential (Solanki *et al.* 2021).Control of hyperglycaemia, early antifungal treatment and aggressive surgical debridement of necrotic tissue if required, are essential for the successful management of mucormycosis (Solanki *et al.* 2021; Garg *et al.* 2021 a,b).Aggressive debridement aids in decreasing fungal load and faster penetration of antifungal therapy (Solanki *et al.* 2021).In addition to timely treatment with prescribed drugs and surgical interventions, judicious use of corticosteroids in COVID-19 patients and adopting appropriate hygienic and sanitization measures would enable reducing cases of CAM (Al-Tawfiq *et al.* 2021).Moreover, patients with diabetes must be advised to control glucose levels (Moona and Islam, 2021).

Antifungal therapies

Liposomal Amphotericin B is the first-line anti-fungal treatment for CAM (Bhatia, 2021; Nambiar *et al.* 2021). Posaconazole and combination therapy of liposomal amphotericin B or amphotericin B lipid complex with caspofungin are options for second-lineor salvage treatment (Nambiar *et al.* 2021). Recommendations for high dose liposomal amphotericin B along with the adequate dosage of intravenous isavuconazole and posaconazole are also available in literature. Both triazoles can also be given as salvage treatment. Prophylaxis with posaconazole can be given in high-risk patients like neutropenic patients who have graft versus host disease. There is inadequate evidence with respect to use of other antifungal combination therapies and for prophylaxis in COVID-19 (Bhatt *et al.* 2021).

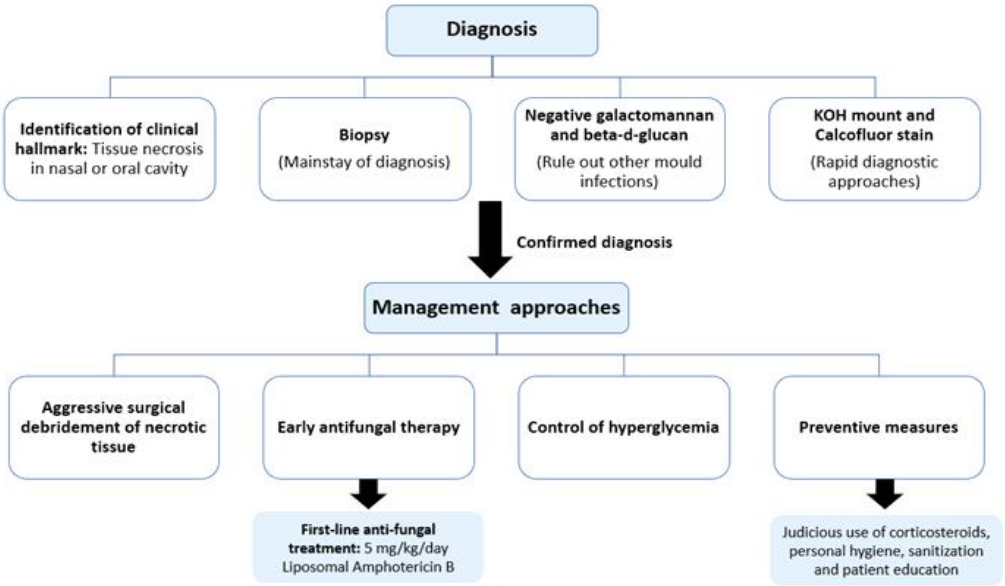

Fig. 3: Diagnosis and management of CAM

According to the European Confederation of Medical Mycology/International Society for Human and Animal Mycology (ECMM/ISHAM) recommendations, of all the available injectable amphotericin B formulations, liposomal amphotericin B is strongly recommended at a dose of 5 mg/kg per day in 200 ml of 5% dextrose over 2–3 h for 3–6 weeks (Rudramurthy *et al.*2021).

Furthermore, as per the Directorate General of Health Services (DGHS)-India, guidelines, liposomal amphotericin B needs to be continued till a favourable response is achieved and disease is stabilized.Subsequently, step down to oral posaconazole (300 mg delayed release tablets twice a day for 1 day followed by 300 mg daily) or isavuconazole (200 mg 1 tablet 3 times daily for 2 days followed by 200 mg daily) is advised.Treatment must be continued until clinical resolution of signs and symptoms of CAM, along with resolution of radiological signs of active disease and elimination of predisposing risk factors like hyperglycaemia and immunosuppression.Steroids must be used judiciously, taking into consideration the correct dosage, right timing and recommended duration. Also, antibiotics must be used rationally.

Empirical therapy with antifungals and steroids necessitates antifungal stewardship.Maintenance therapy is essential for long-term immunocompromised patients.The duration of initial phase of therapy and consolidation therapy are not clearly defined and have to be customized. It may be prudent to give Amphotericin for 4 – 6 weeks followed by oral azoles for 3 – 6 months (Nambiar *et al.* 2021).

Surgical interventions

Surgery is indicated in cases of rhinocerebral and skin/soft tissue involvement (Nambiar *et al.*2021).However, the need for risky and potentially disfiguring surgical interventions increases chances of mortality and morbidity.Surgical interventions entail considerable expertise and interdisciplinary co-ordination, which can only be conducted at advanced centres and thus become more challenging during the pandemic (Sarda *et al.* 2021).Surgical debridement is a crucial aspect of the management of COVID-19 associated rhino-orbito-cerebral mucormycosis (C-ROCM). The scope of surgery may differ from local resection to radical resection of the involved area. An open surgery like maxillectomy, orbital exenteration or craniofacial resection could be reserved for an extensive disease, mainly with involvement of orbit or central nervous system. Debridement of necrotic tissue in rapidly progressive disease, chiefly in diabetics, could increase survival chances. Follow-up surgeries for rehabilitation and reconstruction must be undertaken for improving long-term outcomes (Malhotra *et al.* 2021).

Fig.3 illustrates a simplified algorithm ofdiagnosis and treatment of CAM.

Intraocular Amphotericin injections

In cases of orbital involvement in ROCM, case-specific therapy is guided by the disease extent. Early disease, with preserved vision, might respond to transcutaneous retrobulbar Amphotericin injection (1 ml of 3.5 mg/ml Amphotericin for 3 days). Also, this could be given in cases of sinus debridement where the orbital wall is breached (Malhotra *et al.* 2021).

Preventive Measures

Prevention is possibly the best weapon against CAM that needs control of every risk factor (Sakthivel and Ish, 2021).Judicious use of corticosteroids, antifungals, and broad-spectrum antibiotics is a must. Corticosteroids at recommended doses with strict sugar monitoring is essential. In high-risk COVID-19 patients, strict follow-up is essential. Drugs like tocilizumab must be used based on evidence-based recommendations only, as they decrease immunity (Solanki *et al.* 2021).

Other measures which may play a role in preventing CAM include appropriate sanitization and handling of oxygen gas cylinders, proper decontamination of hospital environment, using disposable oxygen humidifiers, and using clean distilled water in oxygen humidifiers and oxygen concentrators. Stringent maintenance of personal hygiene even after recovery from COVID-19 is mandatory. Educating COVID-19 patients regarding the early signs and symptoms of mucormycosis at the time of hospital discharge could aid in early diagnosis of CAM (Banerjee *et al.* 2021).Self-medication should be discouraged (Gupta *et al.,* 2021).Lastly, systematic surveillance for controlling DM and educating physicians regarding early diagnosis of CAM are advised(Pakdel *et al.* 2021).

FUTURE DIRECTIONS AND WAY FORWARD

It is necessary for physicians to be on the lookout for occurrence of mucormycosis in COVID-19 patients, especially patients with type-2 diabetes mellitus,elderly patients, and individuals with facial pain, orbital pain or blood stained sinus drainage (Chavda and Apostolopoulos, 2021).The lack of substantial evidence for many immune-suppressive drugs necessitate urgent reassessment of current guidelines for COVID-19, including monitoring for late-onset opportunistic fungal infections (Rodriguez-Morales*et al.* 2021).

The way forward for dealing with CAM involves meticulously reinforcing the healthcare system, judiciously using steroids, closely monitoring glycaemic status in COVID-19 patients, regularly monitoring high-risk COVID-19 patients for timely detection of mucormycosis, increasing anti-fungal drug supply and interdepartmental collaboration for appropriate management (Sarda *et al.* 2021).Comprehensive studies for evaluating how COVID-19 triggers mucormycosis are the need of the hour (Al-Tawfiq *et al.* 2021).Additionally, evidence on factors like newer variants of the virus, unclean ventilation systems, and use of industrial oxygen are required for better understanding of the disease pathogenesis. Epidemiological and large-scale data are urgently needed(Sakthivel and Ish, 2021).

CONCLUSION

Till date, majority of CAM cases have been reported from India. This might be attributable to factors like high prevalence of diabetes and rampant use of corticosteroids in the country. Early detection and testing protocols are mandatory. The treatment involves surgical debridement and antifungal drugs for enabling better survival outcomes. Liposomal Amphotericin B continues to be the first-line antifungal therapy for this infection. Furthermore, to reduce the burden of CAM, various measures like rational use of corticosteroids, maintaining optimal glycaemic levels in patients with COVID-19 and maintaining personal hygiene are necessary. Robust research on pathophysiological, diagnostic and management aspects in COVID-19 is needed for enhancing clinical outcomes.

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