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Review

A Comprehensive Review on the Management of COVID-19-Associated Mucormycosis (CAM): The New Basics

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Abstract: The outbreak of coronavirus disease (COVID-19), which comes with several comorbidities, was declared a pandemic in early 2020 by World Health Organization (WHO). Glucocorticoids that are used in severe cases of COVID-19 as therapeutic measures may lead to opportunistic fungal infections in such patients. Mucormycosis is one of these infections and mostly occurs in immune-compromised patients such as those who undergo transplant surgeries. However, it rarely develops in COVID-19 patients, although many cases of COVID-19-associated mucormycosis (CAM) have been found in developing nations, like India. CAM usually develops between 15 days to a few months after hospitalization or complete recovery from coronavirus disease. It is an uncommon yet serious infection that further agitates the severe symptoms of COVID-19 disease. Patients with diabetes mellitus and other comorbidities are likely to be at a higher risk for developing mucormycosis. Concurrent glucocorticoid therapy possibly heightens the risk as it increases blood glucose levels. Dentists, as frontline healthcare workers, maybe the first to be presented with oral manifestations and therefore need to pay special attention. In light of the available pieces of evidence, this review highlights the basics of the underlying condition starting from the pathology, causative factors, and clinical manifestations, including the oral cavity, to diagnosis, treatment, and prevention of mucormycosis with both conventional and advanced approaches. We limited this study to the basic and established methods of CAM management and treatment along with the statistical updates. Other antifungal drugs and novel microbiological peptides are in development and need future studies for their elucidation.

Keywords: corticosteroids; clinical manifestations; diagnostic measures; combination therapy; prevention

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1. Introduction

Immune-compromised diseases lead to a majority of opportunistic conditions such as oral fungal infections, also known as oral mycosis. Often, the impairment of host resistance leads to the initiation of pathogenic conditions in the oral cavity, and progression through local colonization. The use of immunosuppressive drugs and immunodeficiency upon viral infection, especially in COVID-19 patients, has led to a significant increase in the frequency of oral mycosis globally [1,2]. So far, the diagnostic measures for oral mycotic conditions have been dealt with using clinical and cytological/histopathological tests of the oral tissues [3], although advanced diagnostic and treatment methods are being developed to achieve new landmarks.

Mucormycosis and zygomycosis imply a group of distinctive mycoses, caused by two phyla of the fungal kingdom: *Entomophthorales* and *Zygomycota*, respectively [4]. The highly transmitted infectious disease COVID-19 caused by SARS-CoV-2 is responsible for causing respiratory infection [5–7], diffuse alveolar damage, and severe inflammation following immunosuppression as represented by a decrease in numbers of CD4-T and CD8-T cell counts [8].

Treatment protocols for COVID-19 patients usually involve higher doses of corticosteroids which reduce the immune response and increase glucose levels in the blood due to the steroid administration itself or even pre-existing diabetes mellitus which further leads to opportunistic diseases such as mucormycosis [9]. The main symptoms of COVID-19, including hypoxia, hyperglycemia, and hyperferritinemia, go hand-in-hand with predisposing conditions like diabetes mellitus (DM), diabetic ketoacidosis (DKA), and hyperglycemia (Figure 1). Moreover, the presence of high free iron levels in the serum of patients undergoing SARS-CoV-2 therapy may facilitate the attachment of fungal spore coat protein CotH3 to glucose-regulated protein 78 (GRP78) on the surface of endothelial cells. This phenomenon leads to aberrant signaling causing damage to epithelial cells, immune cells, cytokine storm, HIF-1α upregulation, and eventually thrombosis or tissue necrosis [10].

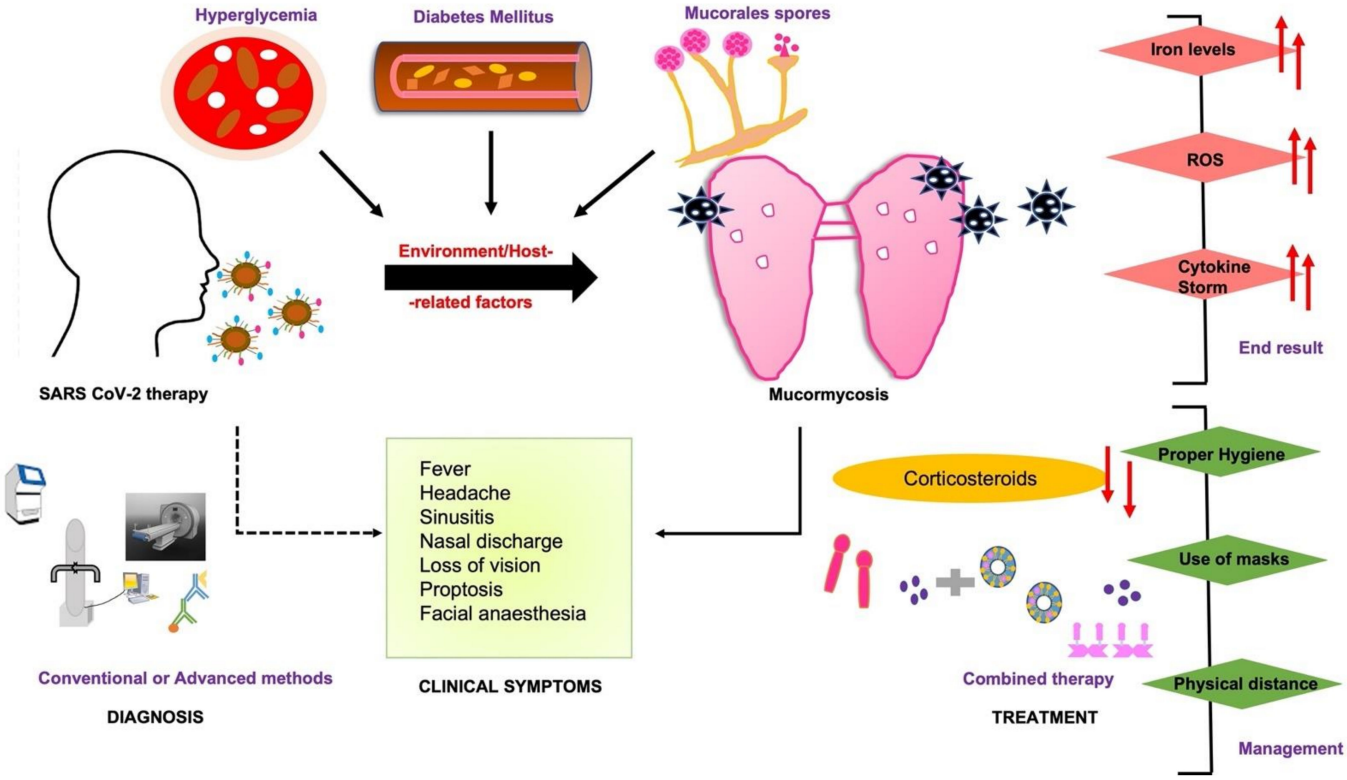

Figure 1. COVID-19-associated mucormycosis (CAM) prognosis depends upon early diagnosis by clinical symptoms, and treatment based on a combined strategy of conventional and advanced diagnostic assays. The early diagnosis may affect the end result and timely management of the disease. The dashed line represents some of the clinical outcomes linked to COVID-19-associated therapy or directly to mucormycosis (bold line).

This review adds to the basic yet advanced knowledge about the management of COVID-19-associated mucormycosis (CAM) highlighting the need of the hour in yet another pandemic surge.

2. Epidemiology

In the United States, the incidence of mucormycosis was reported to be approximately 1.7 cases per 1,000,000 inhabitants every year, which is equivalent to 500 patients in a year [11]. Overall, an average of 2–3% of patients undergoing allogeneic bone marrow transplantation are associated with mucormycosis incidence [9,12]. Until 2009, the highest number of patients was observed from India, the United States, and Australia [13]. In India, the occurrence of mucormycosis is approximately 0.14 cases per 1000 individuals, which is almost 80 times of that in developed countries [11]. In other studies, 98 and 162 cases

of mucormycosis were reported in Iran between 1990 and 2015 and from 1990 to 2011, respectively [14].

Chinese studies have found a relatively higher incidence of secondary infections (8–15%) in COVID-19 patients, although the source of infection has been vague [15–18]. A German study found COVID-19-associated invasive pulmonary aspergillosis (IPA) in 5 (26.3%) out of 19 consecutive critically ill patients [19], whereas in the Netherlands the same incidence was reported to be 19.4% [20].

Mucormycosis, a newly emerging malignancy associated with the coronavirus (COVID-19) infection, had infected at least 7250 people in India by the third week of May 2021 (Table 1); the number reportedly increased to more than 50,000 cases by December 2021. Variable case numbers per million inhabitants for other continents, such as Europe (0.2 cases in Denmark to 95 cases in Portugal), the United States (3.0), Canada (1.2), and Australia (0.6), were anticipated in 2021 [21].

Table 1. List of different states in India with the highest number of CAM cases followed by the number of deaths based on an article in the Hindustan Times published on 21 May 2021. (ND—Not Defined).

Indian States	Number of Cases	Number of Deaths
Maharashtra	1500	90
Gujarat	1163	61
Madhya Pradesh	575	31
Haryana	268	8
Delhi	203	1
Uttar Pradesh	169	8
Bihar	103	2
Chattisgarh	101	1
Karnataka	97	ND
Telangana	90	10

3. General Mycology

Fungi belonging to the order *Mucorales* are majorly divided into six different families wherein *Mucoraceae* is the most frequent cause of mucormycosis [22]. The most important species in order of frequency are *Rhizopus arrhizus (Oryzae)*, *Rhizopus microsporus* var. *rhizopodiformis*, *Rhizomucor pusillus*, *Cunninghmella bertholletiae*, *Apophysomyces elegans*, and *Saksenaea vasiformis* [22–25]. The newly emerging species include *Rhizopus homothallicus*, *Thamnostylum lucknowense*, *Mucor irregularis*, and *Saksenaea erythrospora* [26] (Table 2). *Mucoraceae* may be divided into sporangium producers, sporangiolum producers, and merosporangium producers based on morphology. For instance, lactophenol cotton blue-stained elements such as rhizoids, stolons, and columella or hyphae are able to differentiate between the fungal species [23,24].

The identity of the fungal species does not infer the relevant therapy as diseases caused by these species is phenotypically identical. The optimal temperature for the growth of aerobic *Mucorales* is 28–30 °C for an incubation period of 2–5 days. The clinically relevant *Mucorales* initiate and facilitate the decay of organic material so that exposure to spores of these fungi is inevitable. Despite their ubiquitous existence, the infection caused by the *Mucorales* is not common owing to its low virulence but is an indication of a serious underlying predisposition [4].

Table 2. The table lists different fungal species associated with CAM versus emerging species.

CAM-Associated Species	Prevalence	References
Rhizopus spp.	Mexico, Iran, India 40–50%	[22–27]
Cunninghamella spp.	Global 40–60%	
Lichtheimia spp.	Europe (France) Up to 80%	
Rhizomucor spp.	Australia, France, Italy, India 90–100%	
R arrhizus	Worldwide 60%	
Mucor spp.	USA, Mexico, Iran, Greece 70–90%	
Apophysomyces	Asia (India) 90%	
Emerging Species		
Rhizopus homothallicus	Asia 7.6%	
Thamnostylum lucknowense	Asia	
Mucor irregularis	China, India	
Saksenaea spp.	France, Australia 60–70%	
ToR microspores	India 11%	

4. Immune System Abnormalities

The role of immune modulation in mucormycosis has been evident as natural killer (NK) cells produce cytokines and chemokines such as granulocyte-macrophage colony-stimulating factor (GM-CSF), tumor necrosis factor (TNF-α), and interferon-gamma (IFN-γ), which influence the regulation of other immune cells and have both direct and indirect cytotoxic effects on the fungal growth. Necrotic areas have been evident in tissues with no obvious fungal development suggesting that thrombotic ischemia may occur due to the systemic platelet activation. Moreover, phagocytes release pro-inflammatory cytokines such as TNF-α, interleukin-1 beta (IL-1β), and IFN-γ which activate other immune cells. In this regard, for neutropenic patients with mucormycosis, the use of GM-CSF and granulocyte colony-stimulating factors (G-CSF) is highly recommended [28]. Nevertheless, the phagocytes of normal hosts kill *Mucorales* by the generation of oxidative metabolites and the cationic defensins [29] and therefore remain the major host defense mechanism against mucormycosis. However, evidence of the high prevalence of autoantibodies against immunomodulatory proteins (including cytokines, chemokines, complement components, and cell-surface proteins) in COVID-19 patients further supports the exacerbations associated with mucormycosis [30].

5. Clinical Manifestations

Currently, COVID-19 patients encounter more mucormycosis cases as compared to patients undergoing any other diseases inclusive of clinical manifestations as 1. Rhinocerebral, 2. Pulmonary, 3. Central Nervous System (CNS), 4. Cutaneous, 5. Gastrointestinal, 6. Disseminated, and 7. Miscellaneous (e.g., bones, kidney, oral, heart, and mediastinum) (Figure 2).

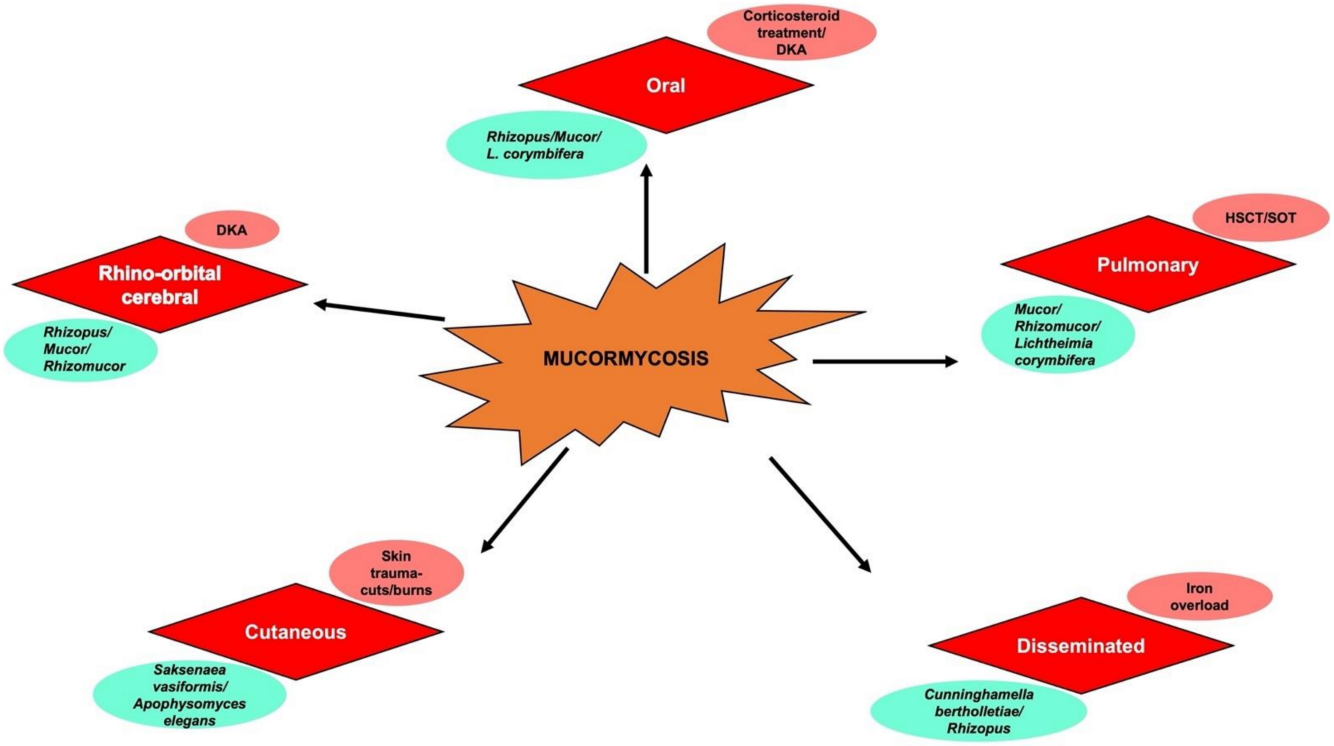

Figure 2. Schematic representation of different types of mucormycosis (in red), underlying risk factors (in pink), and corresponding causative species (in cyan green). DKA—Diabetic Ketoacidosis; HSCT—Hematopoeitic stem cell transplant; SOT—Solid organ transplant.

5.1. Rhinocereberal Mucormycosis

Facial pain, headache, and fever are some of the common symptoms in cases of rhinocerebral mucormycosis (ROCM). ROCM in COVID-19 patients has been presented as a frequent and severe condition with the majority of the cases being identified in India (approximately 70%) and having diabetes as an underlying condition. In a recent study of 80 CAM patients, the association of rhino-orbital cerebral infection with extension into the CNS was confirmed in 37% of the patients. In addition, mortality in patients with ROCM with confirmed CNS involvement was found to be more than two-fold greater than in those without CNS involvement [27]. The related symptoms of CNS involvement are described in the next subsection.

In cases where the infection reaches the nasal turbinates, orbital cellulitis, extraocular muscle paresis, proptosis, and chemosis have been reported. The results of standard roentgenograms and computed tomography (CT) scans display prominent soft-tissue swelling as signs of infection possibly due to the necrosis of frontal lobes extending to posterior brain regions. However, bone destruction is only evident at the later stages of infection marking progressive mucormycosis [31]. Since *Rhizopus* spp. utilizes deferoxamine as a siderophore to supply previously unavailable iron for the fungus growth [32], the growth of *R. oryzae* in DKA patients due to iron release from binding proteins may lead to the development of rhinocerebral mucormycosis.

5.2. CNS Involvement

The most common route of infection of the CNS is known to be via the nose or paranasal sinuses. In intravenous (i.v.) drug abusers, it has been reported to spread hematogenously. Related predispositions such as brain infarcts were also observed in neutropenic patients and drug abusers infected with the human immunodeficiency virus; however, the likely cause of the underlying condition for the development of mucormycosis is neither reported to be the virus nor the i.v. inoculation itself [33,34]. Likely, conditions such as neutropenia, bone marrow transplantation, and viral infections are interrelated

to eventually cause mucormycosis. At times, inflammatory soft tissue infiltration extends to subcutaneous facial tissue along intratemporal and temporal fossae which may lead to the involvement of the CNS [35]. This evidence largely testifies the severity of the mucormycosis infection and possible inter-related effects associated with the emergence of COVID-19 disease.

5.3. Other Forms of Mucormycosis

Leukemic patients and those undergoing bone marrow transplants are most likely to develop pulmonary mucormycosis due to neutropenia. The common symptoms include fever, dyspnea, and chest pain. The inflammatory cells are usually absent and only abnormalities such as tissue necrosis and hemorrhage are evident on roentgenograms due to which the actual intensity of the infection and related damage is higher than the observation [31]. Considering the phenotypical similarities observed in different infectious routes, the careful examination of the upper and lower respiratory tracts of the concerned patients is advisable.

Another common form of mycoses, cutaneous mucormycosis, is caused by fungi deposited into the skin and sometimes to the deeper subcutaneous layer via the use of contaminated Elastoplast bandages. The spores from the contaminated material applied to the skin are able to proliferate and invade both cutaneous and subcutaneous sites [31].

Gastrointestinal mucormycosis has been yet another common issue in countries with the problem of severe malnutrition. The involvement of the stomach, ileum, and colon has been reported more commonly than that of the rest of the digestive system [33]. Patients normally present with the nonspecific signs and symptoms of an intra-abdominal abscess followed by the possibility of hematochezia [34]. Gastrointestinal mucormycosis is most often diagnosed after the patient has died of the infection, but has also been presented with acute gastrointestinal symptoms after recovery from COVID-19 disease [35].

5.4. Oral Manifestations: A Dentist's Perspective

In dentistry, invasive mucormycosis gains increasing interest because of its initial manifestation in the facial and oral tissue often leading to a black necrotic eschar on the palate where ischemic necrosis of the mucoperiosteum with bony denudation may take place [36]. Besides this, ulcers have also been reported on the gingiva, lips, alveolar ridge, cheeks, tongue, and mandible parts [37–39].

Palatal necrosis develops from fungal spores entering through the nose or mouth to invade the orbit or open wounds [40,41] and spreading to the paranasal sinuses, skin of the face, cribriform plate, and brain through vascular channels [42,43]. The penetration of the arterial walls through fungal entry in the blood causes collateral endothelial damage resulting in intravascular thrombosis, infarction, and tissue necrosis [42–45]. In diabetic patients, this vascular clogging may cause severe local tissue ischemia and increased susceptibility to infection [45,46].

CAM affects the sinuses in the majority of cases (>80%), followed by the rhino-orbital cerebral region in at least 50% of the reported cases. The role of dentists is critical since they may be the first clinicians to be presented with oral manifestations in high-risk patients, including those around the rhinomaxillary or rhinocerebral areas. The symptoms may range from mucosal discoloration, swelling, and bone exposure to atypical symptoms such as sinus pain, facial pain, and unanticipated odontalgia of otherwise sound teeth [47].

In this scenario, surgical intervention is both an aid and an alternative to the poor penetration of antifungal agents at the site of infection due to blood vessel thrombosis and resulting tissue necrosis. Hence, debridement of necrotic tissues is a critical step performed by dental surgeons. In many cases, patients who did not undergo surgical debridement of the lesion have been observed to show a relatively higher mortality rate [48]. According to a recent retrospective review of patients with ROCM, the use of intraoperative frozen sections to delineate the margins of infected tissues through calcofluor fluorescence microscopy is suggested so the uninvolved tissues can be spared from the debridement [49,50]. A nasal

endoscopy may not always be an optimized measure to locate the lesion in the sinuses by restricting the access for debridement. Therefore, the Caldwell-Luc operation can be performed as an alternative surgical modality to successfully remove the necrotic tissue of the sinus. Often, an incision is made just above the root surface of the first premolar and molar, and the infected tissue is removed while splinting of teeth is performed, to immobilize them.

6. Diagnosis

Since some of the symptoms are shared between different sources of fungal infection, the specific diagnosis of mucormycosis can be evaluated through major pathologic manifestations such as areas of vasculitis with thrombosis, hemorrhage, and infarction. The identification of morphological differences between *Mucorales* and *Aspergillus* is also a commonly used laboratory practice to diagnose this fungal condition.

6.1. Microscopic Examination

Phenotypic observation and visualization of characteristic hyphae are one of the most definitive ways to characterize the differences between mucormycosis and aspergillosis owing to the former's irregularly shaped and right-angled broad hyphae (10–20 μm in diameter) structure. Both can be differentiated by culture and pathological examination of biopsy specimens. In addition, certain Gram-negative bacilli such as *Pseudomonas aeruginosa* can mimic vasculitic lesions in skin or viscera as produced by *Mucorales* for which hyphae can be easily visualized in routine hematoxylin-eosin-stained sections or the periodic acid–Schiff reaction and Grocott–Gomori methenamine-silver nitrate stains [51]. A rapid diagnosis of mucormycosis could be made through direct histopathological examination of the tissue through fluorescence microscopy using brighteners such as Blankophor and Calcofluor White, which bind to chitin and cellulose in the fungal cell wall and fluoresce under ultraviolet light [10].

6.2. Imaging Methods

CT scans and magnetic resonance imaging (MRI) scans of the head typically reveal only evidence of sinus involvement associated with the opacification of sinuses and thickening of optic muscles, especially the medial rectus muscle as demonstrated by lucencies on a CT scan [51–55]. Proptosis may also be evident in some cases. The results of an MRI scan may also reveal abnormalities in involved structures such as the ocular muscles and sinuses as a byproduct of prominent mucosal thickening and secretions. Another commonly reported abnormality is cavernous sinus thrombosis of vessels due to ischemic changes in the area of distribution by failure in the enhancement of the affected vessels [55]. In the absence of comparative studies, the benefits of CT vs. MRI are not known; however, MRI scanning could be a preferred measure for a diabetic patient for whom intravenous contrast agents may be contraindicated. In addition to imaging methods, functional and metabolic imaging using PET/CT coupled with [18F]-fluorodeoxyglucose (FDG) has been considered a valuable tool in the diagnosis and management of mucormycosis due to its sensitivity and accuracy in picking up anatomic abnormalities. Advanced biosensor-based diagnosis and detection of CAM are discussed in detail in [10].

6.3. Species Identification and Antifungal Susceptibility Testing

Species identification using commercially available kits has aided a better epidemiological understanding of mucormycosis and is indeed valuable for quick and reliable outbreak investigations. For instance, the ID32C kit (BioMerieux, Marcy l'E' toile, France) has been used successfully for the identification of species such as *Lichtheimia corymbifera*, *Lichtheimia ramose*, and *Rhizomucor pusillus*; and API 50CH (BioMerieux) has been used for *Mucor* species [56,57]. Reproducible techniques for antifungal susceptibility testing are important methods to evaluate uniformity in reporting and to facilitate interlaboratory comparisons. Many factors influence in vitro susceptibility testing results, such as endpoint

definition, inoculum size, incubation time, incubation temperature, and the medium used for testing. A range of traditional methods such as broth microdilution, disk diffusion, and agar screening, as well as commercial methods such as YeastOne and VITEK2, that are easy to set up and perform, are useful for this application [51]. Finally, matrix-assisted laser desorption/ionization time-of-flight (MALDI-TOF) (Bruker Biotyper, Germany, and Vitek MS France), mass spectrometry, and T2MR (T2 biosystems) are FDA-approved platforms involving the complex between particles coated with target-specific agents with respect to the altered microenvironment for the rapid detection of mucormycosis [10,58].

6.4. Molecular Assays

Molecular-biology-based assays, including conventional polymerase chain reaction (PCR) [59], restriction fragment length polymorphism analyses (RFLP) [60], DNA sequencing [61] of defined gene regions, and melt curve analysis of PCR products [62], can be used either for the detection of *Mucorales* based on internal transcribed spacer or the 18S rRNA genes [63]. Nonetheless, the low number of patients in culture-based studies is a limiting factor that results in varied sensitivity and specificity, never approaching 100%. Moreover, studies performed with formalin-fixed, paraffin-embedded, or fresh tissue samples [64] lead to variable results as well. Considering the lack of evaluation and other limiting factors, none of the culture or phenotypical approaches can be recommended as a standalone approach in clinical routine diagnostics [64]. In lieu of this, molecular-based diagnosis [65,66] has been gaining attention to yield promising results and confirm the culture-proven cases. Presently, molecular-based diagnostic assays from blood and serum can be recommended as valuable add-on tools that complement conventional diagnostic procedures.

6.4.1. Serology Assays

Serological techniques such as immunohistochemistry (IHC), enzyme-linked immunosorbent assays (ELISA), immunoblots, and immunodiffusion tests have been reported to highlight variable success as ELISA was observed to be more sensitive than double immunodiffusion (DID) tests. SDS-PAGE-based immunoblots responded positively to *R. arrhizus* antigens but recognized only a few of the 20–30 gel-separated bands. *Mucorales*-specific T cells versus control were successfully detected by an enzyme-linked immunospot (ELISpot) assay using heat-killed germinated conidia from patients with invasive mucormycosis [67]. Additionally, serum tests involving the use of a 1,3-beta-D-glucan assay yield promising results for the *Mucorales* group based on the presence of glucan in their spore cell walls [10].

6.4.2. Differential Diagnosis Methods

CAM is mostly characterized by histopathology or culture-based assays as broad, irregular, pauci septate hyphae whereas cryptococcosis and endemic mycoses such as fungal infections are identified by encapsulated yeast cells and budding spherules, respectively. However, unlike aspergillosis and candidiasis, CAM can be identified from both blood and BAL samples. Molecular assays such as Genus-NAAT (Nucleic Acid Amplification Test) and pan fungal PCR, other than mass spectrometry, are recommended for the identification of CAM (Figure 3. However, neither enzyme immunoassays nor antigen detection assays are very efficient, as for other non-CAM fungal species [68].

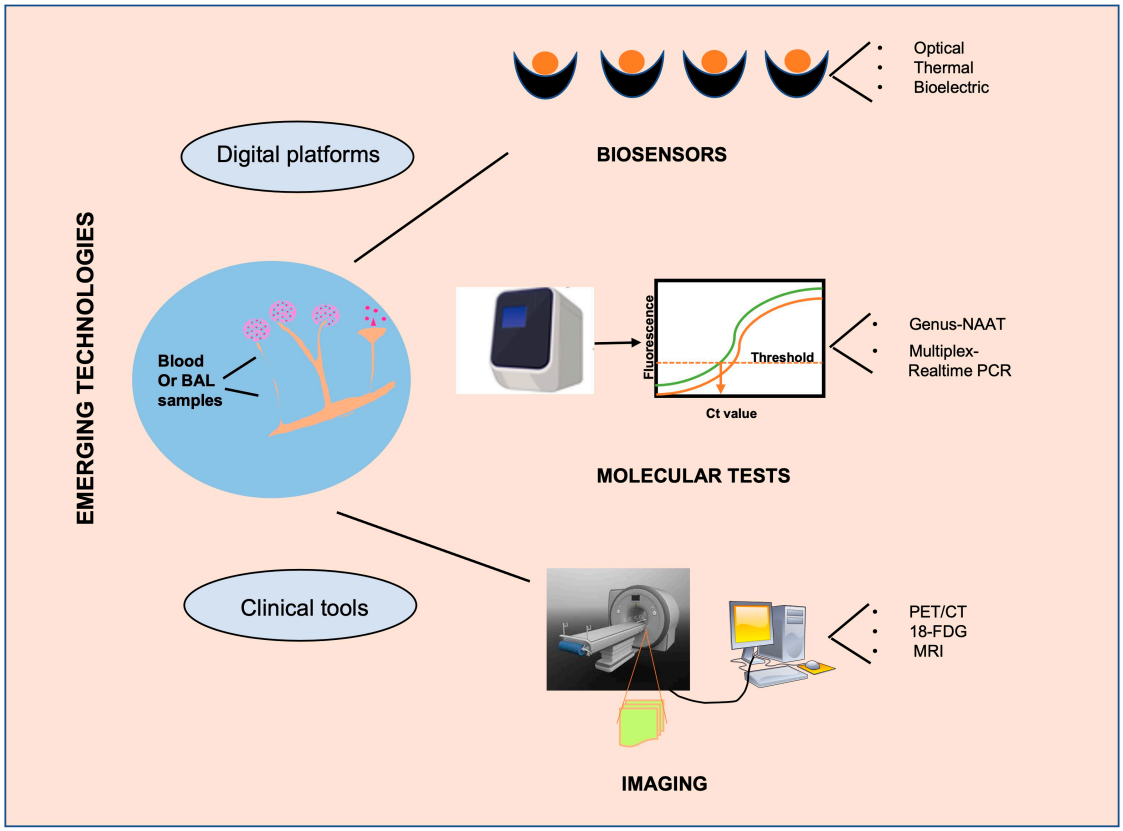

Figure 3. The figure highlights emerging diagnostic technologies specifically for CAM that can eventually lead to a rapid diagnosis, favorable prognosis, and advanced treatment.

7. Treatment

The successful treatment of mucormycosis depends on a synchronized surgical and medical approach. Furthermore, surgical debridement is necessary to remove any of the devitalized tissue and requires immediate action within a few days after diagnosis. DKA, on the other hand, could be rapidly treated by cutting down on immunosuppressive drugs, whenever possible.

7.1. Primary Diagnosis and Prevention

The advantage of using early initiation of polyene antifungal therapy within five days of diagnosis is a significant improvement as compared to the initiation of the same at ≥6 days after diagnosis (83% vs. 49% survival). Hence, an early diagnosis to commence active antifungal therapy is highly recommended wherein a quantitative PCR system has emerged to be highly promising. Besides, MRIs and CT scans are useful for the specific detection of orbital and CNS involvement. Additionally, CT scans are also useful for the early detection of pulmonary mucormycosis, particularly in patients with cancer [47,48]. Other diagnostic advances that can prove to be successful in present times were mentioned in the previous section.

Removal of underlying defects in the host's defense is a critical step when treating patients with mucormycosis. Firstly, where applicable, immunosuppressive medications, particularly corticosteroids, should be dose-reduced or stopped. The recommended daily dosages of corticosteroids such as dexamethasone, prednisolone, and methylprednisolone are 6 mg, 40 mg, and 32 mg, respectively, for about 10 days [69]. Secondly, aggressive management to restore normal blood sugar levels (euglycemia) and consequently, acid-base status in diabetic ketoacidosis conditions, is required [48]. Finally, wherever feasible, the administration of iron and blood transfusions should be avoided.

7.2. Antifungal Measures

Early diagnosis and aggressive medical management of underlying clinical manifestations may lead to a <20% death rate [48]. In this context, antifungal drugs have garnered a lot of attention; i.v. administration of conventional amphotericin B at dosages of 1 mg(/kg/d) is recommended, although a dosage of 1.5 mg(/kg/d) may be required for the treatment of patients who have aggressive and rapidly progressive infections [69]. Certainly, the patient's response, underlying disease, and nature and degree of amphotericin B–related toxicity are some of the factors to be considered in deciding the success rate of any therapeutic measures. The addition of rifampin or tetracycline along with amphotericin B to enhance antifungal activity and administrative therapy with hyperbaric oxygen are some of the unproven measures [70,71] that are not recommended for general use in most patients. The susceptibility tests to decipher the kind of antifungal drug or combination of drugs, such as itraconazole or fluconazole, to administer in therapeutic regimens are also not warranted, due to the lack of standardized procedures. For instance, the combination of liposomal amphotericin B (LAmB, recommended as first-line therapy for nephrotoxic patients, 5mg/kg/d) and posaconazole has shown synergistic results against fungal hyphae formation [72] whereas the neutropenic patients or individuals with graft-versus-host disease could be administered with oral posaconazole as prophylactic doses for the management of the disease. Additionally, posaconazole is an economical alternative with an easy route of administration; however, the main drawback lies with the reduced absorption rate. Moreover, a combination of polyene-caspofungin therapy displayed a significant success in patients with rhino-orbital and ROCM as compared with polyene monotherapy [49]. Isavuconazole, on the other hand, offers some advantages with its high tolerance, lower side effects, bioavailability, and reduced drug-drug interaction, but is yet to be established in further studies [73]. It has been reported to be effective against *Rhizopus delemar* species [69].

The use of iron chelators, such as deferiprone and deferasirox, to treat iron-overloading transfusion-dependent anemias has been approved by the U.S. FDA [74,75] and has displayed improved survival in rodents with mucormycosis [76]. Deferasirox exhibited time-dependent killing as fungicidal effects occurred at 12–24 h of drug exposure with an MIC_{90} of 6.25 μg/mL [77]. The oral administration of deferasirox is rather simple and convenient but with the limited data availability, it must be administered cautiously at intervals (20 mg/kg/d for 2–4 weeks) with regular monitoring of renal and hepatic function. Again, the combination of deferasirox and LAmB therapy remarkably improved survival [78], with a 100-fold decrease in brain fungal burden compared with the monotherapy for which the former has been used off-label as adjunctive therapy for mucormycosis patients [70].

7.3. Salvage Therapy

As mentioned above, posaconazole or deferasirox are reasonable salvage options for patients refractory to polyene therapy and even appear to be a safer alternative for a longer period of administration up to a few months. In the light of increasing evidence for the use of G-CSF-mobilized granulocyte transfusions as additional support for persistently neutropenic patients, the administration of GM-CSF or IFN-γ in non-neutropenic patients has proven to aggravate host response against pro-fungal effects. In a recent murine study, not only did the addition of GM-CSF to LAmB therapy improved the survival of mucormycosis mouse models [79], but also the combined therapy of recombinant G-CSF and GM-CSF, or recombinant IFN-γ in conjunction with LAmB, proved successful for the treatment of mucormycosis [78,79].

7.4. Nanomedicine

Antifungal drugs display limitations like optimal dosage, infusion-related side effects, and high risk of nephrotoxicity, among other therapy-limiting effects. Recently, the use of nanosystems for delivery of Am-B via oral, topical, or even pulmonary routes appears to have become a promising alternative and is currently under development [79]. The lipid

formulation of drugs such as AmB or nystatin can be augmented to reduce the toxicity of the conventional drugs owing to their hydrodynamic size and easy route of administration. The recent studies highlighted the use of silver nanoparticles (AgNPs), Zirconium oxide nanoparticles (ZrO_2NPs), and nano-emulsion NB-201, which exhibit antifungal properties with higher toxicity against *Mucorales* due to the presence of corresponding moieties and relatively low toxicity in human cells [73].

8. Link to SARS-CoV-2 Variant

The exclusive presence and surge of mucormycosis cases during the second wave led to speculations of its direct association with the COVID-19 delta variant. Since the COVID-19 delta variant is more contagious and resistant to vaccines than the wild-type strain, it carries a higher risk of hospitalization with a predisposition for rhinocerebral mucormycosis [80]. It is likely that other than the environmental, geographic, and genetic factors, the onset of mucormycosis is caused by the COVID-19 delta variant due to its ability to affect the pancreas, eventually contributing to intense hyperglycemia [81]. This, in turn, ultimately leads to the same predisposing factors as mentioned above for CAM patients causing endothelial injury and immune dysfunction.

According to a recent study by Alshahawey et al. [21], India reported an increase in mucormycosis prevalence from 12.9 cases/year during 1990–1999 to 35.6 cases/year during 2000–2004, then to 50 cases/year during 2006–2007, and eventually 89 cases/year during 2013–2015. The annual prevalence of global mucormycosis may be ~910,000 cases worldwide with 900,000 cases reported from India only. As of 20 July 2021, India counted 45,432 confirmed cases and 4252 deaths from black fungal infections as per the reports of the Ministry of Health and Family Welfare, which is far higher than the global rate. Of these, 80–94% of the cases had a history of diabetes, approximately 14.9% were suffering from DKA, and almost 86% of the patients were on corticosteroid treatment post-COVID-19 disease with predominance in male patients [10,21]. The neighboring countries, such as Pakistan and Bangladesh, have also shown an increasing trend in the number of black fungus cases during the wave of the COVID-19 delta variant [82].

In the south Asian countries with weak public health infrastructure, factors such as low vaccination rates and large immunocompromised populations may represent an epicenter for producing new variants. However, cases have also been reported in countries such as Brazil, Chile, Mexico, Paraguay, the United States, Italy, and the United Kingdom. Similarly, with the new omicron variant circulating, the possibility of CAM returning is convincing, as indicated by 500 new registered cases in the northern state, Haryana, in India. In Indian states, Gujarat and Maharashtra being the most affected during the COVID-19 delta variant infections, the number of CAM cases has again started to appear in the Mumbai city of Maharashtra [83]. Furthermore, 300 new cases were reported from middle east countries, which makes it crucial to consider precautionary factors as wearing proper masks, timely identification, maintaining hand hygiene, physical distance, avoiding mass gathering, and sufficient mass vaccination [83] to combat the collateral effects of COVID-19, especially in developing countries (Figure 4).

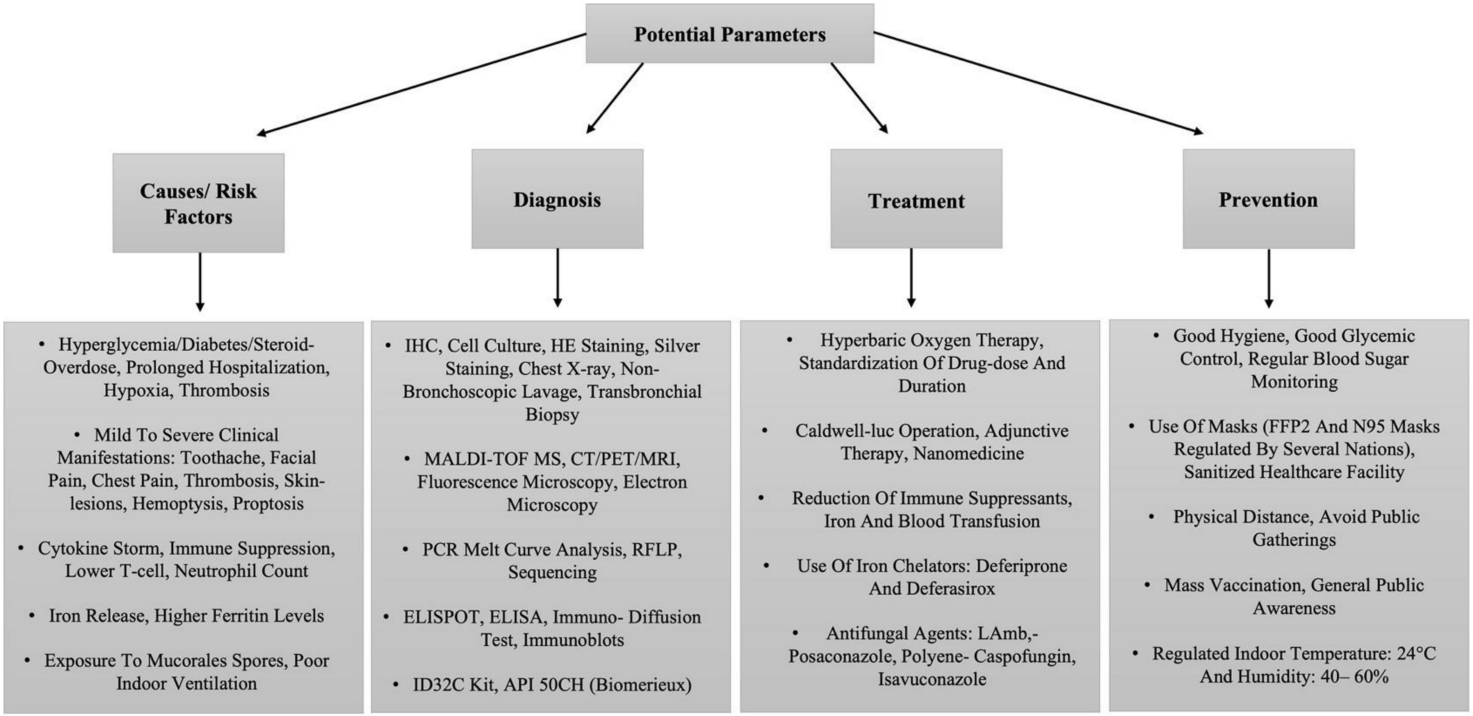

Figure 4. The tabular representation of a list of potential parameters related to the management of CAM.

SARS-CoV-2 and Mucormycosis: Underlying Factors

Diabetes Mellitus is a predominant risk factor for increased severity of COVID-19 infection and higher mortality. Increased ACE2 receptor and GRP78 expression, dysregulated immune response, alveolar and endothelial dysfunction, an acidic environment (DKA) causing hyperglycemia that favors SARS-CoV-2 replication, and a hyperferritinemic state due to increased availability of iron, eventually makes DM the most common risk factor for mucormycosis [10].

In severe cases of COVID-19, lymphocytopenia has been observed as the pathological mechanism of SARS-CoV-2, majorly affecting T cells (CD4+ and CD8+) [27]. However, T cells play an important role in controlling invasive *Mucorales* infection through various cytokines (IL-4, IL-10, IL-17, and interferon-gamma) that damage the fungal hyphae, indicating that severe COVID-19 infection on its own is a risk factor for mucormycosis [27,47].

Nevertheless, chronic antibiotic use by itself is one of the prime risk factors for opportunistic fungal infections including mucormycosis which in some cases can even lead to the emergence of antimicrobial resistance [27].

Not all COVID-19 patients present co-morbidities such as DM and DKA; therefore, in India, which is known as the diabetes capital of the world, the highest rates of mucormycosis cases were found after the COVID-19 surge that accounted for more than 70% of cases [30,31]. Moreover, associations with poor hygiene and ventilator-associated infections lead to the high prevalence of the same in developing countries, with India leading the charts owing to its high population density. Moreover, in COVID-19 patients, >88% of the mucormycosis cases are localized as sinus and cerebral as compared with the pulmonary (>24%) and cutaneous prevalence (>19%) in non-CAM patients [27] (Table 3).

Different intervention factors, particularly the hospitalization infrastructure have crucial roles to play in the outbreak of CAM in developing countries, including crowded hospitals, unavailability of healthcare resources, overburdened healthcare workers, and poor diagnostic quality [83]. On the other hand, developed countries' hospitals ensure quality control of oxygen supply, proper sanitization of oxygen cylinders, disposable oxygen humidifiers, and even the use of clean distilled water in oxygen humidifiers and concentrators. Of note, during the extreme pandemic periods (March 2020 to May 2021) in India, the high-standard hospitals observed 0 CAM cases among >5000 hospitalized COVID-19 patients [84]. Moreover, people in developing countries can often procure medications without a prescription, making zealous use of steroids, hence exacerbating the situation. Nonetheless, differential gender susceptibility with 78% of CAM cases being reported in male patients [27] is another aspect that needs to be investigated in future studies.

Table 3. Prevalence of COVID-19-associated mucormycosis cases in India and other countries by February 2022.

Country	No. of Cases	Affected Organ	References
India	2849	Rhino Orbital Cerebral	[85,86]
USA	5	Rhino Orbital Cerebral	[87–90]
Italy	1	Rhino Orbital Cerebral	[91]
Iran	18	Rhino Orbital Cerebral	[92–94]
Turkey	1	Rhino Orbital Cerebral	[95]
Mexico	1	Rhino Orbital Cerebral	[96]
India	1	Pulmonary	[97]
UK	1	Pulmonary	[98]
USA	2	Pulmonary	[99,100]
Australia	1	Pulmonary	[101]

Table 3. *Cont.*

Country	No. of Cases	Affected Organ	References
India	2	Gastro-Intestinal	[33,102]
Brazil	1	Gastro-Intestinal	[103]
USA	1	Cutaneous	[104]

9. Conclusions

COVID-19-associated mucormycosis is a severely critical condition with symptoms such as fever, loosening of teeth, swelling below the eyes, and pain in the maxillary sinus area which may be fatal in cases when it reaches the brain. However, early diagnosis of CAM may save the life of a patient. As a dentist, one should be cautious about the post-COVID-19 infection history of the patient and about the medications he or she was administered during this period. The overall prognosis depends upon early diagnosis and treatment, site of infection, underlying conditions, and the immune status of the patient. Antifungal agents and surgeries including the use of iron chelators, reversal of immunosuppression, metabolic deficit correction, and hyperbaric oxygen are some of the active solutions with variable effects. However, adopting preventive measures is equally important to circumvent the chances of infection. Overall, a combined strategy of conventional and new diagnostic assays along with public and healthcare awareness is desirable to guarantee profound management of COVID-19-associated comorbidities.

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