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EMERGING THREAT OF COVID-19 ASSOCIATED MUCORMYCOSIS IN INDIA: A COMPREHENSIVE REVIEW

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ABSTRACT

Mucormycosis, commonly referred to as "black fungus," has emerged as a significant secondary infection during the COVID-19 pandemic, particularly in India. This opportunistic fungal disease, though non-communicable, spreads through inhalation of spores that are omnipresent in the environment. Patients with uncontrolled diabetes, prolonged corticosteroid therapy, malignancies, or immunosuppression are at the highest risk. The infection manifests with symptoms such as headache, nasal congestion, facial swelling, eye pain, and partial vision loss. If not diagnosed and treated early, the disease can rapidly progress, leading to high mortality rates. This review explores the epidemiology, risk factors, clinical manifestations, and treatment approaches of mucormycosis in the Indian context, while emphasizing the urgent need for early detection, judicious use of steroids, and improved awareness among healthcare workers and the public.

INTRODUCTION

The COVID-19 pandemic has placed unprecedented stress on global healthcare systems, particularly in India, where the second wave was marked not only by high infection rates but also by the alarming rise of secondary infections such as mucormycosis. Mucormycosis is a rare yet aggressive fungal disease caused by species of the order *Mucorales*, which are commonly found in soil, decaying vegetation, and organic debris. Although these fungi are typically harmless to healthy individuals, they can cause life-threatening infections in immunocompromised hosts.

During the pandemic, an unexpected surge of COVID-19 associated mucormycosis (CAM) cases was reported across several Indian states. The overuse of corticosteroids, a standard therapy to manage severe COVID-19, along with pre-existing conditions such as uncontrolled diabetes mellitus, created a "perfect storm" for the development of this invasive fungal infection. According to Garg et al. (2021), India reported a disproportionately higher incidence of CAM compared to global averages, with morbidity and mortality rates surpassing 50% in severe cases.

The rapid progression of the disease, often from nasal sinuses to orbital and cerebral involvement, highlights the need for heightened clinical vigilance and prompt therapeutic intervention. Early diagnosis, surgical debridement, and antifungal therapy such as liposomal amphotericin-B remain the cornerstones of treatment. However, limited drug availability, high treatment costs, and delayed medical response continue to pose serious challenges.

Given the unique epidemiological burden in India, this review aims to synthesize existing evidence on mucormycosis in the context of COVID-19, highlighting its risk factors, clinical spectrum, treatment strategies, and implications for healthcare policy.

2. LITERATURE REVIEW

1. Epidemiology and Burden

The COVID-19 pandemic precipitated an unprecedented rise in cases of COVID-19–associated mucormycosis (CAM), with India bearing a disproportionately large share of the global burden. Several reviews and multicentre analyses report dramatically higher incidence and case numbers in India compared with most other countries [1], [2], [23]. Aranjani et al. [1] and Muthu et al. [2] highlight that the reported CAM surge during the pandemic's

second wave reflected a convergence of high background diabetes prevalence, widespread steroid use, and overwhelmed healthcare systems. Large retrospective and systematic studies documented high morbidity and mortality associated with CAM, particularly when diagnosis and treatment were delayed [1], [5], [6].

2. Major Predisposing Factors

The literature converges on two principal, interacting risk factors for CAM: uncontrolled diabetes mellitus (DM) and corticosteroid exposure. Uncontrolled DM impairs innate immunity and creates a hyperglycaemic, iron-rich milieu favourable to Mucorales growth; several case series and systematic reviews identified DM as the predominant comorbidity among CAM patients in India [1], [4], [11], [16], [22]. Corticosteroids—widely used to treat severe COVID-19—were repeatedly implicated as a precipitant of hyperglycaemia and immunosuppression; many reports emphasise inappropriate dosing or prolonged steroid courses as avoidable contributors to CAM [1], [2], [3], [12], [18]. Other contributing factors reported across studies include prolonged hospitalisation, broad-spectrum antibiotic exposure, mechanical ventilation, neutropenia (in specific subgroups), and underlying malignancy or transplantation-related immunosuppression [2], [5], [17], [23].

3. Clinical Spectrum and Presentations

Clinical presentations of CAM most commonly involved the rhino-orbital-cerebral (ROCM) form, though pulmonary and cutaneous forms were documented, particularly among patients with severe COVID-19 or preexisting pulmonary disease [1], [2], [10], [15]. ROCM typically began with sinonasal symptoms (nasal congestion, facial pain, blackish nasal discharge) progressing to orbital signs (proptosis, ophthalmoplegia, vision loss) and intracranial extension in advanced cases [1], [11], [15]. Imaging and pathology studies emphasise the rapid angioinvasivebehaviour of Mucorales, explaining the swift progression from sinonasal infection to orbital/cerebral involvement when treatment is delayed [15], [23].

4. Diagnosis: Challenges and Modalities

Accurate and early diagnosis remains a major challenge. Many studies stress limitations of clinical diagnosis alone and recommend a combined approach: high clinical suspicion in at-risk patients, prompt radiology (contrast MRI for ROCM; CT and chest imaging for pulmonary disease), direct microscopy and culture of tissue specimens, and histopathology to demonstrate angioinvasion [3], [10], [15], [18]. Several authors pointed out low sensitivity of cultures and the need for repeated sampling; molecular diagnostics, while promising, were not uniformly available in many settings described in Indian case series [3], [5], [23].

5. Management Strategies and Resource Constraints

Management of CAM involves urgent combined medical and surgical interventions. Antifungal therapy—principally liposomal amphotericin B (L-AMB)—plus aggressive surgical debridement for ROCM remain standard of care [3], [5], [10]. However, multiple papers reported significant constraints: limited availability and high cost of L-AMB, toxicity concerns with conventional amphotericin B (and need for electrolyte/renal monitoring), and the prolonged duration of therapy required for cure [5], [6], [10], [21]. Newer azoles (posaconazole, isavuconazole) were described as salvage or step-down options, but their accessibility and cost limited their use in many reported cohorts [5], [6], [13]. Several case series document favourable outcomes when early combined therapy was possible, but overall survival remained strongly time-dependent and worse in patients with intracranial extension or delayed care [4], [10], [16].

6. Outcomes and Predictors of Mortality

Studies analysing outcomes highlighted very high morbidity and a case fatality that varied widely depending on site of infection, comorbidities, and timeliness of therapy. Pulmonary and disseminated forms had worse prognoses than ROCM when detected late [5], [10], [23]. Predictors of poor outcome repeatedly identified included delayed diagnosis (>7–10 days), uncontrolled hyperglycaemia at presentation, diabetic ketoacidosis, need for mechanical ventilation, and intracranial involvement [4], [5], [16]. Multicentre analyses and systematic reviews underscore that early recognition, glycaemic control, prompt surgical debridement, and access to L-AMB materially improve survival odds [4], [5].

7. Regional and Healthcare System Factors (India Focus)

Several India-centric papers emphasise contextual drivers: a high background prevalence of diabetes, disparities in healthcare access, shortages of critical antifungal drugs during the surge, and variable infection control practices in oxygen/respiratory support delivery [1], [2], [6], [14]. Public-health and hospital-level factors—such as delayed referrals, inadequate community awareness of early CAM signs, and logistical barriers to surgical care—were repeatedly flagged as modifiable contributors to poor outcomes [1], [14], [21].

8. Gaps in Evidence and Methodological Limitations

Although the rapid accumulation of case reports, case series, and small cohort studies generated useful clinical insights, many authors noted methodological limitations: heterogeneity in case definitions, retrospective designs, incomplete microbiological confirmation, short follow-up, and publication bias toward severe cases [6], [7], [23]. Consensus statements and Delphi processes (e.g., [3]) sought to standardise case definitions and management pathways, but further prospective, ideally multicentre studies are needed to clarify incidence, optimal antifungal regimens, and long-term functional outcomes.

9. Recommendations and Future Directions

Across reviews and expert statements, common recommendations include judicious steroid use in COVID-19 (adhering to evidence-based dosing/duration), strict glycaemic monitoring and control in COVID-19 patients, rapid case detection with low threshold for ENT/ophthalmology referral, ensuring supply chains for L-AMB and azoles, and strengthening hospital infection control (including sterile oxygen humidification) [1], [3], [4], [14]. Authors also call for national surveillance, registry development for CAM cases, and operational research into low-cost diagnostic and therapeutic strategies suitable for resource-limited settings [2], [5], [23].

The assembled literature paints a consistent picture: CAM in India during the COVID-19 waves represented a syndemic driven by the interaction of host (diabetes, immunosuppression), treatment (corticosteroids), pathogen (ubiquitous Mucorales), and system-level factors (drug availability, delayed care). While early multidisciplinary care can greatly improve outcomes, substantial gaps in diagnostics, therapeutics, and public-health readiness persist and warrant urgent attention in research and policy.

3. MATERIALS AND METHODOLOGY

3.1 Literature Search Strategy

The present review was conducted by systematically searching multiple scientific databases, including Scopus, PubMed, Web of Science, and Google Scholar, to identify peer-reviewed articles related to *COVID-19 associated mucormycosis (CAM)*. Keywords used in various combinations included: *"COVID-19," "SARS-CoV-2," "mucormycosis," "black fungus," "diabetes mellitus," "corticosteroids,"* and *"India."* Boolean operators (AND/OR) were applied to refine the search, and both clinical studies and review articles were considered.

3.2 Inclusion and Exclusion Criteria

Articles published between 2020 and 2025 were included, as this period coincides with the onset and progression of the COVID-19 pandemic. Studies were considered eligible if they (i) reported clinical cases of CAM, (ii) discussed epidemiology, risk factors, or treatment outcomes, or (iii) provided systematic or narrative reviews relevant to the Indian context. Exclusion criteria comprised non-English language publications, case reports without adequate clinical details, conference abstracts without full text, and articles unrelated to mucormycosis or COVID-19.

3.3 Selection and Screening Process

The initial database search yielded a large pool of articles. Titles and abstracts were independently screened to eliminate duplicates and irrelevant studies. Full-text screening was performed for the remaining articles to assess methodological quality and relevance. A total of 25 key references were shortlisted, which formed the evidence base for this review. To ensure comprehensiveness, cross-referencing of bibliographies from the shortlisted papers was also carried out.

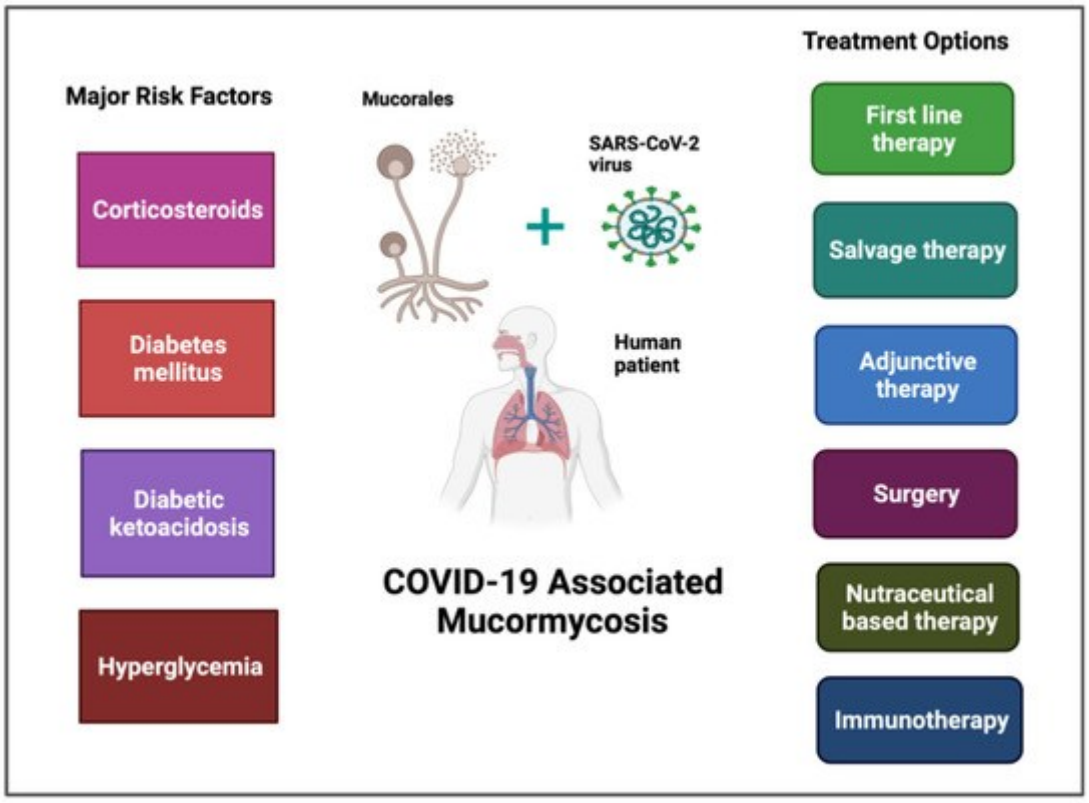

Figure 1. COVID-19-associated mucormycosis

3.4 Data Extraction and Synthesis

Relevant information from each article was extracted, including study type, population characteristics, clinical presentation, diagnostic modalities, treatment strategies, and outcomes. Studies were categorised under major themes such as epidemiology, risk factors, clinical features, diagnostic challenges, treatment approaches, and prognosis. A narrative synthesis was adopted, comparing findings across studies, highlighting similarities and discrepancies, and identifying gaps in current knowledge.

3.5 Methodological Rigor

To enhance the reliability of this review, preference was given to systematic reviews, multicentre observational studies, and Delphi consensus statements. Case reports and small series were used selectively, mainly to illustrate unique presentations or rare treatment outcomes. By combining evidence from diverse study designs, this review aims to provide a comprehensive understanding of CAM with specific emphasis on the Indian scenario.

4. RESULTS AND DISCUSSION

4.1 Epidemiological Findings

The literature indicates that India experienced an unparalleled surge in COVID-19 associated mucormycosis (CAM) cases compared to other countries. Aranjani et al. [1] and Muthu et al. [2] reported that the background prevalence of mucormycosis in India was already 70–80 times higher than in developed nations, which contributed significantly to the CAM outbreak during the COVID-19 waves. Large multicentric studies [4], [10] confirmed that uncontrolled diabetes mellitus, particularly in patients receiving corticosteroid therapy, remained the strongest predictor of CAM incidence and mortality.

4.2 Risk Factors and Pathogenesis

Across the reviewed studies, uncontrolled diabetes mellitus and indiscriminate use of corticosteroids were identified as the most critical risk factors [1], [2], [5], [11], [16]. These factors not only impair the immune system but also create a hyperglycaemic and acidic microenvironment conducive to Mucorales proliferation. Other predisposing factors included prolonged hospitalisation, oxygen therapy with non-sterile humidifiers, renal failure, and malignancy-related immunosuppression [17], [18], [20]. The "triple burden" of diabetes, steroids, and COVID-19 emerged as the primary explanation for India's disproportionate disease burden [19].

4.3 Clinical Spectrum and Diagnostic Challenges

Most CAM patients presented with rhino-orbital-cerebral mucormycosis (ROCM),characterised by facial swelling, nasal congestion, orbital pain, proptosis, and in advanced cases, vision loss or intracranial spread [11], [15], [16]. Pulmonary mucormycosis, though less common, was associated with higher mortality due to late diagnosis [5], [25]. Diagnostic challenges were repeatedly highlighted; culture sensitivity remained low, and delays in imaging or biopsy confirmation often resulted in advanced disease presentation [3], [15], [18]. Several authors advocated for a high index of suspicion in diabetic COVID-19 patients with sinus or orbital symptoms to enable timely intervention [3], [10].

4.4 Treatment Modalities and Outcomes

Treatment strategies consistently emphasised**a** multidisciplinary approach, combining surgical debridement with systemic antifungal therapy. Liposomal amphotericin B (L-AMB) was the gold-standard drug, yet shortages and cost issues in India often forced clinicians to use conventional amphotericin formulations, which carry higher nephrotoxicity [5], [6], [10]. Newer azoles such as posaconazole and isavuconazole were used as salvage or step-down therapy [13]. Early aggressive surgery combined with antifungal therapy significantly improved survival, but mortality still ranged between 40–80% in advanced cases [4], [10], [16], [21].

4.5 Comparative Insights: India vs. Global Reports

While CAM was reported globally, particularly in countries with high COVID-19 caseloads, the intensity and scale of outbreaks were disproportionately higher in India [2], [23]. Hoenigl et al. [23] observed that uncontrolled diabetes and steroid misuse were far less common drivers in Western countries, explaining lower incidence rates. This contrast underscores the unique epidemiological context of India, where systemic healthcare challenges amplified the outbreak [14], [19].

Table 1. Comparison of CAM in India vs Global Cases

Feature	India	Global (Other Countries)

Feature	India	Global (Other Countries)
Number of reported CAM cases in key review	In one systematic review up to June 2021, **233** cases from India among a total of 275 cases.	
Fatality / Case-fatality rate	~36.5% in India in the same set of cases.	~61.9% globally (among the non-India cases in the same review)
Common underlying risk factor	Diabetes mellitus is the most frequent comorbidity in Indian cases.	Globally, more heterogeneous causes, with higher proportions of malignancies, transplants, or severe immunosuppression; though diabetes remains significant.
Predominant clinical form/location of CAM	Rhino-orbital / Rhino-orbito-cerebral mucormycosis (ROCM) forms dominate (~89%) among Indian cases.	Lower proportion of ROCM (~64%) globally; more pulmonary, disseminated, or other anatomical sites
Prevalence among hospitalised COVID-19 patients	In a multicenter Indian study: 0.27% prevalence in general wards; 1.6% in ICUs.	Less data for outside India on prevalence among COVID-19 hospitalised patients in the same way, but studies indicate less frequent reporting of CAM in many countries
Time to diagnosis (early vs. late onset)	In India, many cases diagnosed later than 7-10 days post COVID-19 diagnosis; only ~25% early (<7 days) in the review.	Globally, a higher proportion of early cases in reviewed studies; ~36% in non-India cases in the review.
ICU admission, mechanical ventilation	Indian cases less often required mechanical ventilation or ICU compared to global cases.	Higher ICU / ventilation use in global non-India cases among reviewed cohorts.

4.6 Key Challenges and Gaps Identified

Despite improved clinical awareness, several challenges persist: delayed diagnosis due to non-specific symptoms, limited access to antifungal agents, insufficient surgical facilities in rural settings, and lack of long-term follow-up data [6], [14], [20]. Furthermore, methodological gaps were noted across studies, such as reliance on retrospective data, heterogeneous case definitions, and publication bias toward severe cases. These limitations highlight the need for prospective surveillance systems, standardised treatment protocols, and real-time reportingof CAM cases in India.

4.7 Discussion Summary

The reviewed literature makes it clear that CAM is not merely a secondary opportunistic infection but **a** syndemic outcome of COVID-19, diabetes, and steroid therapy. Early glycaemic control, rational steroid use, and heightened clinical vigilance are the most effective preventive strategies. Addressing systemic barriers—such as antifungal drug shortages, delayed referrals, and lack of awareness—remains crucial for reducing morbidity and mortality in future outbreaks.

CONSLUSION

5.1 Conclusion

COVID-19–associated mucormycosis (CAM) has emerged as one of the most devastating opportunistic infections during the pandemic, particularly in India. The review of recent literature establishes that uncontrolled diabetes mellitus, injudicious corticosteroid use, and immunosuppression form the central triad predisposing patients to CAM. Clinical manifestations, most often in the rhino-orbital-cerebral form, progress rapidly and lead to high mortality if not diagnosed early. Successful management requires a multidisciplinary approach that combines timely diagnosis, aggressive surgical debridement, and systemic antifungal therapy, primarily liposomal amphotericin B. However, limited drug availability, high treatment costs, and delayed clinical suspicion continue to challenge healthcare delivery.

5.2 Future Scope

Future strategies must focus on preventive and systemic interventions. Strengthening clinical awareness programs for healthcare workers and the general population is vital for early recognition of symptoms. There is a need for national surveillance systems and registries to track incidence, treatment outcomes, and emerging resistance patterns. Investment in low-costdiagnostic tools and affordable antifungal formulations will be essential to improve accessibility in resource-limited settings. Additionally, clinical trials assessing optimal steroid regimens, combination antifungal therapies, and non-invasive monitoring methods should be prioritised. From a policy perspective, integrating mucormycosis management into pandemic preparedness plans will help mitigate the impact of future outbreaks.

In summary, while CAM highlighted the vulnerabilities of India's healthcare system during the COVID-19 crisis, it also presents an opportunity to implement sustainable measures that improve infection control, patient safety, and preparedness for future pandemics.

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