ADVANCEMENTS IN THE DIAGNOSIS AND MANAGEMENT OF MUCORMYCOSIS IN PATIENTS WITH DIABETES MELLITUS: AN INTEGRATED APPROACH FROM INTERNAL MEDICINE AND DENTAL SCIENCES

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ABSTRACT

Objective: To synthesise the current evidence on diagnostic modalities, therapeutic strategies, and interdisciplinary care models for mucormycosis in patients with diabetes mellitus, with particular focus on the role of the oral cavity as a portal of entry in the rhino-orbital-cerebral form of the disease.

Methods: This PRISMA 2020-compliant systematic review searched PubMed, Embase, Scopus, and Cochrane from January 2020 to October 2025. Two independent reviewers screened 1,247 records and assessed 62 full-texts. Fifteen studies were included: systematic reviews, case reports, case series, and observational studies involving adult diabetic patients with confirmed mucormycosis. Quality appraisal was performed using AMSTAR-2 for systematic reviews and the Newcastle-Ottawa Scale (NOS) for observational studies.

Results: From 15 included studies (5 systematic reviews and 10 primary studies), rhino-orbital-cerebral (ROC) involvement predominated in 70-86% of diabetic mucormycosis cases. The oral cavity served as portal of entry in 50-60% of ROC presentations, with *Rhizopus* species accounting for approximately 68% of isolates. Uncontrolled diabetes mellitus (DM) (HbA1c >9%) conferred substantially elevated risk. Polymerase chain reaction (PCR) applied to bronchoalveolar lavage fluid (BALF) achieved the highest diagnostic sensitivity at 97.5% (95% CI 83.7-99.7%), while tissue and blood PCR yielded 86.4% (95% CI 78.9-91.5%) and 81.6% (95% CI 70.1-89.4%), respectively. Computed tomography (CT) and magnetic resonance imaging (MRI) confirmed predominant ethmoid (86%) and maxillary (79%) sinus involvement. Multimodal therapy combining liposomal amphotericin B (L-AmB) with surgical debridement achieved 57-75% survival. Interdisciplinary consultation within 24 hours and perioperative glycaemic control below 180 mg/dL each independently improved outcomes.

Conclusions: DM remains the dominant substrate for mucormycosis and uncontrolled glycaemia the single most modifiable risk factor. Integrated internal medicine and oral surgery collaboration, with internists incorporating oral examination into routine diabetic reviews and dentists maintaining suspicion for palatal lesions, is essential. Rapid-referral protocols and joint medical-surgical management improve survival and should be institutionalised in high-burden endemic settings.

Keywords: Mucormycosis, diabetes mellitus, rhino-orbital-cerebral, oral cavity, interdisciplinary care, systematic review

INTRODUCTION

Mucormycosis is not a subtle disease. It announces itself with vascular invasion and tissue death, kills faster than most infections a physician encounters, and historically has struck those patients least equipped to survive it.

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The causative organisms are environmental moulds of the order Mucorales, principally the genera *Rhizopus, Mucor, Rhizomucor*, and *Lichtheimia*.[1] The condition is uncommon in the general population, with incidence estimates ranging from 0.005 to 1.7 cases per million, but within the immunocompromised, this rarity dissolves rapidly; DM accounts for 54-88% of documented cases in the published literature.[1-3] South Asia presents a particularly sobering picture. In India and Pakistan combined, prevalence reaches 140 per million population, a seventy-fold elevation above global figures, attributable to the staggering burden of undiagnosed or poorly controlled diabetes and the practical realities of limited access to specialist care.[1]

The biology underpinning this predisposition is well characterised. Hyperglycaemia systematically undermines neutrophil chemotaxis, phagocytic function, and intracellular killing capacity.[1,2] Diabetic ketoacidosis (DKA), present in 14-40% of

mucormycosis cases, adds a further layer of vulnerability by lowering serum pH, which releases iron from transferrin, thereby providing Mucorales with the free iron essential for their growth and sporulation.[2,4] At the molecular level, the fungal surface protein CotH3 binds to GRP78, a mammalian chaperone that is overexpressed on vascular endothelium in hyperglycaemic states.[2] This interaction initiates endothelial invasion, precipitates vascular thrombosis, and drives the tissue necrosis that defines the clinical picture.

ROC mucormycosis accounts for 40-75% of all presentations in diabetic patients.[4,5] What is less appreciated, even among internists who manage these patients, is that the oral cavity is not merely a bystander in this process. The hard palate serves as the sentinel site of entry in 50-60% of ROC cases, a fact with profound implications for clinical practice.[6,7] Fungal spores gain access through dental procedures or pre-existing periodontal disease, germinating readily in glucose-rich oral mucosa. From this point, infection travels with alarming speed via palatine vessels into the paranasal sinuses, the orbit, and eventually the intracranial compartment, often within days.[6-8] This trajectory leaves no room for diagnostic hesitation.

The characteristic black eschar of palatal mucormycosis, that late and unmistakable sign of ischaemic necrosis from vascular thrombosis, is in truth a marker of advanced disease.[6] The clinical problem lies in what precedes it: subtle mucosal discoloration, unexplained loss of palatal sensation, and dental pain without an obvious dental cause are the earlier signals, and they are routinely dismissed as periodontal disease or diabetic neuropathy.[6,8] Every such dismissal represents a delay in intervention that substantially worsens prognosis. This is the diagnostic gap that integrated medical and dental care must close. The COVID-19 pandemic exposed this gap at scale, generating an epidemic of mucormycosis that made the need for interdisciplinary protocols impossible to ignore.

MATERIALS AND METHODS

Protocol and Reporting

This systematic review was conducted in full adherence to PRISMA 2020 guidelines.[9] This review was not prospectively registered with PROSPERO. The absence of prior registration is acknowledged as a limitation; no protocol deviations occurred during conduct of the review.

Eligibility Criteria: We included adult patients aged 18 years or older with confirmed mucormycosis and documented DM. The intervention of interest encompassed any diagnostic modality, therapeutic strategy, or preventive approach applied to mucormycosis. Primary outcomes were all-cause mortality and 90-day survival; secondary outcomes included diagnostic accuracy, treatment response rates, complications, and disease recurrence. Eligible study designs comprised systematic reviews, meta-analyses, case reports, case series, and observational studies. Studies involving paediatric populations and those not published in peer-reviewed journals were excluded.

Search Strategy: An electronic search was conducted across PubMed/MEDLINE, Embase, Scopus, and Cochrane CENTRAL covering the period from 1 January 2020 to 31 October 2025. Search terms combined controlled vocabulary with free-text keywords as follows: ("mucormycosis" OR "Mucorales" OR "Rhizopus") AND ("diabetes mellitus" OR "hyperglycaemia") AND ("rhino-orbital" OR "maxillofacial" OR "oral cavity") AND ("diagnosis" OR "treatment" OR "management").

Study Selection and Data Extraction: Two reviewers (MI from internal medicine and MK from oral surgery) independently screened all retrieved citations against predefined eligibility criteria. Disagreements were resolved through discussion with the senior author (SJK). Agreement was excellent, with Cohen's kappa of 0.89. Standardised data extraction captured study characteristics, population demographics, interventions employed, and all reported outcomes.

Quality Assessment: Systematic reviews were appraised using AMSTAR-2.[10] Observational studies (cohort and cross-sectional designs) were assessed with the Newcastle-Ottawa Scale (NOS). Case reports and case series were appraised using the Joanna Briggs Institute (JBI) Critical Appraisal Checklists for Case Reports and Case Series, respectively, as the NOS was developed for cohort and case-control studies and is not validated for case-level data.[11] All five systematic reviews in the final sample were rated high confidence on AMSTAR-2; all case reports and case series satisfied the JBI Critical Appraisal Checklist criteria. Given the mixed-design evidence base (systematic reviews, observational studies, case series, and case reports), the overall level of evidence is Oxford

CEBM Level 3-4, and conclusions are interpreted accordingly with appropriate caution.

RESULTS

Study Characteristics: The 15 included studies comprised 5 systematic reviews,[1,6,8,12,13] 4 case reports,[2,5,14,15] 2 case series,[16,17] and 4 reviews or observational studies.[7,18,19,20] The systematic reviews collectively synthesised data from hundreds of prior publications, lending the pooled estimates considerably more weight than the individual primary studies could provide alone. Quality appraisal confirmed high confidence on AMSTAR-2 for all five systematic reviews; all case reports and case series met the JBI Critical Appraisal Checklist criteria.

Epidemiology and Risk Factors: DM featured in 54-88% of all mucormycosis cases across the included literature, with the pooled estimate converging at 72%.[1-3] Among diabetic patients who developed mucormycosis, 50-76% had uncontrolled glycaemia at presentation (HbA1c >9%), while DKA was documented in 14-40% of cases.[1,2] Uncontrolled hyperglycaemia (HbA1c >9%) was associated with substantially elevated risk relative to well-controlled diabetes (HbA1c <7%).[1] The patients presenting to medical wards in Peshawar and across the region with uncontrolled diabetes are precisely those for whom this diagnosis should remain prominently in mind.

Pathophysiology and Clinical Presentations: *Rhizopus* species accounted for approximately 68% of cases across the series reviewed.[1,2] The ROC form constituted 70-86% of all mucormycosis presentations in diabetic patients, a pattern consistent across South Asian and international cohorts.[4,5] Within ROC cases, the oral cavity was the initial presentation site in 50-60%, with necrotic lesions visible most commonly on the hard palate.[6,7] The speed with which this infection progresses from a palatal ulcer to intracranial extension within days demands that both dentists and internists treat any suspect oral lesion in a diabetic patient as an emergency until proven otherwise.

Diagnostic Approaches: PCR-based methods, evaluated in a 2025 systematic review and meta-analysis by Brown et al., demonstrated high performance across all specimen types.[13] BALF PCR achieved the highest sensitivity at 97.5% (95% CI 83.7-99.7%) with specificity of 95.8% (95% CI 89.6-98.4%). Tissue PCR offered sensitivity of 86.4% (95% CI 78.9-91.5%) with specificity of 90.6% (95% CI 78.1-96.3%). Blood or serum PCR provided sensitivity of 81.6% (95% CI 70.1-89.4%) with specificity of 95.5% (95% CI 87.4-98.5%), representing a less invasive option for patients in whom BALF collection is not feasible. All PCR methods achieved turnaround within four hours for blood and BALF specimens, a practical advantage that cannot be overstated in a disease where hours determine outcome.

CT and MRI demonstrated predominant involvement of the ethmoid (86%) and maxillary (79%) sinuses, consistent with infection ascending from the palate and nasal cavity.[19,20] MRI proved superior to CT for detecting early invasion, cavernous sinus extension, and perineural spread and should be the preferred modality when intracranial involvement is suspected.[19,20] Tissue biopsy revealing broad aseptate hyphae confirmed the diagnosis in approximately 85% of cases. Fungal culture remains the reference standard for species identification and antifungal susceptibility testing, though its variable sensitivity (50-80%) and turnaround of 24-72 hours make it unsuitable as a sole diagnostic tool. The diagnostic performance characteristics of all modalities are summarised in Table 1.

Table 1: Diagnostic Performance Characteristics of Modalities Used in Mucormycosis

Diagnostic Modality	Sensitivity (%)	Specificity (%)	Turnaround Time
BALF PCR	97.5 (83.7-99.7)	95.8 (89.6-98.4)	<4 hours
Tissue PCR	86.4 (78.9-91.5)	90.6 (78.1-96.3)	4-12 hours
Blood/Serum PCR	81.6 (70.1-89.4)	95.5 (87.4-98.5)	<4 hours
CT/MRI Imaging	85-94	85-90	<1 hour
Histopathology	85	95	4-12 hours
Fungal Culture	50-80	100	24-72 hours

BALF: bronchoalveolar lavage fluid; PCR: polymerase chain reaction; CT: computed tomography; MRI: magnetic resonance imaging. PCR sensitivities and specificities with 95% confidence intervals are from Brown et al. 2025 systematic review and meta-analysis.[13] Multimodal diagnostic approaches reduce time to treatment initiation and optimise overall accuracy.

PRISMA Flow Diagram: The PRISMA 2020 flow diagram summarising the study selection process is presented in Figure 1.

IDENTIFICATION
Records identified through database searching: PubMed (n=456), Embase (n=398), Scopus (n=312), Cochrane (n=81); Total: n=1,247
SCREENING
Records after duplicates removed: n=856 | Records excluded after title/abstract screening: n=794 | Full-text articles assessed for eligibility: n=62
INCLUDED
Studies included: n=15 | Systematic reviews (n=5), Case reports (n=4), Case series (n=2), Reviews/Observational (n=4)

Figure 1: PRISMA 2020 flow diagram. The identification phase yielded 1,247 records across four databases. After duplicate removal and two-reviewer screening, 62 full-texts were assessed for eligibility. Final inclusion comprised 15 studies: 5 systematic reviews, 4 case reports, 2 case series, and 4 reviews or observational studies.

Medical and Surgical Management: L-AmB at 5-10 mg/kg per day remains the first-line antifungal agent, with response rates of approximately 70%.[12,21] Isavuconazole has demonstrated non-inferior outcomes as salvage therapy with a more favourable nephrotoxicity profile.[21] The combination of amphotericin B with an azole yielded markedly lower mortality at 6.6% compared to 31.5% with amphotericin B monotherapy, while sequential therapy with amphotericin B followed by an azole achieved 13.7% mortality.[12] Treatment duration conventionally runs to 4-6 weeks of intravenous therapy before an oral step-down is considered. [5,15]

Glycaemic management is not merely supportive; it is therapeutic in its own right. Maintaining perioperative blood glucose below 180 mg/dL through structured insulin protocols was associated with reduced disease recurrence.[4,5] Proper management of underlying diabetes is essential for treatment success.[1,5] Without addressing the metabolic substrate that Mucorales exploit, antifungal treatment alone is insufficient. Surgical debridement is the cornerstone of management, with approximately 55% of patients undergoing operative intervention and an associated overall mortality of 21.8%.[12] The gold standard combines early debridement with concurrent antifungal therapy.[4,21] Orbital exenteration was required in approximately 30% of advanced cases. Early surgical debridement within 48 hours of diagnosis, combined with optimal glycaemic control, emerged as the strongest positive prognostic indicator across the series reviewed.[4,5]

Outcomes and Prognosis: Multimodal therapy combining L-AmB with surgical debridement achieved survival rates of approximately 57-75% in recent cohorts.[12] Interdisciplinary consultation initiated within 24 hours was consistently associated with superior survival compared to single-specialty management.[4,5] Disease recurrence occurred in approximately 15% of cases, and when it did, inadequate glycaemic control was the dominant associated factor.[5] These figures, while representing genuine progress over historical mortality rates, are a reminder that survival remains contingent on speed of diagnosis and quality of metabolic control.

DISCUSSION

This PRISMA-compliant systematic review of 15 studies confirms what experienced clinicians in high-burden settings have observed for years: DM is the substrate on which mucormycosis thrives, present in 54-88% of

cases. Three findings merit particular attention. The oral cavity is the primary portal of entry in 50-60% of ROC cases, placing the dentist in an unusually powerful position as the first clinician to encounter the disease at a stage still amenable to surgical control. The combination of molecular diagnostics, L-AmB, and timely surgery has pushed survival to 57-75%, a figure unimaginable in earlier decades. And interdisciplinary consultation within 24 hours independently improves outcomes, meaning that the organisational structure of care is itself a determinant of mortality.

Traditional fungal culture, with its 50-80% sensitivity and 24-72 hour turnaround, is inadequate for a disease that kills in days. Brown et al.'s 2025 systematic review and meta-analysis definitively established PCR's performance across specimen types, with BALF achieving 97.5% sensitivity when bronchoscopy is feasible, tissue PCR at 86.4%, and blood PCR at 81.6% with a turnaround under four hours.[13] Paired with advanced CT and MRI to characterise anatomical extent,[19,20] particularly MRI's superiority for early intracranial extension and perineural spread, the current diagnostic toolkit is far better than what was available even five years ago. The challenge now is access: in district hospitals across Khyber Pakhtunkhwa and the wider region, PCR is not always reachable, and clinical acumen combined with rapid histopathology remains the practical first line.

The modifiable risk factor in this equation is not the fungus. The fungus is everywhere. The modifiable factor is the metabolic environment we allow to persist. Uncontrolled diabetes with HbA1c above 9% confers substantially elevated risk[1] yet accounts for 50-76% of mucormycosis cases in diabetic patients, meaning that the population most at risk is also the population in whom prevention is most tractable.[1,2] Perioperative glycaemic control targeting below 180 mg/dL reduces recurrence, and there is every reason to extrapolate that sustained population-level glycaemic improvement would translate into measurable reductions in mucormycosis incidence.

The single most operationally important finding of this review is that early interdisciplinary consultation, within 24 hours, independently improves survival.[4,5] This places an obligation on hospital administration and clinical leadership as well as on individual practitioners. For the dentist, the relevant red flags are painless palatal discoloration in a diabetic patient, unexplained tooth mobility, disproportionate unilateral facial pain without a dental explanation, and failure to respond to antibiotic treatment. For the internist, oral cavity examination should not be a luxury; it should be a standard component of the diabetic review, particularly in patients with HbA1c above 9% or any history of DKA. Joint treatment planning that synchronises glycaemic optimisation, antifungal initiation, and surgical debridement timing is not coordination for its own sake; it is the therapeutic synergy on which survival depends.

The evidence base for this review rests primarily on case reports, case series, and systematic reviews of similarly structured studies rather than prospective cohort data or controlled trials. A disease with this mortality and this rarity is unlikely to generate randomised evidence in the near term. Statistical heterogeneity across the included literature precluded formal quantitative meta-analysis for most outcomes. Studies from South Asia, the highest-burden region, remain underrepresented in the international literature relative to disease prevalence, and the findings cannot be assumed to translate uniformly across healthcare systems with different resource profiles.

CONCLUSIONS

Diabetic mucormycosis is a condition that rewards speed and punishes delay. Therapeutic advances comprising molecular diagnostics, liposomal amphotericin B, and coordinated surgical debridement have together pushed survival from the historically dismal to the cautiously acceptable range of 57-75%. They can only be deployed in time if the diagnostic framework includes the oral cavity, if internists and dentists communicate immediately rather than sequentially, and if glycaemic control is treated as a priority from the moment of admission. Training dental providers and internists in early recognition of oral manifestations, building rapid referral pathways that enable same-day interdisciplinary consultation, and embedding integrated care protocols in high-burden endemic areas are the concrete interventions this disease demands.

DECLARATIONS

Authors' Contributions

MI, MK, and SJK conceived the study design. MI and SJK conducted the literature search and data extraction with an internal medicine focus; MK contributed oral and maxillofacial surgical expertise and clinical perspective. All three

authors contributed equally to data synthesis, manuscript drafting, critical revision, and final approval of the submitted version.

Conflicts of Interest
The authors declare no conflicts of interest.

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