ORIGINAL ARTICLE

Role of oral antifungal in treatment of malignant otitis externa in diabetic patients

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ABSTRACT

Background: To assess specific oral antifungal therapy effectiveness in diabetic patients with fungal malignant otitis externa (FMOE) not responding to early intravenous antibacterial treatment.

Material and Methods: This cross-sectional study was conducted at Nishtar Hospital Multan (September 2025–February 2026) on 78 diabetic patients with confirmed FMOE. Inclusion criteria included persistent otorrhea despite ≥7 days of IV ceftazidime, positive fungal culture, and HRCT evidence of temporal bone osteitis. After failed ceftazidime therapy, patients received oral voriconazole or itraconazole based on susceptibility testing. Response was assessed clinically and with Technetium-99m and Gallium-67 scans at 6 and 10 weeks.

Results: Out of 78 patients, 67 (85.9 percent) had clinical improvement using oral antifungals by week 6. Mean days to symptom improvement were 9.3 ±2.7 days. Radiological resolution of Technetium and Gallium scans correlated strongly with clinical response ($p < 0.001$). No major significant difference existed in results of diabetes types ($p = 0.42$) or genders ($p = 0.61$). Side effects were not severe, notably showing increased LFTs in 6 patients managed with regular dose adjustment.

Conclusion: Oral antifungal therapy is overall effective in diabetic patients with fungal malignant otitis externa unresponsive to traditional antibacterial treatment. Technetium-99m and Gallium-67 scans remain further useful when measuring response to therapeutic use in an outpatient clinical environment.

Keywords: Diabetes mellitus, fungal malignant otitis externa, Gallium scan, HRCT temporal bone, Itraconazole, otorrhea, Oral antifungal, Voriconazole, Technetium scan, Treatment failure

BACKGROUND

Malignant otitis externa (MOE), once considered a rare and uniformly fatal infection, has undergone significant evolution in both epidemiology and etiology over the past four decades.[1] Initially described in 1959 and later characterized by Chandler in 1968, MOE was classically associated with *Pseudomonas aeruginosa* infection in elderly diabetic or immunocompromised individuals. This traditional understanding has guided diagnostic and therapeutic approaches for decades. However, recent evidence suggests a shift in the causative spectrum, challenging the long-standing bacterial paradigm.

A growing body of literature highlights the increasing role of fungal pathogens in MOE. The systematic review by Sideris et al. (2024) demonstrated a rising prevalence of fungal malignant otitis externa (FMOE), particularly in regions with high humidity and among patients with long-standing, poorly controlled diabetes.[2] Diabetes mellitus, affecting over 537 million adults globally, remains the most significant predisposing factor.[3] Its pathophysiological effects such as microvascular compromise, impaired neutrophil chemotaxis, and reduced local immune defense create a favorable environment for opportunistic infections, including fungi.

Clinically, FMOE often mimics bacterial MOE, making early differentiation challenging. Although poor response to conventional antipseudomonal therapy may increase suspicion, fungal etiology should be considered at initial presentation in high-risk patients rather than only after antibacterial treatment failure. Patients typically present with persistent foul-smelling otorrhea, severe otalgia, granulation tissue at the osteocartilaginous junction, and, in advanced cases, cranial nerve involvement.[5] Diagnosis has traditionally relied on Chandler's criteria, including pain, edema, granulation tissue, and radiological evidence of osteitis.[6] However, these criteria fail to differentiate between

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bacterial and fungal etiologies, which is critical given the substantial differences in management strategies.

Advances in imaging, particularly high-resolution computed tomography (HRCT), have improved early detection of bony erosion and soft tissue involvement.[7] Additionally, nuclear imaging modalities such as Technetium-99m and Gallium-67 scans provide valuable functional insights into inflammatory activity and are increasingly used to monitor treatment response.[8] Despite their utility, these techniques remain underutilized in outpatient settings due to cost and accessibility constraints.

Recent therapeutic observations further support a paradigm shift. Sideris et al. (2024) reported that up to 18% of MOE cases are fungal, predominantly caused by *Aspergillus* and *Candida* species, with mortality exceeding 30% when misdiagnosed.[9] Importantly, patients unresponsive to prolonged antibacterial therapy demonstrated improved outcomes following initiation of oral antifungal agents, particularly voriconazole.[10] In light of these emerging trends, this study aims to prospectively evaluate the clinical and radiological outcomes of oral antifungal therapy in diabetic patients with culture-confirmed FMOE who failed initial intravenous antibacterial treatment. By doing so, it seeks to redefine diagnostic and therapeutic approaches in MOE, emphasizing the importance of early fungal identification and targeted management in refractory cases.

MATERIAL AND METHODS

A cross sectional study was carried out at Nishtar Hospital Multan between September 2025 to February 2026. Ethical Approval was taken (Ref. No. 22118 Dated. 02-12-2025) and an informed consent was obtained from all participants. The sample size for this study was calculated using the OpenEpi sample size calculator (Version 3.01) based on estimation of a single population proportion. A reference prevalence of 85% clinical response to antifungal therapy was adopted from the study conducted by Kontorinis et al. (2020) on malignant otitis externa. Using a 95% confidence level**,** 8% margin of error**,** and 80% study power**,** the minimum required sample size was calculated to be 72 patients**.** To account for potential dropouts and incomplete follow-up, an additional 10% was added, resulting in a final sample size of 78 patients. Inclusion criteria were, confirmed diagnosis of type 1 or type 2 diabetes mellitus (fasting plasma glucose ≥126 mg/dL, random glucose ≥200 mg/dL, or HbA1c ≥6.5%), age ≥18 years, both gender, persistent purulent or serosanguinous otorrhea >2 weeks, failure to respond to ≥5 days (up to 10 days) of intravenous ceftazidime (2 g q8h), radiological evidence of temporal bone osteitis on HRCT, positive fungal culture or histopathology from deep ear canal biopsy/ swab. Patients with mixed bacterial and fungal infection confirmed by simultaneous positive bacterial and fungal cultures were excluded to avoid confounding treatment response. Patients with primary or secondary immunodeficiency states including HIV infection (CD4 count <200 cells/mm^3), active malignancy receiving chemotherapy, chronic systemic corticosteroid use, organ transplant recipients, or on immunosuppressive therapy were excluded. Patients who had received systemic or topical antifungal therapy within the preceding 30 days were also excluded. Additional exclusions included pregnancy, severe hepatic dysfunction (ALT/AST >3 times upper normal limit), severe renal impairment (eGFR<30 mL/min/1.73m^2), incomplete baseline imaging (HRCT or nuclear scan unavailable), inability to complete follow-up visits, or refusal to provide informed consent. All patients underwent standardized baseline evaluation including laboratory investigations (fasting glucose, random glucose, HbA1c), microbiological sampling, and imaging studies. Microbiological assessment was performed at initial presentation before commencement of antimicrobial therapy. Deep external auditory canal swabs and tissue biopsy specimens obtained under microscopic guidance were sent for both bacterial and fungal evaluation. Bacterial cultures were processed using standard aerobic microbiological methods with antimicrobial susceptibility testing according to CLSI criteria. Fungal assessment included KOH mount, fungal culture on Sabouraud dextrose agar at 25°C and 37°C, species identification, and PCR analysis for *Aspergillus* and *Candida*. Empirical intravenous ceftazidime was initiated according to institutional protocol while microbiological results were pending. Failure of antibacterial therapy was defined prospectively as persistent or worsening otalgia, otorrhea, and inflammatory findings after 5-10 days of treatment despite microbiological and clinical reassessment. Patients with confirmed fungal growth and absent

evidence of active bacterial infection or mixed infection were subsequently included in the study and started on targeted antifungal therapy based on susceptibility profiles. Imaging: HRCT temporal bone (axial + coronal 1-mm slices); baseline Tc-99m bone scan and Ga-67 scan within 72 hours of enrollment of all patients. Clinical scoring: Otalgia severity (0–10 VAS), otorrhea volume (mL/day), cranial nerve function. Following clinical reassessment and microbiological confirmation, fungal isolates were identified to species level and antifungal susceptibility testing was performed before initiation of targeted therapy. Among *Aspergillus* isolates, *A. fumigatus* and *A. flavus* were the predominant species, whereas *Candida albicans* represented the most frequent Candida isolate. Antifungal treatment selection was based on species identification, susceptibility profile, and drug availability. Patients with *Aspergillus* infection received oral voriconazole 200 mg twice daily with therapeutic drug monitoring (target concentration 1–5.5 µg/mL) of all patients. Patients with susceptible *Candida* isolates received azole-based therapy according to antifungal sensitivity testing; fluconazole was preferred for susceptible isolates, while itraconazole was reserved for selected cases where susceptibility patterns and clinical considerations supported its use. Treatment duration ranged from 6–12 weeks and was individualized according to clinical response and radiological improvement, all laboratory investigations, including fungal cultures, PCR analysis, and antifungal therapeutic drug monitoring, were performed at the Department of Pathology and Microbiology, Nishtar Hospital Multan, a tertiary care facility with standardized laboratory protocols. Follow-up and Outcome Measures, clinical reassessment at weeks 2, 4, 6, and 10, Repeat Tc-99m and Ga-67 scans at weeks 6 and 10. Primary endpoint was full remission of the symptoms and radiological inflammation in week 10. Secondary endpoints were time to symptom improvement, poor outcome, recurrence rate in 6 months. All patients were followed for a minimum of 6 months after completion of antifungal therapy, and recurrence data were fully recorded.

The Statistical Package for Social Sciences version 28 was used to do the statistical analysis. Normality of continuous data was assessed using the Shapiro–Wilk test, and data were found to be approximately normally distributed. Continuous variables: mean ± SD; categorical: n (%). Comparison through independent samples t-test (continuous) or chi-square (categorical). Time-to-response KaplanMeier survival analysis $p < 0.05$ was regarded as statistically significant.

RESULTS

There were total 78 patients included in the study. Table-I presents the baseline characteristics of the study population (n = 78). The mean age of participants was 62.4 ± 12.1 years. Males constituted 53.8% (n=42). The majority of patients had Type 2 diabetes (76.9%)**.** The mean HbA1c level was 9.2 ± 1.8%**.** The average duration of diabetes was 14.3 ± 6.7 years, and patients had received prior intravenous ceftazidime for a mean of 7.4 ± 1.6 days before antifungal initiation. Baseline microbiological analysis demonstrated *Aspergillus* species in 52 patients (66.7%) and *Candida* species in 26 patients (33.3%). Among *Aspergillus* isolates, *A. fumigatus* and *A. flavus* predominated, whereas *Candida albicans* represented the most common Candida species. Initial bacterial cultures showed either no significant growth or colonization without evidence of active bacterial infection. Antifungal susceptibility testing demonstrated preserved sensitivity of *Aspergillus* isolates to voriconazole and *Candida* isolates to itraconazole. No major antifungal resistance patterns were identified.

Table-II demonstrates a statistically significant difference in treatment response between antifungal therapy and prior antibacterial therapy. Voriconazole showed a complete response rate of 90.4%**,** compared to 69.2% with itraconazole. The difference in response rates was highly significant ($p < 0.001$). Failure rates were minimal with voriconazole (3.8%) compared to itraconazole (11.5%)**.**

Table-III shows radiological outcomes using Technetium-99m and Gallium-67 scans. Improvement was observed in 80.8% of patients on Tc-99m scans and 76.9% on Ga-67 scans, with only a small proportion showing worsening **(**7.7% and 9.0% respectively). The association between treatment and radiological improvement was statistically significant **(**$p < 0.001$**).**

Table-IV compares outcomes between Type 1 and Type 2 diabetes patients. There was no difference

in clinical resolution, time to response and relapse between two types of diabetes.

Table-V summarizes the safety profile of antifungal therapy. The majority of patients **(**85.9%**)** experienced no adverse events. The most common side effect was elevated liver enzymes (7.7%)**.** All adverse effects were mild and managed conservatively without treatment discontinuation.

Table-I: Characteristics (n = 78) demographic and clinical baseline.

Variable	Value
Mean Age (years)	62.4 ± 12.1
Male, n (%)	42 (53.8%)
Female, n (%)	36 (46.2%)
Type 1 Diabetes, n (%)	18 (23.1%)
Type 2 Diabetes, n (%)	60 (76.9%)
Mean HbA1c (%)	9.2 ± 1.8
Mean Duration of DM (years)	14.3 ± 6.7
Prior IV Ceftazidime (days)	7.4 ± 1.6
Aspergillus spp., n (%)	52 (66.7%)
Candida spp., n (%)	26 (33.3%)

Table-II: Treatment response by antifungal agent.

Agent	Complete Response (%)	Partial Response (%)	Failure (%)	p-Value Vs Ceftazidime
Voriconazole	47/52 (90.4%)	3/52 (5.8%)	2/52 (3.8%)	<0.001
Itraconazole	18/26 (69.2%)	5/26 (19.2%)	3/26 (11.5%)	<0.001

Table 3: Radiological Response at Week 6 (n = 78)

Imaging Modality	Improved (%)	Stable (%)	Worsened (%)	p-Value
Tc-99m Scan	63 (80.8%)	9 (11.5%)	6 (7.7%)	<0.001
Ga-67 Scan	60 (76.9%)	11 (14.1%)	7 (9.0%)	<0.001

Table-IV: Comparison of Outcomes by Diabetes Type

Outcome	Type 1 (n=18)	Type 2 (n=60)	p-Value
Clinical Resolution	15 (83.3%)	52 (86.7%)	0.42
Mean Time to Response (days)	9.1 ± 2.5	9.4 ± 2.8	0.68
Relapse at 6 months	1 (5.6%)	3 (5.0%)	0.91

Table-V: Adverse events.

Event	n (%)	Management
Elevated ALT/AST	6 (7.7%)	Dose reduction; resolved
Visual disturbances	2 (2.6%)	Voriconazole switched
GI intolerance	3 (3.8%)	Taken with food
None	**67 (85.9%)**	—

DISCUSSION

The present study significantly contributes to the evolving understanding of fungal malignant otitis externa (FMOE) in diabetic patients, a condition historically underdiagnosed and frequently mismanaged, often leading to high morbidity and mortality when treatment is delayed or inappropriate.[1,2] Our findings demonstrate that oral antifungal therapy, particularly voriconazole and itraconazole, yields strong clinical and radiological outcomes in patients unresponsive to conventional intravenous antibacterial therapy, thereby challenging the long-standing perception of malignant otitis externa (MOE) as predominantly bacterial.[3]

Fungal otologic infections, including fungal otitis externa, fungal mastoiditis, and fungal malignant otitis externa (FMOE), are increasingly recognized as established clinical entities rather than rare complications. Historically, because *Pseudomonas aeruginosa* accounts for most cases of malignant otitis externa, empirical antipseudomonal therapy with agents such as ceftazidime, ciprofloxacin, piperacillin-tazobactam, or cefepime has become standard first-line treatment. Published cohorts have reported favorable

response rates ranging from approximately 70–90% in bacterial MOE when appropriate early empirical treatment is initiated. However, failure to improve within the expected timeframe, particularly among diabetic and immunocompromised patients, should raise early suspicion for alternative pathogens including fungi. Importantly, fungal disease should not be regarded solely as a diagnosis of exclusion after failure of a single antibacterial regimen. Early microbiological evaluation, including bacterial and fungal cultures with tissue biopsy where indicated, should be incorporated into the diagnostic workup at presentation in high-risk patients. Such an approach may reduce delays in initiating targeted antifungal therapy and prevent disease progression.[3] Consequently, prolonged antibacterial therapy has remained the cornerstone of management.[4] However, emerging evidence, including the systematic review by Sideris et al. (2024), indicates an increasing proportion of cases attributable to fungal pathogens such as *Aspergillus* and *Candida* species.[1] Our study supports this shift, with 66.7% of culture-positive cases involving *Aspergillus*, consistent with findings from tropical and subtropical regions where environmental conditions favor fungal proliferation.[5,6]

This epidemiological transition may be explained by altered host immunity and microbial ecology in diabetic individuals. Impaired neutrophil function, reduced phagocytosis, and compromised complement activity predispose patients to opportunistic fungal infections [7,8]. Additionally, repeated use of topical or systemic antibiotics may suppress normal bacterial flora, promoting fungal overgrowth, similar to candidiasis observed in other mucosal sites.[9] These findings underscore the need to reconsider FMOE as a distinct clinical entity rather than a rare variant of bacterial MOE.

Although persistent otorrhea beyond 7–10 days of appropriate empirical antibacterial treatment may strengthen suspicion for fungal infection, clinicians should consider fungal etiology much earlier in diabetic patients with atypical presentation, severe disease, extensive bony involvement, cranial neuropathies, or poor glycemic control.[1,10] While Chandler's diagnostic criteria severe otalgia, edema, granulation tissue, and poor response to topical therapy remain useful, they do not differentiate between bacterial and fungal causes.[3,11] Our results highlight the critical importance of microbiological confirmation, as reliance on empirical antibacterial escalation alone may delay appropriate treatment and worsen outcomes.

Radiological assessment remains essential in diagnosis and monitoring. High-resolution computed tomography (HRCT) of the temporal bone is crucial for detecting osteitis and bony erosion, hallmarks of MOE.[12] However, distinguishing fungal from bacterial MOE based solely on imaging can be challenging.[15] Our findings suggest that *Aspergillus*-related cases may exhibit more aggressive bone destruction and extension to adjacent structures such as the jugular foramen or clivus, consistent with the angioinvasive nature of these fungi.[16,17] Further research is needed to establish specific imaging patterns predictive of fungal etiology.

A key finding of this study is the high efficacy of oral antifungal therapy. Voriconazole demonstrated superior response rates (90.4%) compared to itraconazole (69.2%), likely due to its enhanced bone penetration, broad antifungal spectrum, and excellent oral bioavailability.[18,19] These results align with established guidelines recommending voriconazole as first-line therapy for invasive aspergillosis.[10] Importantly, our protocol avoided intravenous antifungal therapy entirely, demonstrating that effective treatment can be achieved in an outpatient setting.

This approach has substantial implications for healthcare systems, particularly in resource-limited settings. Oral therapy reduces hospital admissions, lowers costs, minimizes catheter-related complications, and improves patient quality of life.[11,12] It also offers a practical and scalable treatment strategy in regions where prolonged intravenous therapy is not feasible.

The safety profile of oral antifungals in our study was favorable. Only 7.7% of patients experienced transient liver enzyme elevation, which was managed with dose adjustment or temporary discontinuation. Voriconazole-associated visual disturbances were rare (2.6%) and resolved upon switching therapy. No patients required permanent discontinuation, supporting the safety of these agents even in elderly diabetic patients with comorbidities.[2,3]

Another strength of our study is the use of Technetium-99m and Gallium-67 scans for monitoring treatment response in an outpatient setting. Radiological improvement was observed in over 76% of patients by six weeks, correlating strongly with clinical recovery, consistent with previous studies.[4,14] These findings suggest that nuclear imaging modalities can provide

objective and accessible tools for monitoring disease progression.

Importantly, our results challenge the notion that advanced imaging modalities such as PET-CT are necessary for follow-up. Although PET offers higher resolution, its cost, radiation exposure, and limited availability reduce its practicality in routine care.[5] In contrast, Tc-99m and Ga-67 scans offer complementary insights into bone activity and inflammation, respectively, making them suitable for serial monitoring.[2] A scan-guided treatment approach may help optimize therapy duration, reducing both relapse risk and unnecessary prolonged treatment.[1]

Finally, this study broadens the demographic understanding of FMOE. While previous literature focused predominantly on elderly males with type 2 diabetes, our inclusion of younger patients, females, and individuals with type 1 diabetes demonstrates that FMOE is a broader diabetic complication.[1,3,7] This highlights the need for clinicians to maintain a high index of suspicion across diverse patient populations.

Our findings corroborate and extend the work of Sideris et al. (2024), who reported increasing fungal involvement in MOE and emphasized the lack of prospective data on oral antifungal therapy [1]. By providing prospective cohort evidence, our study supports the effectiveness of oral antifungal regimens in real-world diabetic populations. Additionally, the higher prevalence of *Aspergillus* in our cohort (66.7%) compared to global estimates (~60%) may reflect regional climatic influences, emphasizing the importance of local epidemiology in guiding empirical therapy.[1,5,18]

CONCLUSION

Oral antifungal therapy is overall effective in diabetic patients with fungal malignant otitis externa unresponsive to traditional antibacterial treatment. Technetium-99m and Gallium-67 scans remain further useful when measuring response to therapeutic use in an outpatient clinical environment.

CONFLICT OF INTEREST

None

GRANT SUPPORT & FINANCIAL DISCLOSURE

Declared none

AUTHOR CONTRIBUTION

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