A Treatment Protocol for Management of Bacterial and Fungal Malignant External Otitis: A Large Cohort in Tehran, Iran

Mehrdad Hasibi, MD1, Mohammadtaghi Khorsandi Ashtiani, MD1, Masoud Motassadi Zarandi, MD1, Nasrin Yazdani, MD2, Pedram Borghei, MD1, Ali Kuhi, MD1, Sasan Dabiri, MD1, Reza Hosseini, MD3, and Sara Sardashti, MD4

Abstract
Aims: High rates of negative microbiologic test results highlight the potential role of empiric antimicrobial agents in management of malignant otitis externa (MOE). This study investigates the clinical presentation, laboratory findings, and response to empiric treatment in a large group of patients admitted to a tertiary academic hospital in Tehran, Iran.
Methods and Materials: We recruited 224 patients diagnosed with MOE in a prospective observation from 2009 through 2015. All patients received a 2-agent antibacterial regimen at baseline (phase I). Patients with no improvement within 10 days and/or nonresponders to a second course of antibacterials were switched to antifungals (phase II). Response to treatment was observed and documented in both groups.
Results: All patients had physical symptoms for more than 12 weeks before admission. In total, 127 patients responded well to antibacterials. Eighty-seven out of 97 patients who were switched to antifungals had complete response to treatment; patients in the latter group had significantly higher A1C levels at baseline.
Conclusion: Our findings provide evidence to develop clinical guidelines that accelerate diagnosis and treatment of MOE to improve patient outcomes.

Keywords
malignant otitis externa, skull base osteomyelitis, antifungal agents, empiric therapy

Introduction
Malignant otitis externa (MOE), also known as skull base osteomyelitis, is a severe complication of external auditory canal infection that expands to skull base and temporal bone; MOE is most commonly diagnosed among diabetic and immunocompromised patients. The disease is potentially lethal if not properly treated; cranial nerves, venous sinuses, meninges, and brain parenchyma may be involved. The usual presenting symptom is severe, persistent, and unilateral temporal headache that may awake the patient at night. The ear canal is inflamed, and granulation tissue is usually seen with an intact tympanic membrane when examined through an otoscope. Hearing loss, facial nerve palsy, swallowing dysfunction, and hoarseness are occasionally present.1–3

Medical treatment is the mainstay of therapy in MOE, and appropriate choice of medication is of essence.6 Early initiation of treatment can prevent cranial nerve involvement and improve prognosis if already existing. For diagnosis, auditory canal discharge is usually sent for direct microbiologic evaluation and culture studies; occasionally samples from granulation tissue or skull base may be assessed when necessary. Pseudomonas aeruginosa is the causative pathogen among 50% to 90% of the patients.1 Less frequently, non-Pseudomonas agents may be isolated specifically in nondiabetic patients.5 Staphylococci, Streptococci, and gram-negative bacilli (eg, Klebsiella) are the etiologic cause in 5% to 20% of cases, and fungi (mainly Aspergillus spp.) are the causative agent among another 5% to 20%.9 Ciprofloxacin is known as the treatment of choice for pseudomonal MOE; however, combination anti-microbial regimens are often prescribed to cover resistant strains that are
more reported in recent years.\textsuperscript{4,10} On the other side, culture results can be misleading both due to polymicrobial colonization of the ear canal and pretreatment with antimicrobials specifically among patients referred to tertiary centers.\textsuperscript{11}

Diagnosis and treatment of fungal MOE is not readily accessible and requires high clinical suspicion.\textsuperscript{11,12} Microbiologic studies do not help with definitive diagnosis since pseudomonas is present as the normal flora of the ear canal.\textsuperscript{11,13} Moreover, patients usually require long-term antifungal therapy.\textsuperscript{14}

Considering the large number of culture-negative MOE patients referred to our center and the clinical observations on the satisfactory effects of empirical antimicrobial therapy, we set up a prospective study. We aimed to evaluate the clinical course and response to treatment in a tertiary academic hospital. This is the first time a cohort of over 200 patients diagnosed and treated with MOE has been evaluated; we also sought to address the gap in development of a comprehensive guideline for treatment and management of MOE.

**Methods and Materials**

In a prospective observational study, we evaluated all hospitalized patients with the diagnosis of MOE between the years 2009 and 2015 (7 years) in a tertiary academic hospital. Patients were diagnosed with MOE if all the following items were present:

1. History: being diagnosed with diabetes or other immunocompromised states.
2. Symptoms and signs:
   a. Severe unilateral headache in temporal or preauricular and posterior auricular areas, not proportional to physical exam findings, chronic and aggravating.
   b. History/presence of discharge in auditory canal.
3. Clinical exam findings (observed through otoscope):
   a. Inflammation or discharge in external canal and/or
   b. Presence of granulation tissue in the canal or behind the tympanic membrane.
4. Imaging studies:
   a. Presence of cortical temporal bone erosion and soft tissue involvement inferior to mastoid and temporal bone in brain computed tomography, with no space occupying lesions that can explain the prolonged intense headaches;
   b. Increased uptake in temporal area in 3-phase bone scintigraphy (TPBS).

In addition to mentioned criteria, erythrocyte sedimentation rate (ESR) was measured and documented for all patients.

**Checklist**

A checklist was designed and completed in 1 to 2 weeks based on disease course and treatment regimen.

The following items were included:

1. data regarding the diagnostic criteria (as explained previously);
2. prescribed medications, observed complications, response to treatment, and changes made to regimen;
3. physical exam findings (daily) with emphasis on changes in ear canal inflammation/discharge as well as severity of patient headaches.

**Treatment and response to treatment**

**Phase I.** Based on standard protocols,\textsuperscript{15} we initiated empirical antibacterial treatment for resistant pseudomonas (ciprofloxacin with either a carbapenem [97 patients] or ceftazidime [127 patients]) for 7 to 10 days. Hemoglobin A1C was assessed as an index of glycemic control on admission. Renal function and cardiovascular system were assessed as well. Insulin and/or oral agents were started, with frequent monitoring of plasma glucose levels after consultation with endocrinology unit.

To observe and document response to treatment, we performed daily assessment. Changes in intensity of temporal headache was scaled from 0 (no improvement) to 10 (complete improvement) based on patient reports (subjective/quantitative measure); in ear canal examination, severity of inflammation and amount of discharge was considered as a qualitative measure (objective/qualitative measure). Patients were then classified into 3 groups based on the 2 measures; the classification system is explained here based on obtained scores:

- **Group 1:** patients who reported no improvement in headaches after antibacterial treatment (subjective measure scores: 0 to 4).
- **Group 2:** patients who reported moderate improvement in headaches (subjective measure scores: 5 to 7) OR patients who reported improved headaches (subjective measure scores: 8 to 10) with persistent ear canal inflammation/discharge (moderate response).
- **Group 3:** patients who reported improved headaches and had improved clinical findings in ear canal examination (satisfactory response).

Based on this classification, patients were managed as follows:

- **Group 1:** Patients classified as group 1 were changed to antifungal agents after 7 to 10 days; antibacterial drugs were stopped (phase II of the study).
Group 2: The same antibacterial regimen was continued for another 7 to 10 days for patients in group 2; scores were reappraised thereafter.

Group 3: Intravenous antibacterial regimen was changed to oral antibiotics within several days for patients classified as group 3; they were discharged from hospital.

Since regression of granulation tissue and improvement of cranial nerve palsies take longer than 4 weeks, ESR was considered as an appropriate laboratory measure to evaluate efficacy of treatment on day 7 or 10.12

Phase II. Two groups of patients were recruited for phase II:

1. patients with scores below 5 during initial 7 to 10 days (classified as group 1 in phase I);
2. patients with scores below 8 after an extra week of treatment with antibacterial drugs (patients classified as group 2 in phase I who still had below 8 scores after second round of antibacterial treatment).

For the aforementioned patients, antibacterial regimen was stopped, and antifungal therapy was replaced (Figure 1). Oral itraconazole and amphotericin B were initiated for 66 and 31 patients, respectively, with bone concentrations 4.7 and 5 times their plasma concentrations.16 We selected antifungal drugs based on severity of clinical signs, presence of complications, and renal, hepatic, and cardiac function. Itraconazole was prescribed in the form of 100 to 200 mg capsules twice daily based on renal function; amphotericin B was injected with a dose of 1 mg/kg.

Statistical analysis

For analysis of data, we used the Statistical Package for the Social Sciences (SPSS, IBM Inc, Armonk, New York, USA) version 16.0. Frequencies and percentages were calculated for demographic, clinical, and laboratory characteristics of patients.

Patients were categorized based on the type of treatment they responded to. In the final analysis, we had 2 groups; group a comprised of patients with complete response to antibacterial treatment (group 3 as well as group 2 patients who had responded to a second round of antibacterials in phase I); group B constituted of all patients with satisfactory response to antifungal medications in phase 2. The 2 groups were compared with regards to clinical and pare-clinical findings (chi-square and paired t tests). Level of significance was considered to be .05.

Ethical considerations

The study protocol was approved by the Institutional Review Boards of Tehran University of Medical Sciences. The study was also part of a dissertation. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and
institutional guidelines on human experimentation (through written informed consents) and with the Helsinki Declaration of 1975, as revised in 2008. Identifying information was not documented, and all the data recorded from patient files were kept confidential by the research team.

Results

In total, 224 patients (male = 160) were enrolled in the study from April 2009 to May 2015. Most patients (n = 201) were in the age range of 61 to 80 years. Diabetes was known as the predisposing factor for all patients; 3 patients had received kidney transplants and had immunosuppressive therapy as an added risk factor for MOE.

History and clinical presentation

Otorrhea and temporal headaches were the common presenting symptoms. Otorrhea was often the earliest symptom, with headaches occurring after 2 weeks to 6 months. Forty-seven participants had cranial nerve (CN) involvement upon referral (CN VII = 43 patients, CN IX-X = 3 patients, CN VI = 1 patient).

Approximately, half of our patients (n = 108) had consulted a physician after 12 weeks of headache. Almost all with cranial nerve palsies had hospital visits in less than 4 weeks; however, all of them had suffered temporal headaches for over 12 weeks. Physical exam, laboratory test results, and preadmission treatment regimens for the patient population are shown in detail in Table 1.

Treatment and response to treatment

As explained in the methods section, all participants were initially treated with a standard 2 drug antibacterial regimen. Based on clinical scores, 113 (59.3%) patients had good and 21 (9.3%) had moderate response in the first 7 to 10 days; 14 out of 21 responded well to the second course of antibacterials. Overall, 127 patients had improved with antibacterial agents (group A); 87 out of 97 (who did not respond to antibacterials) were switched to antifungal regimen and responded well to this treatment (group B). For 10 patients who had no changes in symptoms after 2 weeks of antifungal therapy, other regimens/interventions were implemented based on individual needs (including: vancomycin [for MRSA coverage], facial nerve decompression, necrotic tissue debridement, and heparin therapy [for a case of lateral sinus thrombosis]) with favorable outcomes.

Figure 1 shows a diagram of patient recruitment in the study.

All patients were discharged 2 weeks after improvement of symptoms. We managed and followed up patients with oral quinolones in group A for 3 to 12 months and with oral itraconazol for group B for 6 to 12 months.

| Table 1. Baseline Physical Exam Findings, Lab Tests, and Treatment Regimens Among Patients. |
|---------------------------------|-------------------------------|--------------------------|
| Baseline Finding                | Frequency (%)                 |
| Ear canal examination           |                               |
| Granulation tissue              | 60 (26.7)                     |
| Inflammation/edema              | 188 (83.9)                    |
| Discharge/otorrhea              | 209 (93.3)                    |
| Erythrocyte sedimentation rate (mm/h) |                  |
| <35                             | 21 (9.3)                      |
| 36-75                           | 70 (31.2)                     |
| 76-100                          | 117 (52.2)                    |
| >100                            | 16 (7.1)                      |
| A1C (g/dL)                      |                               |
| <7 (good control)               | 8 (3.5)                       |
| 7-10 (poor control)             | 163 (72.2)                    |
| >10 (very poor control)         | 53 (23.6)                     |
| Injection antibiotics before admission |                       |
| Cefazidime                      | 26 (11.6)                     |
| Ceftriaxone                     | 14 (6.2)                      |
| Ciprofloxacin                   | 32 (14.2)                     |
| Oral/topical antibiotics before admission |               |
| Ciprofloxacin (drop)            | 192 (85.7)                    |
| Ciprofloxacin (tablet)          | 157 (70)                      |
| Cefixime (tablet)               | 64 (28.5)                     |

Between-group comparisons

Mean age of the patients in the 2 groups was similar. Men comprised a significantly higher proportion of patients in group B (69 vs 18). Other variables documented and compared between the 2 groups are indicated in Table 2. Most group B patients (n = 56) had decreased ESR in first 1 to 2 weeks of treatment.

Follow-up

From 47 participants with cranial nerve involvement, 22 were in group A and 25 in group B. From 22 patients with cranial nerve involvement in group A, 8 showed complete and 9 showed moderate improvement; 5 had no improvement. From 25 in group B, 7 had complete response, 10 showed moderate improvement, and 10 had no change in nerve function. For the 10 patients who had no change in symptoms after 2 weeks (in group B), other combination regimens, facial nerve decompression, necrotic tissue debridement, surgical biopsy, and heparin therapy (for a case of lateral sinus thrombosis) were implemented and led to improved outcomes.

After discharge, 6 patients in group A had relapse with headaches and increased ESR levels. After primary clinical assessment, computed tomography scans were ordered to rule out bone sequestrum; antibacterial regimens were ceased, and antifungals were replaced. All 6 showed improvement.
Patients in Group B received itraconazole capsules for 6 to 12 months and were followed for 1 to 3 years through scheduled visits and serial ESR tests. No symptoms or signs of recurrence or relapse were observed.

**Side effects**

Eight patients had mild to moderate gastrointestinal complaints with itraconazole but did not require discontinuation of treatment. Nine out of 32 patients had increased creatinin (Cr) levels (>2.2 mg/dl) with amphotericin B. Five responded well to supportive measures and hydration. We had to stop treatment in 4; increasing Cr levels had stopped in a week, and itraconazole was started for them. All of them had normal Cr after 4 to 6 weeks. They also received antifungal for 6 to 12 months.

**Discussion**

Malignant otitis externa remains a public health threat specifically among diabetic and immunocompromised patients. Despite the high mortality and morbidity of MOE, no guidelines exist for diagnosis and treatment. Our study depicts a comprehensive picture of a large cohort of patients diagnosed with MOE and highlight the role of empiric antifungal therapy. A main strength of the present study was to establish diagnosis based on an all-inclusive system (clinical, laboratory, and imaging findings). The study was conducted in a tertiary academic hospital with referrals from all over the country. This has been the largest sample of MOE patients studied up to our knowledge.

Similar to other studies, most of the participants were men in their 60s to 80s, had uncontrolled diabetes, and only a minority (3.5%) had A1C levels lower than 7. All patients had received antibiotics before referral, making culture-negative specimens a major challenge. The anatomic structure of the ear and humidity of the auditory canal that yield a proper environment for colonization of Pseudomonas and Aspergillus species would also hinder culture-based diagnosis. These challenges have led to efforts for development of non–culture based methods of diagnosis; however, tests such as galactomannan (a serum marker of fungal infection) have not proven helpful in recognition of fungal osteomyelitis. Retrieval of bone specimens (through navigation) although practiced is not harmless and may cause vascular injury. The place of surgical intervention is not well defined in the management of MOE, yet inappropriate medical management causes frequent early debridement surgeries. Exposing intact skull bones may on the other side expand infection. Considering the mentioned challenges, authors decided not to rely on culture studies for diagnosis and management of patients in the present study.

In the present study, empirical antibacterial or antifungal regimens were prescribed in a specific timeframe; outcomes showed significant reductions in mortality, morbidity, and the need for surgical intervention. Previous studies also confirm these findings by indication of suitability of empirical combination anti-pseudomonal regimens for culture-negative patients. Evidence also affirms such regimens for resistant strains of Pseudomonas, although not occasionally prescribed for fungal MOE.

Patients in group B (receiving antifungals) had several characteristics compared to group A (responsive to antibacterials); most of them were men, who presumably are more prone to fungal growth due to outdoor activities in warm and humid weather. Many of them had symptoms for over 12 weeks, and the higher prevalence of cranial nerve involvement confirms their late referral. Their diabetes was also poorly controlled, with significantly higher A1C levels. Nevertheless, cranial nerve involvement and nonresponse to antifungal therapy (need for surgery) in this group was considerably less prevalent than similar studies. We suggest that the early initiation of antifungal drugs may be the main contributing factor to the observed outcome.

Overall, relapse was reported in 2.6% of the patients, comparably lower than previous studies. The relapse observed among group A patients (4.7%) and their response

<table>
<thead>
<tr>
<th>Variable</th>
<th>Bacterial Malignant Otitis Externa, No. (%)</th>
<th>Fungal Malignant Otitis Externa, No. (%)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>56 (44.1)</td>
<td>18 (20.6)</td>
<td>74 (34.5)</td>
</tr>
<tr>
<td>Male</td>
<td>71 (55.9)</td>
<td>69 (79.3)*</td>
<td>140 (65.4)</td>
</tr>
<tr>
<td>Headache before admission</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4 wk</td>
<td>5 (3.9)</td>
<td>0</td>
<td>5 (2.3)</td>
</tr>
<tr>
<td>5-8 wk</td>
<td>24 (18.9)</td>
<td>0</td>
<td>24 (13.5)</td>
</tr>
<tr>
<td>9-12 wk</td>
<td>87 (68.5)</td>
<td>0</td>
<td>87 (40.6)</td>
</tr>
<tr>
<td>&gt;12 wk</td>
<td>11 (8.7)</td>
<td>87 (100)*</td>
<td>98 (45.7)</td>
</tr>
<tr>
<td>Erythrocyte sedimentation rate (before)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;35</td>
<td>21 (16.5)</td>
<td>0</td>
<td>21 (9.8)</td>
</tr>
<tr>
<td>36-75</td>
<td>43 (33.9)</td>
<td>22 (25.2)</td>
<td>65 (30.3)</td>
</tr>
<tr>
<td>76-100</td>
<td>61 (48.0)</td>
<td>51 (58.6)</td>
<td>112 (52.3)</td>
</tr>
<tr>
<td>A1C level</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;7</td>
<td>8 (6.3)</td>
<td>0</td>
<td>8 (3.7)</td>
</tr>
<tr>
<td>7-10</td>
<td>119 (93.7)</td>
<td>44 (51.6)</td>
<td>163 (76.1)</td>
</tr>
<tr>
<td>&gt;10</td>
<td>0</td>
<td>43 (49.4)*</td>
<td>43 (20.0)</td>
</tr>
<tr>
<td>Cranial nerve involvement</td>
<td>22 (17.3)</td>
<td>25 (28.7)*</td>
<td>47 (21.9)</td>
</tr>
</tbody>
</table>

*aP < .05.
to antifungal drugs can be either due to mixed bacterial/fungal infections or incidence of new fungal infection after antibacterial therapy.

Patients in group B who responded well to antifungals had significantly higher A1C levels (>10). In accordance with this finding, previous research introduces diabetes mellitus as a risk factor for acquisition of early invasive fungal infection; gyrated hemoglobin levels over 8 have been associated with ineffective CD4+ T-cell lymphocyte function.25,26

A limitation to the present study could be that imaging modalities including Ga67 scintigraphy or scintigraphy combined with SPECT/CT were not accessible to help decide on termination of treatment. However, we recommend that the long-term (6-12 month) regimen can establish a confidence margin for termination of antifungals. The serial measurement of ESR could serve as an appropriate marker to evaluate efficacy of treatment. Furthermore, utilization of liposomal forms of amphotericin B instead of conventional forms could be associated with less nephrotoxicity, and monitoring the serum levels of itraconazole can aid with better response to treatment.27,28

We believe that the high rates of culture-negative specimens of MOE patients in other settings in Iran29 as well as the notable delay before proper treatment of fungal otitis among immunocompromised elderly patients in previous studies due to misleading culture results justify our approach in not relying on culture studies before initiation of empiric antifungal therapy.29,30,31

We suggest that these findings provide evidence for prescription of empirical antifungal drugs to patients who are unresponsive to or relapse on antibacterials. We recommend that the longer duration of treatment in the present study facilitates fungal eradication when debridement is not performed. Given limitations of culture studies and complications of surgical biopsy or debridement, early initiation of antifungals can prevent expansion of the infection and cranial nerve involvement. Further studies on higher efficacy antifungals such as voriconazole may yield more information to tailor treatment guidelines. We also assume that more investigations about empirical antifungal therapy in patients with primary response and later relapse on antibacterials will provide us with valuable findings.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This study was supported by the Tehran University of Medical Sciences (Grant number: 9211163007).

References

18. Guevara N, Mahdyoun P, Pulcini C, Raffaneli C, Gahide I, Castillo L. Initial management of necrotizing external otitis:


