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**RESEARCH ARTICLE**

# MALIGNANT OTITIS EXTERNA: A REVIEW OF INVESTIGATIONS AND MANAGEMENT

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**ABSTRACT**

Malignant otitis externa (also known as malignant external otitis, necrotising otitis externa, necrotizing external otitis, skull base osteomyelitis and osteomyelitis of the temporal bone) is a rare and potentially life-threatening complication of otitis externa, historically with mortality rates as high as 60%. Management of this condition has varied over the years from radical surgical debridement to medical management only, to tempered combinations of the two. Malignant otitis externa is most often found in the elderly diabetic population and is associated with poor glycaemic control as well as immune compromise. Malignant otitis externa also has a predisposition towards the male gender. Due to the rarity of presentation and variety of management no randomised control trials exist for the management of malignant otitis externa. As a result of this there are no protocols to guide the management of malignant otitis externa. The majority of publications relating to malignant otitis externa are case-series and single case-reports. The paucity of randomised control trials arises from the rarity of condition and the ethical conundrum that would be presented by trialling different management. This review of 71 publications relates to MOE with particular attention to the success of medical, surgical and adjunctive therapies as well as radiological assessment and monitoring of disease. There is a lack of statistical significance in the existing literature, this review will not improve that; however amalgamating the current information will aid management of MOE by providing the necessary information to clinicians.



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## INTRODUCTION

Toulmouche first described a progressive osteomyelitis of the temporal bone in 1838 (Toulmouche, 1838). It was in 1968 when Chandler specifically outlined the clinical features describing Malignant Otitis Externa (MOE) as a separate clinical entity (Chandler, 1968). The word "malignant" in MOE is a misnomer, a descriptive rather than pathological term. It was coined due to the aggressive behaviour, poor clinical outcomes and high mortality rate (Chandler, 1968). Other nomenclature includes necrotising otitis externa/external otitis, temporal bone osteomyelitis or skull base osteomyelitis (Prasanna Kumar and Singh, 2015). Incidence is increasing potentially due to increased awareness in the condition (Prasanna Kumar *et al.,* 2013). In the UK 2.5 cases of MOE were treated per year in a population of 250,000 (Pankhania *et al.,* 2015), agreeing with other international reviews suggesting 10 cases per million per year (Pulcini *et al.,* 2012; Carfrae and Kesser, 2008), remaining most prevalent in the elderly and diabetic populations (Rubin Grand *et al.,* 2004).

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Symptoms of MOE are initially otalgia and discharge, but these fail to respond to simple therapy. Infection spreads from skin of the external auditory canal into adjacent structures causing pain and systemic upset. Examination findings include canal wall oedema, inflammatory polyps and granulation tissue from the floor of the canal, as well as ongoing discharge and pain out of keeping with simple otitis externa. A high index of clinical suspicion is required and it is not an unusual occurrence for a patient to be seen numerous times before a diagnosis of MOE is made. There can be significant delays between onset of symptoms and appropriate treatment;this delay can be as high as 13 weeks, with a range of 1 to 12 months (Guevara *et al.,* 2013). The commonest aetiology is *Pseudomonas aeruginosa* but other bacteria/fungi have also been found to be affecting pathogens (Liu *et al.,* 2012). Early recognition and aggressive anti-microbial therapy have been the mainstays of treatment, and in diabetic patients exemplary glycaemic control aids recovery. Aggressive surgical debridement has previously had mortality rates above 50% (Chandler, 1968), therefore the usage of surgical intervention has been limited more recently to local debridement and tissue biopsy.

## AIMS

To amalgamate the knowledge from multiple case-series to generate a consensus on the most appropriate way to investigate and treat MOE is the aim of this review. Publications reviewed are from different institutions with different patient populations ultimately producing non-standardised subject groups, there is no direct comparison to be drawn and as a result of this results will lack statistical significance. There is much that can be drawn from these publications, general successes and failures can be reviewed, investigations can be shown to effective or ineffective. Overall the aim is to give clinicians a roundup of what separate institutions have found successful and to bring these ideas together.

## METHOD

An electronic database literature search was conducted using search terms: *"Malignant otitis externa, malignant external otitis, necrotizing otitis externa, necrotizing external otitis, necrotising otitis externa, necrotising external otitis, invasive otitis externa, invasive external otitis"*. The following databases were used: PubMed/MEDLINE, Cochrane Library (CENTRAL), Database of Abstracts of Reviews of Effects (DARE), including publications between 1968 to January 2016. Publications were excluded following manual review of abstracts if deemed not relevant to review. There were no exclusions based on publication language. 602 publications were narrowed down to 71 following abstract review + excluding single case reports and case-series of less than 5 people. Letters to editors were also excluded.71 publications contained information on 1592 patients, averaging 22.4 patients per series.

### MEDICAL MANAGEMENT

#### Pathogens

MOE is most commonly a bacterial rather than fungal pathology with *Pseudomonas aeruginosa* (*P. aeruginosa*) as causative pathogen in the majority of cases (Guevara *et al.,* 2013). *P. aeruginosa* develops antibiotic resistance in several ways (Cornelis, 2008) creating difficulty in sufficiently treating infections. Not all institutions appear to take, or report on taking, microbiological samples in all cases. Of publications between 1981 and 2006 that reported cultured organisms, there were 287 samples. Of this group 263 (91.6%) grew *P. aeruginosa*, of the remaining 24 cases 17 were negative cultures, 5 grew *methicillin resistant staphylococcus aureus (MRSA),* 1 grew *Staphylococcus aureus*, and 1 grew *Candida albicans*:

Since then the pattern of pathogenic microbes changed. Case-series reporting cultured microbes between 2007 and 2015 show stark difference in the proportions of pathogenic bacteria. Table 2 highlights two obvious facts. That *P. aeruginosa* has fallen in prevalence from 91.6% to 54.2% and a much wider range of pathogens have been cultured, suggesting that we can no longer assume *Pseudomonas* to be the offending pathogen and as a result of that our choice of initial antimicrobial should be more considered.

**Table 1. Percentage of cultured pathogens between 1981 and 2006**

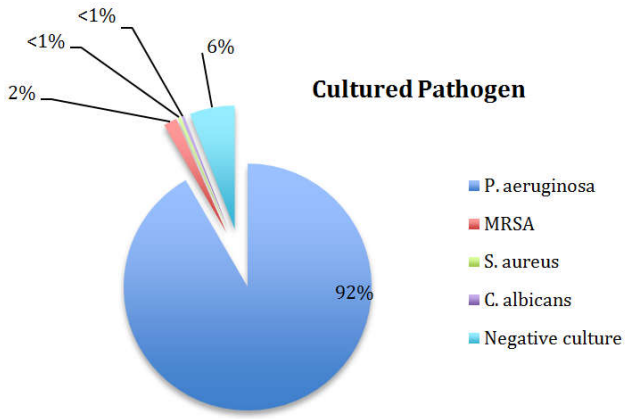


**Table 2. Demonstrating range of pathogens cultured since 2007 in case-series with over 5 subjects**

| Pathogen | Number of cultures |
|---|---|
| *Pseudomonas sp* | 236 |
| *Aspergillussp* | 28 |
| *MRSA* | 17 |
| *Staphylococcus sp* | 11 |
| *Klebsiellasp* | 6 |
| *Proteus sp* | 6 |
| *Unspecified fungal* | 6 |
| *Candida sp* | 4 |
| *Diphtheroids* | 2 |
| *"Polymicrobial"* | 2 |
| *Streptococcus sp* | 1 |
| *Enterobacter* | 1 |
| *Actinomyces* | 1 |
| *E-coli* | 1 |
| *Unspecified Gram negative* | 1 |
| *Unspecified anaerobe* | 1 |
| Negative culture | 70 |
| Unknown | 41 |
| Total | 435 |

In case-series between 1981 and 2006, 108 subjects underwent bacterial sensitivity testing showing 7% of cultured *P. aeruginosa* had resistance to flouroquinolones. Since 2007 of the 199 cultured samples that were assessed for sensitivity and/or resistance, 129 samples cultured *P. aeruginosa*, of which 21were resistant to flouroquinolones, this suggests that resistance to flouroquinolones has more than doubled from 7% to 16%. Varying figures on the sensitivity and resistance of bacterial strains tell us that in the medical age we are in, of developing bacterial resistance and limited new antibiotic treatments, clinicians need to be specific in the prolonged treatment of MOE. In the acute scenario it is obviously important to start antibiotic treatment early despite not knowing the specific culture or sensitivity, however it should be routine practice to obtain samples of purulent material or to take simple ear swabs (and tissue samples if possible) prior to commencing antibiotic therapy so that therapy can be focused once results of culture and sensitivity are available. There is an increasing frequency of fungal pathogens causing MOE since 2007, showing the importanceof considering appropriate management for fungal pathogens. Fungal pathogens are more likely to be found in immune compromised individuals, and are most likely to arise from the *Aspergillus* species (Parize *et al.,* 2009). Voriconazole could be considered as a first line

agent against fungal MOE. It has fewer side-effects and is less "toxic" than amphotericin B which is commonly used against invasive fungal infections (Parize *et al.,* 2009); voriconazole also has the benefit of being an orally administered medication and therefore could expedite discharge.

**Antimicrobial agents**

It becomes incredibly difficult to analyse what regimes are the most successful, this is largely due to the fact that there are very few institutions that stick to the same schedule. Case-series are just that, reviews of previous cases. There are no protocols to follow and any microbiological advice is dependent on the individual or department giving that advice. As a result of this there is a vast variety of first line treatments in the literature, not just this but huge variations in treatment duration and modality of antimicrobial delivery. Throughout time antimicrobial therapy for MOE has changed.Early case-series on antimicrobial management of MOE compared combination therapy (aminoglycosides and penicillins) against mono-therapy (penicillin only).It was found that combination therapy reduced the risk of recurrence and had lower mortality rates. In fact patients who relapsed on mono-therapy were converted to combination therapy which often led to resolution on disease. Mortality in this review was 15%, a number that would go on to improve over the decades (Doroghazi *et al.,* 1981). From 1989 flouroquinolones, such as ciprofloxacin and ofloxacin, became commonplace in the management of MOE due to their antipseudomonal properties (Hickey *et al.,* 1989). Early case-series showed hugely promising results, not only in safety but in treatment success. Two series, involving a total of 102 patients (Rubin *et al.,* 1989; Sade *et al.,* 1989), revealed that ciprofloxacin cured 91% of the 34 patients treated with ciprofloxacin, whereas the remaining 68 patients, who were treated with aminoglycosides and β-lactam penicillins, suffered side-effects almost 50% of the time and also required longer inpatient stay. Following on from this, between 1990 and 2006 124 patients were included in case-series reviewing the efficacy of ciprofloxacin (Lang *et al.,* 1990; Levy *et al.,* 1990; Gehanno, 1990) revealing clinical resolution of disease in 96%. Common agents used in conjunction with ciprofloxacin include Tazocin (tazobactam and piperacillin) and 3$^{rd}$ generation cephalosporins (most often ceftriaxone or ceftazidime). Since 2000 cure-rates in those managed with a combination of 3$^{rd}$ generation cephalosporins and flouroquinolones have averaged at 90.6%, with success rates in individual series ranging from 70% to 100%. Contrasting success has been seen in series using cephalosporins as mono-therapy, with cure rates far lower at 66% (Pulcini *et al.,* 2012; Guevara *et al.,* 2013; Martel *et al.,* 2000; Djalilian *et al.,* 2006; Franco-Vidal *et al.,* 2007; Glynn and Walsh, 2009; Hariga *et al.,* 2010; Pérez *et al.,* 2010; Gassab *et al.,* 2011; Soheilipour *et al.,* 2013; Bhat *et al.,* 2015; Chawdhary *et al.,* 2015; Al-Noury and Lotfy, 2014). Antibiotic duration has been adjusted on a clinical basis supported by monitoring inflammatory markers and radiological investigation but often a minimum of 6 weeks of systemic antibiotics are required to attain disease resolution. Series have shown that reducing that duration to 3 weeks leads to a far greater risk of relapse (Pulcini *et al.,* 2012), there is also no change in outcome between courses of antibiotics lasting 6 weeks and courses lasting 6 months. Many institutions appear to have loose protocols for an initial broad-spectrum intra-venous course for a varying duration of weeks. The rise in negative cultures creates some problems in focusing antimicrobial therapy. It is in these cases where combination therapy with broad-spectrum cephalosporins and flouroquinolones has shown success (Pérez *et al.,* 2010).

**Surgical intervention**

Surgical intervention ranges from local debridement to radical mastoidectomy and subtotal-petrosectomy. The question as to whether there is a role for surgical intervention in the treatment of MOE is a difficult one to answer, often authors comment that radical debridement is used in cases where medical management has failed, however in subsequently successful treatmentone cannot say whether it was the addition of surgery or the on-going medical intervention that eventually lead to resolution. What can be positively stated about surgical intervention is the use of tissue biopsy. A 2014 UK review of cases found that of 25 patients, 13 had undergone tissue biopsies, 7 of these biopsies cultured organisms in patients that had previously had sterile swabs, highlighting the benefit of taking biopsies to help guide treatment (Williams *et al.,* 2014). Tissue samples can also undergo PCR that can provide information on fungal pathogens that have escaped previous culture (Gruber *et al.,* 2015) and in some centres up to 40% of patients undergo some form of histological investigation based on surgical biopsies (Pulcini *et al.,* 2012). General consensus remains that aggressive surgical intervention should only be reserved for cases that continue to deteriorate despite maximal medical therapy. The main role of surgery in the management of MOE lies in the biopsy of tissue to aid pathogen identification to direct medical therapy.

**Radiological imaging**

The difficulty posed for radiological investigation in MOE is that disease affects soft tissue and bone with different imaging techniques highlighting abnormalities in different ways. Computed tomography and magnetic resonance imaging are readily accessible in most medical institutions, and are the most commonly used. Nuclear medicine studies are not available in all institutions but offer vital information in the investigation of MOE. Radiological imaging can be used to: confirm diagnosis, grade extent of disease, grade disease severity, suggest prognosis, and monitor disease progression and resolution. Imaging is used in conjunction with clinical suspicion with different imaging supplying different information and therefore providing some, but not all, of the complete diagnostic picture.

**Diagnosis**

In 1984 a study compared 5 different modalities in 10 patients with a clinical diagnosis of MOE (Strashun *et al.,* 1984). The stark difference, admittedly in a small patient pool, was that in 100% of the cases both Gallium-67 (Ga-67) and Technitium-99 (Tc-99) showed evidence of MOE, however only 33.3% of CT scans confirmed a diagnosis of MOE. One must bear in mind that although MOE does have certain clinical characteristics it does not necessarily present radio logically in

an entirely uniform way, explaining why CT scanning does not necessarily have the diagnostic sensitivity of scintigraphic studies. CT scanning does have significant benefits in spatial mapping of disease over scintigraphic studies. A retrospective series of 10 patients in 1991 (Marsot-Dupuch *et al.,* 1991) found both CT scanning and MRI were able to determine extent of bony and soft tissue involvement, this helped guide prognosis. A benefit of MRI is that it can demonstrate meningeal involvement more effectively than CT. One of the few prospective studies focused on comparing MRI and CT (Al-Noury and Lotfy, 2011), concluding that both complement each other and demonstrate differences in bone and soft-tissue assessment. Tc-99 is successful in combination with CT scanning for confirming the diagnosis of MOE (Martel *et al.,* 2000) and is useful when osteolysisis present. This is however a late phase of the disease process and therefore may not be as useful as other investigations for initial diagnosis. Overall the general consensus from the case-series reporting on Tc-99 is that it is sensitive for the diagnosis of MOE, however it is best used in conjunction with more spatially aware imaging modalities such as CT scanning to specifically map out disease areas. Ga-67 is used for monitoring disease and confirming disease resolution, it is rarely used for diagnosis of MOE and is commonly referenced as a monitoring tool to guide resolution and cessation of treatment. There is however one of the larger case-series relating to radiological investigation that shows Ga-67 SPECT (Single-photon emission computed tomography) to be a very useful tool in the diagnosis of MOE, in 95.6% (44/46) of cases Ga-67 SPECT was accurate for the presence of MOE,suggesting that although other imaging modalities are used more frequently in the diagnosis of MOE, the use of Ga-67 should not be discounted for diagnostic purposes although usage may be better suited to disease monitoring (Jacobsen and Antonelli, 2010).

**Severity and prognosis**

Disease extent is widely considered to be a radiological marker of severity and prognosis. The modalities that are more useful at mapping extent of disease are those that are more spatially specific, such as CT and MRI. Intracranial dural enhancement and abnormal flow void are specific MRI findings that are related to poor outcome (Kwon *et al.,* 2006); MRI scans have been retrospectively reviewed to assess the internal carotid artery flow-void and patterns of spread. Abnormal flow void and wider spread patterns were suggestive of poor outcome, simply suggesting that greater disease extension is indicative of poorer outcome (Lee *et al.,* 2010). A (relatively) large 75 patient case-series (Joshua *et al.,* 2008) demonstrated nasopharyngeal and temporomandibular-joint involvement with the presence of bone erosion confirmed on CT scanning was associated with longer treatment periods and reduced survival, important links found in this series include associated co-morbidities with more extensive disease on CT linked to poor diabetic control and increased age.

**Disease monitoring**

MOE requires prolonged antimicrobial treatment often without a clear end-point. With the risk of early treatment cessation carrying significant risk of recurrence it is of paramount importance to conclude therapy at an appropriate time. Case-series support the idea that MRI and CT scanning are useful for advising on on-going soft-tissue and bony changes but not for resolution of disease (Martel *et al.,* 2000; Al-Noury and Lotfy, 2011; Marsot-Dupuch *et al.,* 1991; Ceruse *et al.,* 1998; Grandis *et al.,* 1995; Rubin *et al.,* 1990; Gold *et al.,* 1984; Courson *et al.,* 2014). Scintigraphy is more effective at monitoring disease compared to MRI or CT scanning. There has been shown to be a discrepancy between the benefits of Tc-99 and Ga-67 in disease monitoring. Tc-99 scans remain positive long after clinical resolution whereas Ga-67 matches the clinical picture (Al-Noury and Lotfy, 2011), as Tc-99 is closely correlated to osteolysis. Ga-67 has been shown to represent disease resolution after just 6 weeks (Djalilian *et al.,* 2006) and when used as Ga-SPECT has close correlation with clinical resolution in up to 95% of cases (Al-Noury and Lotfy, 2011).

**Hyperbaric oxygen therapy (HBOT)**

A 2010 Australian case-series reported on the effects of HBOT on 17 patients with MOE (Saxby *et al.,* 2010). 15 patients completed the course, 1 patient did not tolerate HBOT and the other withdrew due to respiratory complications. Of the patients completing the course there were 5 who experienced complications including: pulmonary oedema, seizures, tympanic membrane perforation and claustrophobia. Inpatient duration was 48 days on average with a mean follow up time of 47 months. 12 of the 17 patients were disease free at follow up, this statistic did however include 3 patients who died of causes separate to their MOE, MOE was the cause of death for 3 patients and the remaining 2 suffered a recurrence of disease. HBOT has also been used for the management of intractable pain associated with MOE (Pérez *et al.,* 2010) with some satisfactory results. A Cochrane review (Phillips and Jones, 2013) was conducted on HBOT for MOE in 2013. This review found no studies of suitable quality to perform the necessary analysis and therefore concluded further research was required in this field.

## DISCUSSION

MOE remains a significant challenge facing ENT teams across the world. Treatment requires multidisciplinary input to maintain excellent aural hygiene, manage medical co-morbidities and focus antimicrobial therapy based on local trends in pathogens and specific culture findings. Success in curing MOE has improved hugely since early published mortality rates were as high as 60%. Over the last 2 decades cure-rates have been as high as 100% in some case-series, but more commonly range from 80-95%, this is due to earlier diagnosis, understanding of condition, reducing surgical intervention and aggressive prolonged antimicrobial therapy. Giving specific recommendations is challenging. With no high-quality trials into management of MOE there is no high-grade evidence that can be used to sway judgment and advise specific treatments. Because of variations in disease presentation and delays of presentation, coupled with the rarity of condition it is almost impossible to plan for and arrange a randomised control trial into the management of MOE. Therefore any recommendations made should be discussed

with local multi-disciplinary teams including microbiology teams and ENT teams. Initial management of MOE should include early microbiological sampling to advise future treatment. First line antimicrobials should be in line with local microbiology guidelines under the advice of local microbiology teams. Despite that, consistency in antibiotic choice would vastly help future research and give consistent advice to clinicians. With the view that *P. aeruginosa* is still the most common organism, broad-spectrum intravenous antibiotics with known *Psuedomonal* cover in combination with other agents have been shown to be more effective than mono-therapy. Combinations that have been shown to improve outcomes include. Following initial broad-spectrum intravenous antibiotics treatment should be focused when sensitivities become available, but without sensitivities initial combination therapy has been shown to be effective also. Intravenous therapy should continue for up to 2 weeks or when there is clinical improvement. A targeted oral antibiotic course should follow for a minimum of 6 weeks, with ciprofloxacin often used as a step-down treatment when sensitivities are not available. Close follow up of these patients is vital to ensure cure and also to catch any disease relapse as soon as possible. Surgical intervention has been consistently shown to have greater mortality when used in an aggressive manner. Despite historical evidence suggesting this there are some institutions that continue to use aggressive surgical intervention when medical therapy has failed. The concern is that aggressive debridement exposes previously uninfected tissue to contaminated tissue risking further invasive infection. Limiting surgical intervention to minimal local debridement and aural toilet can help speed up recovery, however the main role now of surgical intervention is to obtain tissue samples for histological and microbiological analysis. First line radiological intervention should include both computed-tomography and magnetic-resonance-imaging as they complement each other well and help map out disease extent which can give an idea of prognosis. Regarding disease monitoring, Ga-67 SPECT is more sensitive at assessing disease resolution compared to other modalities. Creation of hospital guidelines would standardise care in institutions based on local/regional pathogens and develop consistency in the management of MOE. The greatest input on improving outcomes in MOE would be to target primary care. Education on the importance of early diagnosis would encourage primary-care practitioners to engage sooner with hospital ENT teams to get early investigations with an aim to prevent spread before it occurs. In conjunction with this there should be greater emphasis on prevention over cure, meticulous glycaemic control and diabetes management would go great lengths to reduce the incidence of MOE as well as improving the general health of many patients.

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