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Original Article

Management and Clinical Outcomes of 37 Patients with Necrotizing Otitis Externa: Retrospective Review of a Standardized 6–Week Treatment Pathway

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BACKGROUND: Necrotizing otitis externa is an invasive infection, affecting older patients, with significant associated morbidity. Despite this, there are no randomized controlled trials that address management, and therefore, treatment approaches may vary considerably. We describe the management and outcomes of 37 patients managed using a multidisciplinary treatment pathway for necrotizing otitis externa over a 5-year period. The pathway is based on a standardized antibiotic regime of 3 weeks of intravenous ceftazidime plus oral ciprofloxacin, followed by a further 3 weeks of ciprofloxacin.

METHODS: This is a retrospective review of all patients diagnosed with necrotizing otitis externa since the introduction of our pathway in 2016. We include data on patient demographics, comorbidities, microbiology, length of stay, and length of antimicrobial treatment. Outcome data, including mortality, relapse and treatment failure, and adverse effects of treatment, are presented.

RESULTS: The median age of our patients was 82 years. About 54% of patients had diabetes mellitus or another cause of immunocompromise. *Pseudomonas aeruginosa* was isolated in 68%. The median duration of inpatient stay was 9 days, and median treatment duration was 6 weeks. Of 37 patients, 32 were cured (86%), and of the remaining 5 patients, there were 2 mortalities unrelated to necrotizing otitis externa and 3 patients with recurrent infections due to anatomical abnormalities.

CONCLUSION: We note favorable treatment outcomes when using a standardized multidisciplinary pathway and a 6-week course of antibiotic therapy.

KEYWORDS: malignant otitis externa, necrotizing otitis externa, infection

INTRODUCTION

Necrotizing otitis externa (NOE), also termed "malignant otitis externa," is an infection of the external auditory ear canal that invades adjacent bone and can result in osteomyelitis of the skull base and temporomandibular joint, with associated cranial neuropathies typically of the facial, glossopharyngeal, vagal, and hypoglossal nerves.[1] It typically presents with severe otalgia and otorrhea and is most commonly caused by *Pseudomonas aeruginosa*. Risk factors include advanced age and diabetes mellitus.[2] An increasingly elderly and multi-morbid population may therefore contribute to the rising incidence of this condition reflected in Hospital Episode Statistic data.[3-5]

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The mortality from NOE has reduced markedly from 50%, when the condition was first described by Chandler in 1968, down to approximately 20%.[6-8] This reduction in mortality can be attributed to advances in cross-sectional imaging to aid diagnosis, regular aural toilet, targeted antimicrobial therapy, and management of comorbidities. Although the importance of these facets of care is well recognized, approaches to the management of NOE are heterogeneous across specialists in both otolaryngology and infectious disease. Treatment duration and protocols vary, with a perceived need to balance the risks of treatment failure against the risk of treatment-associated complications and the potential for inducing antimicrobial resistance. This can be partly attributed to the lack of a robust evidence base to guide clinical practice. One example of this variation is the route and duration of antibiotic therapy; duration may vary between 6 weeks and 3 months, with some, all, or none of this being administered intravenously.[1,9]

At our center, University College London Hospitals NHS Foundation Trust (UCLH), we have adopted a standardized treatment pathway. All suspected or confirmed cases are discussed among a multidisciplinary team that includes ENT surgeons, microbiologists, infectious diseases physicians, and radiologists.

Our standard antibiotic regimen consists of 3 weeks of combination therapy with intravenous ceftazidime and oral ciprofloxacin, followed by a further 3 weeks of oral ciprofloxacin alone. The successful use of a combination of ceftazidime and quinolone has been described in the literature, including 46 patients treated by Franco-Vidal et al[10] with a cure rate of 95% and 32 patients treated by Pulcini et al[11] with a favorable outcome in all patients.

Management is further tailored according to microbiological susceptibility results. Our outpatient parenteral antibiotic therapy (OPAT) service allows us to minimize the need for patients to remain in hospital to receive intravenous treatment.

We describe below our experience with the above regimen for 37 consecutive patients, focusing on clinical outcomes, length of treatment and length of inpatient stay, and adverse events.

METHODS

Our current pathway for managing patients with suspected NOE is outlined in Figure 1. The case definition used for NOE was the presence of otalgia or otorrhea, combined with radiological changes on CT or MRI that were reported by the consultant radiologist as in keeping with NOE. These changes included an opacified external auditory canal (EAC) associated either with bony erosion of the EAC seen on CT (with or without erosion of the adjacent lateral and central skull base) and/or extension into the adjacent soft tissues. Soft tissue assessment specifically focused on the involvement of fat: the retrocondylar fat in the mandibular fossa, around the facial nerve exiting the stylomastoid foramen, and the cranial aspect of the parapharyngeal fat.

Recent UK consensus definitions for NOE have since been presented by the UK NOE Collaborative, derived via a Delphi method involving UK specialists in ENT, infection, and radiology, and our case definition is aligned with these.[12]

Our inclusion criteria were all patients with a diagnosis of NOE made at our institution, using the above case definition, between January 2016 and February 2021. Since we aim to describe our real-world clinical experience, no specific exclusion criteria were applied. Patients with NOE were known to the Infectious Diseases team, and an electronic database of these patients was established and maintained. Data were gathered retrospectively using paper and electronic medical records. Informed consent was sought prior to initiating treatment for all patients. The study was approved by the Audit and Research Committee at the Hospital for Tropical Diseases, UCLH, which stated that as this was a retrospective review of routine clinical data being analyzed for service development purposes, further formal ethical approval was not required.

We assessed the baseline characteristics of the 37 patients. This included demographic data on age and sex, and the presence of comorbidities including diabetes mellitus, chronic kidney disease, and other forms of immunocompromise. We gathered data on clinical features of presentation, specifically the presence or absence of cranial nerve palsy. Microbiological data were collected to identify the proportion of patients where *P. aeruginosa* was identified. Prior topical and systemic antimicrobial treatment was inconsistently recorded so this was excluded from the data analysis. We gathered data on the mean and median durations of in-patient admission, treatment, including the length of intravenous therapy, and follow-up. We also calculated how many patients were treated with antibiotics other than those that form our standard protocol.

In our experience, repeat imaging findings immediately at the end of treatment do not correlate with cure—patients who are clinically cured and do not need further antibiotics often still have abnormal imaging (although improved when compared to the imaging at presentation), likely due to a lag between radiological and clinical improvement. Therefore, we do not use imaging to assess cure and also note that the recent UK NOE Collaborative definition of cure is based on clinical features only. We perform MRI 3 months posttreatment to provide a baseline at cure, in the event of further relapse, and we consider repeat imaging for patients prior to this in the event of clinical deterioration.

We describe outcome data for our cohort, defining cure using the UK NOE Collaborative consensus definition of "no pain or otorrhoea for a minimum period of 3 months after completing antibiotic therapy."[12] Patients were considered to have a partial response if they had some response to initial treatment but had ongoing or recurrent symptoms. Relapse was defined as new otalgia or otorrhea following the cessation of treatment, with no other cause identified. Adverse effects of treatment were also documented.

RESULTS

Baseline characteristics are illustrated in Table 1; they demonstrate the importance of both age and diabetes mellitus as risk factors for NOE and support the role of *P. aeruginosa* as a causative agent. In fact, since many patients received empirical oral or topical quinolone treatment via primary care services (without microbiological sampling) prior to referral to our center, 10 patients (27%) had no growth on microbiological samples, and therefore, it is likely that more than 68% of patients had an infection due to *P. aeruginosa*. We also note

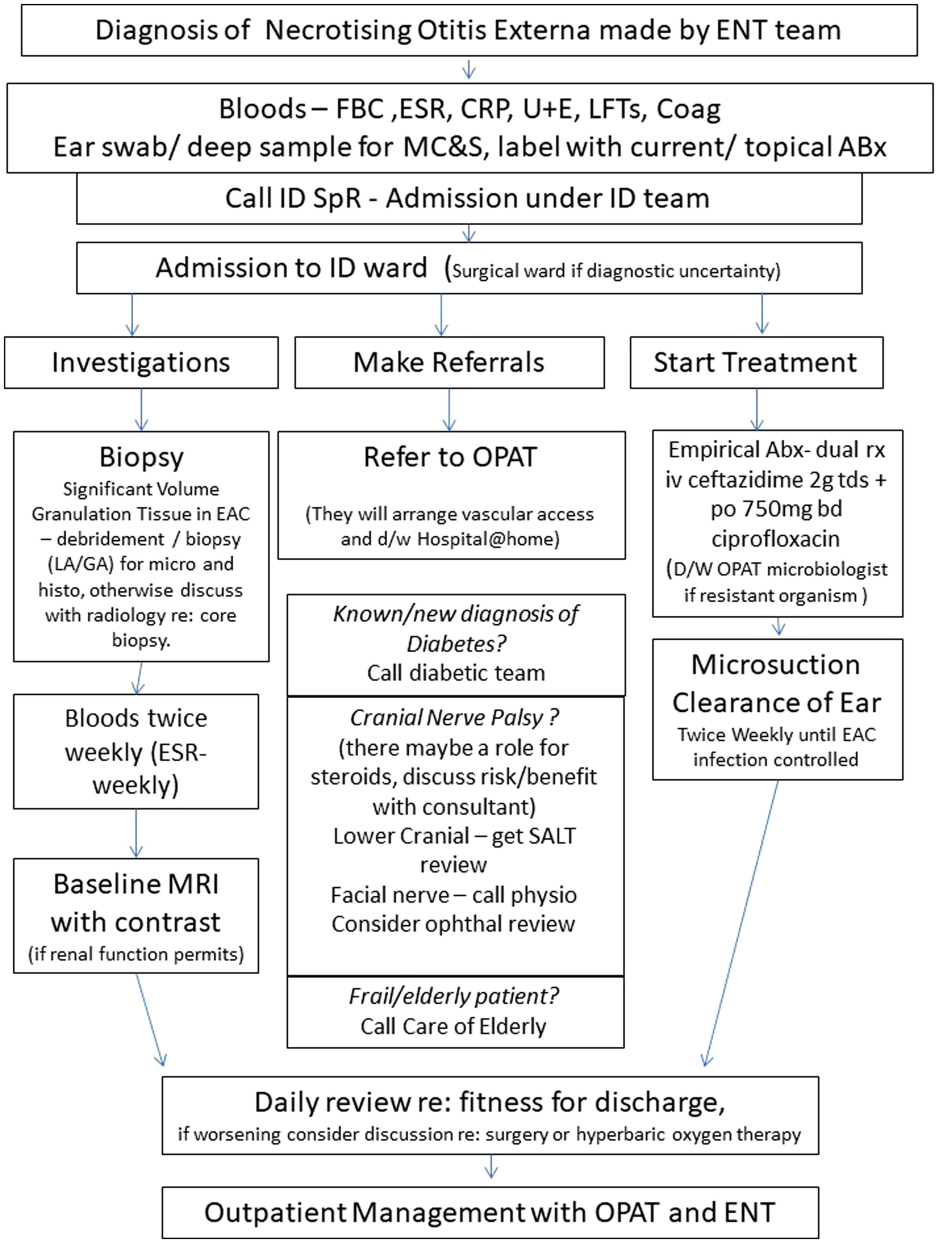

Figure 1. Local pathway for initial management of necrotizing otitis externa (NOE) patients.

Table 1. Baseline Characteristics of Patients

Characteristics	n (%)
Median age (interquartile range; years)	82 (74-90)
Male to female ratio (M : F)	2.7 : 1
Diabetes mellitus	18 (49)
Chronic kidney disease	7 (19)
Immunocompromise	2 (5)
Cranial nerve palsy	10 (27)*
Pseudomonas aeruginosa isolated	25 (68)
Treated with antimicrobials other than ceftazidime and ciprofloxacin	11 (30)

*All 10 patients with cranial nerve palsy had facial nerve palsy. One patient also had hypoglossal nerve palsy, and 1 patient also had abducens, glossopharyngeal, and vagus nerve palsy.

that facial nerve palsy is a common complication of NOE, affecting 10 patients, while involvement of other cranial nerves was less common.

Management and outcome data are illustrated in Tables 2 and 3, respectively. The median duration of intravenous and total antibiotic treatment was 3 and 6 weeks, respectively. The median length of stay was 9 days, and follow-up was for a median of 7 months following completion of treatment.

Of 37 patients in total, 2 patients died (5%) and 32 patients (86%) were cured. Neither of the deaths was a direct consequence of uncontrolled infection. One patient was a 92-year-old female with a background of dementia, severe frailty, and full dependence with activities of daily living, who died due to multi-organ failure following a recently fractured neck of femur. The other patient was a 90-year-old male with a background of dementia and frailty, who died due

Table 2. Antibiotic Management, Length of Stay, and Follow-Up of Patients

Management	Median Duration (Interquartile Range)
Total antibiotic duration (weeks)	6 (6-12)
Total intravenous treatment duration (weeks)	3 (3-6)
Length of stay (days)	9 (7-21)
Median length of follow-up (months)	7 (3-25)

Table 3. Treatment Outcomes for Patients

Treatment Outcomes	n (%)
Death during treatment	2 (5)
Relapse	8 (23)
Cure	32 (86)
Partial response	3 (8)*
Treatment-related adverse events	6 (16)

*All three patients had anatomical abnormalities increasing risk of recurrent infection (osteoradionecrosis, n = 2; eroded external ear canal, n = 1).

to septic shock and heart failure following a severe community-acquired pneumonia. Both patients were on treatment for NOE around the time of death.

Eight patients (23%) had a relapse after completion of treatment; of these 8 patients, 5 patients were ultimately cured with further treatment, while 3 had a partial response at the end of treatment but were not cured (8%). Two of these patients had preexisting osteoradionecrosis with recurrent infections, and the third patient had recurrent infections due to an eroded external auditory canal. Therefore, all 3 patients who were not cured had anatomical risk factors for recurrent infections.

Two patients had persistent cranial nerve palsy following treatment (1 patient with facial palsy, and 1 patient with facial and hypoglossal nerve palsy). Both patients had complete resolution of otalgia and otorrhea after a single course of treatment.

Mean and median total antibiotic durations were 9 and 6 weeks, respectively, and mean and median length of stays were 16 and 9 days, respectively.

Eleven patients (30%) were treated with antimicrobials other than ceftazidime and ciprofloxacin**,** following clinical advice from microbiology or infectious diseases specialists, which is provided either during routine clinical follow-up or via regular multidisciplinary meetings, as part of our standard approach. In 8 of these cases, there were documented reasons for using an alternative antibiotic regime. These included resistance to first-line antimicrobials on susceptibility testing, empirical change in treatment due to lack of response, and addition of a gram-positive agent to treat concurrent skin and soft tissue infection in a patient with a fistula (on a background of osteoradionecrosis).

In total, 6 patients (16%) suffered 6 separate adverse treatment-related events. These included ciprofloxacin-induced tendinopathy, vomiting due to ciprofloxacin, piperacillin-tazobactam-induced mouth ulcers, piperacillin-tazobactam-induced neutropenia, renal impairment secondary to co-trimoxazole, and chest pain and ECG abnormalities due to a peripherally inserted central catheter. No cases of *C. difficile*-associated diarrhea were noted, and no patients developed microbiologically identified resistant *P. aeruginosa* while on treatment.

CONCLUSION

The literature on the management of NOE, and outcomes, is relatively limited. Instituting a dedicated multidisciplinary protocol for the management of NOE patients has been shown to result in a more rapid resolution of the condition with a reduced inpatient length of stay.[13]

Our multidisciplinary approach builds upon existing protocols in the literature and includes colleagues from Radiology, Infectious Diseases, Microbiology, and Otology. This helps facilitate access to radiology services for scanning and reporting, rapid placement of long-term intravenous lines, and early discharge planning. As a result, we can minimize the length of stay for our patients, with a median of 9 days in hospital, benefiting both patients and the healthcare system. Co-ordinated outpatient management is facilitated via a weekly multidisciplinary meeting between the OPAT, Radiology, and Otology teams.

There are no randomized controlled trials that assess antibiotic therapy for NOE, leading to significant heterogeneity in the face of uncertainty. Prolonged antibiotic courses increase the risks of antimicrobial resistance and adverse effects in a higher-risk cohort of older and co-morbid patients. On the other hand, the risk of treatment failure and accompanying morbidity due to overly short courses is clearly also of concern.

Our data indicate that a 6-week course of treatment appears to meet the right balance with a high cure rate and a relatively low incidence of adverse events.

Our cure rate of 86% is lower than the 95% cure rate of Franco-Vidal (2007). There are a few potential reasons for this, which may relate to patient characteristics. In total, 5 patients were not cured. These included 2 patients who died, frail patients in their 90s who both died from causes other than NOE, and therefore prior to potential cure. Excluding these cases from the analysis would give a cure rate of 91%. The remaining three patients who were not cured suffered from anatomical abnormalities predisposing to recurrent infections (1 patient with eroded ear canal, and 2 patients with osteoradionecrosis), for whom permanent cure of infection would not have been a realistic goal of treatment. Excluding these three patients would give a cure rate of 94%.

Our antibiotic approach is supported by other published data, including data from Pulcini et al[11] demonstrating the efficacy of shorter courses with ceftazidime and ciprofloxacin, as well as data from other UK institutions demonstrating the successful use of shorter courses.[14,15] Clearly, data from randomized controlled trials is required to determine the optimal length of antibiotics.

Six of our 37 patients (16%) experienced adverse effects relating to their prolonged antimicrobial therapy. Fortunately, none developed *Clostridiodes difficile*–associated diarrhea, which is a well-recognized

risk of treatment with cephalosporins and fluoroquinolones. The incidence of other adverse effects in our sample, however, highlights the importance of appropriate counseling and monitoring in elderly multimorbid patients who are at particular risk of developing adverse effects to prolonged anti-microbial treatment.[16]

A clear limitation of this case series is the low number of patients since NOE is a relatively uncommon disease. A prospective multi-center study of NOE is being launched in the United Kingdom, and its findings are eagerly anticipated.

Ethics Committee Approval: The study was approved by the Audit and Research Committee at the Hospital for Tropical Diseases, UCLH (08/06/21), who stated that as this was a retrospective review of routine clinical data being analysed for service development purposes, further formal ethical approval was not required.

Informed Consent: Written informed consent was obtained from the patients who participated in the study.

Peer-review: Externally peer-reviewed.

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