The association between radiological spreading pattern and clinical outcomes in necrotizing external otitis

W. Leentje van der Meer a, c, 1, Ahmed B. Bayoumy b, c, * e, 1, Josje J. Otten a, c, Jerome J. Waterval b, c, Henricus P.M. Kunst b, c, e, Alida A. Postma a, d, e

a Department of Radiology & Nuclear Medicine, Maastricht University Medical Center, the Netherlands
b Department of Otorhinolaryngology and Head and Neck Surgery, Maastricht University Medical Center, the Netherlands
c Department of Otorhinolaryngology and Head and Neck Surgery, Radboud Institute for Health Sciences, Radboud University Medical Center, the Netherlands
d School for Mental Health & Neuroscience, Maastricht University, Maastricht, the Netherlands
e Dutch Academic Alliance Skull Base Pathology, Maastricht University Medical Center, Maastricht/Nijmegen, the Netherlands

Article history:
Received 22 March 2022
Received in revised form 24 May 2022
Accepted 30 May 2022

Keywords:
Necrotizing external otitis
Malignant external otitis
Skull base osteomyelitis
Clinical manifestation
Spreading routes
Antibiotic exposure
Facial nerve palsy

Abstract
Objectives: Necrotizing external otitis (NEO) is a rare infectious disease of the skull base. The purpose of this study was to determine whether clinical outcomes of NEO can be correlated to different infectious spread patterns.

Methods: Retrospective chart review from 2010 to 2019 with NEO patients, who were divided into two cohorts: single spreading patterns (group A) or complex spreading patterns (group B) as diagnosed by CT. Clinical symptoms, diagnostic and treatment delay, course of disease, complications, and duration of antibiotic exposure were retrospectively collected from patient records.

Results: 41 NEO patients were included, of which 27 patients belonged to group A (66%). The disease-related mortality rate was 12.2% among the entire cohort, no differences were found between group A and B. Higher rates of N.VII (42.9% vs 14.8% P = 0.047) and N. IX palsies were found in group B compared to group A (28.6% vs 3.7%, P = 0.039). The median duration of antibiotic use was significantly different for a complex spreading pattern, clinical recovery and hospitalizations. Complications were associated with higher diagnostic delay and with a complex spread pattern. The median duration of follow-up was 12.0 (IQR 6.0–19.5) months.

Conclusion: NEO is a severe disease, with significant mortality and morbidity (cranial nerve palsies). The radiological spread pattern may assist in predicting clinical outcome. Furthermore, complex spread patterns are associated with higher rates of clinical nerve palsies (N. VII and N.IX), complications, surgery rates and longer duration of antibiotic use. Diagnostic delay was associated with mortality, complications and facial palsies.

Level of evidence: Level IV.

1. Introduction

Necrotizing external otitis (NEO) is a rare disease affecting the skull base that can be life-threatening. An infection of the external auditory canal (EAC) can spread into the tympanic bone, through the fissures of Santorini, the tympanomastoid fissure, or the foramen of Huschke along the skull base, affecting soft tissue and bone structures (van der Meer et al., 2019). NEO is a form of skull base osteomyelitis which can be caused by otogenic, sinogenic, and odontogenic infections (Glikson et al., 2017; Handzel and Halperin, 2003; Mardinger et al., 2003). Elderly, diabetic and immunocompromised patients (e.g.
HIV-infected, immunosuppression-exposed patients) are specifically at risk (Carfrae and Kesser, 2008). Patients with NEO initially present with persisting otalgia and otorrhea, unresponsive to topical agents (van Kroonenburgh et al., 2018). Often, the initial epithelial defect of the EAC has already closed, whereas the underlying process of osteomyelitis is progressive. In a later stage, temporomandibular joint pain, cranial nerve dysfunction, trismus and pain during mastication, unremitting headache, and cervical lymphadenopathy (Handzel and Halperin, 2003; Rubin Grandis and BFt Yu, 2004) can be present according to the extent of spread (Sreepada and Kwartler, 2003; Rubin and Yu, 1988). Until now, the prognostic value of cranial nerve involvement remained unclear (van Kroonenburgh et al., 2018; Sreepada and Kwartler, 2003; Adams and Offiah, 2012; Mani et al., 2007). However, it may indicate the extent of the disease along the skull base (De Ru et al., 2010). During the diagnostic stage, the computed tomography scan (CT) is made to differentiate between external otitis and NEO, and to exclude other conditions such as ear canal carcinoma. Furthermore, it is also used to evaluate the extent of possible osseous destruction. On MRI, progression of bone marrow, soft tissue involvement and intracranial can be assessed for both initial diagnosis and follow-up (Lee et al., 2011; van der Meer et al., 2021). After initial diagnosis, PET-scans are often used to monitor the therapy response. NEO is usually treated with intravenous antibiotics for the duration of 6 weeks to 6 months. The most commonly used antibiotic therapy consists of ciprofloxacin in case of oral treatment or intravenous pseudomonas-sensitive beta-lactam antibiotics, such as piperacillin/tazobactam or meropenem (van Kroonenburgh et al., 2018). NEO is known to affect the temporal bone, however infratemporal structures such as retrocondylar fat, parapharyngeal structures, temporomandibular joint, and the masticator muscles can all be affected as well. Several NEO imaging studies have described NEO by directional spread: anterior, medial/crossed, and intracranial spreading patterns (van Kroonenburgh et al., 2018; Arja et al., 2012) (Fig. 1). For example, anterior spreading can affect the temporomandibular joint and/or the styloid foramen in the infratemporal fossa. In the case of the medial route, the infection can spread to the parapharyngeal fat; and in case of the crossed spreading route, the infection spreads to the clivus where it crosses the midline (Table 1). Intracranial spread (e.g. to the brain parenchyma) is a feared complication as it can lead to intracranial abscess formation. This study is (one of) the largest series of patients with NEO presented to date with a diverse range of presentation in terms of severity, age and treatment. The primary aim of this study was to investigate spreading patterns of NEO patients in relation to the mortality rate. Secondary aims were to investigate clinical recovery, recurrence, hospitalizations, complications, cranial neuropathies, and the exposure to anti-microbial therapy in relation to the spread pattern of NEO.

2. Methods

2.1. Participants

A retrospective chart series was performed on a cohort of 41 NEO patients who presented between 2010 and 2019 at the Department of Otorhinolaryngology-Head and Neck Surgery at the Maastricht University Medical Center, The Netherlands. Patients followed the diagnostic and treatment algorithm provided in supplement 1. Patients diagnosed with NEO were included in the study if they met the following criteria:

1) clinically diagnosed NEO (based on clinical symptomology)
2) diagnosed skull base osteomyelitis on CT
3) no history of previous conditions which can affect the skull base, such as radiation therapy or surgery.

2.2. Outcome measures

Clinical symptoms, course of disease, complications, treatment duration, antibiotic regimen and antibiotic duration were retrospectively collected from the electronic patient records. Patients were divided into two groups: single spreading route (group A) or complex spreading route (group B). CT at the time of initial diagnosis was used to assess the extension pattern. The extension patterns were classified as the method described by Kwon et al. (2006) in anterior, medial, crossed and/or intracranial spreading. Spreading route was determined using a systematic assessment of these compartments. One dedicated radiology resident (WvdM) and one neuroradiologist (AP) evaluated the CT scans with regard to these NEO spreading patterns. Discrepancies were solved by consensus between both.

2.3. Statistical analysis

Data was presented as numbers with percentages, medians with interquartile range (IQR) or means with standard deviations. Depending on the kind of parameter, distribution, parametric or nonparametric tests including the Mann-Whitney U test, Kruskal Wallis, and the student t-test, chi-square test or ANOVA were used to test for differences within and between groups. This study was
Table 1

| Parameter                        | Entire cohort (n = 41) | Group A (n = 27) | Group B (n = 14) | P-value |
|----------------------------------|------------------------|------------------|------------------|---------|
| Male (%)                         | 32 (78.0)              | 22 (81.5)        | 10 (71.4)        | 0.665a  |
| Age (median, IQR)                | 83 (74–88)             | 85 (78–89)       | 81 (68–87)       | 0.128b  |
| Diabetes (n, %)                  | 22 (53.7)              | 14 (51.9)        | 8 (57.1)         | 0.885c  |
| Exposure to immunosuppression (n, %) | 3 (7.3)               | 1 (3.7)          | 2 (14.3)         | 0.581d  |
| Affected side (n, %)             |                        |                  |                  |         |
| Left                             | 20 (46.7)              | 15 (55.6)        | 5 (35.7)         | 0.477d  |
| Right                            | 23 (53.1)              | 12 (44.4)        | 9 (64.3)         |         |
| Otological findings (n, %)       |                        |                  |                  |         |
| Edematous EAC                    | 35 (77.8)              | 19 (70.4)        | 14 (100)         | 0.114c  |
| Polyp EAC                        | 26 (57.8)              | 17 (63.0)        | 8 (57.1)         | 0.8122c |
| TM perforation                   | 7 (15.6)               | 4 (14.8)         | 3 (21.4)         | 0.678b  |
| Chronic otitis media             | 4 (8.9)                | 3 (11.1)         | 1 (7.1)          | 1.000c  |
| Extension pattern (n, %)         |                        |                  |                  |         |
| Anterior (single)                | 27 (66.9)              | 27 (100)         | -                | -       |
| Anterior, medial                 | 9 (20)                 | -                | 9 (64.3)         |         |
| Anterior, intracranial           | 1 (2.2)                | -                | 1 (7.1)          |         |
| Anterior, medial, intracranial   | 3 (6.7)                | -                | 3 (21.4)         |         |
| Anterior, medial, crossed, intracranial | 1 (2.2)             | -                | 1 (7.1)          |         |

TMJ: temporomandibular joint; EAC: external auricular canal; TM: tympanic membrane.

a Chi-square-test.
b Mann-Whitney U test.
c Fisher-exact test.
d ANOVA-test.

reported according to the Strengthening the Reporting of Observational Studies in Epidemiology statement (von Elm et al., 2008). IBM SPSS Statistics V.25 was used for the statistical analysis. A p-value less than 0.05 was accepted as statistically significant.

2.4. Ethical considerations

The study (METC 15-4-203) was exempted from ethical approval by the Medical Ethical Review Committee of the Maastricht University Medical Center, on basis that the data were collected as part of routine clinical care and were evaluated retrospectively. The study was considered a review of clinical practice and ethical approval was not required. This study was conducted in accordance with the Declaration of Helsinki (Morris, 2013). All data in this study was anonymized.

3. Results

In total, 41 NEO patients were included with a median age of 83 years (IQR 74–88.0), and of whom 32 patients (78.0%) were male. There were 22 patients (53.7%) who were diabetic, and three patients (7.3%) had exposure to immunosuppression. The summary of the baseline patient characteristics can be found in Table 1. In 38 of 41 patients (93%), a culture of the EAC was taken. Twenty-four (58.5%) cultures were positive for Pseudomonas aeruginosa. Other positive cultures included: Candida species (26.8%), Staphylococcus aureus (19.5%), and others (9.6%). No growth was observed in 14.6%. Table 2 shows the microbiological characteristics of this cohort. Furthermore, in 37 NEO patients EAC biopsies were taken and ruled out malignancy. The most common clinical complaints at presentation were otalgia (87.8%), hearing loss (70.7%) and otorrhea (68.3%). In total, 11 patients (26.8%) had cranial neuropathies, which were either isolated or combined cranial neuropathies. The most common neuropathy was paralysis of the facial nerve which affected 10 patients. Furthermore, the CT images of the petrosal bone of 27/41 patients were classified as a single spreading route (group A). All single spreading routes followed the anterior spreading pattern. Fourteen patients were classified as a complex spreading route (group B; Table 1).

3.1. Clinical outcomes in relation to the spreading route

The overall all-cause mortality rate in this study was 34.2% (N = 14), while the disease-related mortality was 12.2% (n = 5). One patient refused antibiotic treatment, thirteen NEO patients deceased while receiving antibiotic treatment, 3/13 discontinued treatment on their own behalf, and 11/13 patient died due to comorbidities (pneumonia, cardiac arrest, bladder carcinoma, dementia). The disease-related mortality rates were 11.1% and 14.3% for group A and B, which was not statistically different (ANOVA, P = 0.401). Clinical recovery was observed in 26 patients (63.4%), with no significant difference in clinical recovery between group A and B (55.6% vs 78.6%, P = 0.147). Recurrence occurred in three patients (7.3%), and hospitalizations occurred in 10 patients (24.4%). Recurrence occurred in one patient after stopping antibiotic treatment, in another patient NEO occurred on the contralateral side, and in one patient symptoms reoccurred despite long-term antibiotic use. For both clinical outcomes, there were no significant differences between group A and B. In total, 15 patients had a complicated course of disease (36.6%), with more complications in group B compared to group A (64.3% vs 22.2%, P = 0.008). Complications included facial nerve palsies (n = 7), multiple cranial nerve palsies (n = 3), thrombosis of the sigmoid sinus (n = 2) and other complications (n = 3). Furthermore, the rate of disease-related surgery was significantly higher for patients in group B compared to group A (57.1% vs 18.5%, P = 0.012). The prevalence of N.VII (42.9% vs 14.8%, P = 0.047) and N.IX (28.6% vs 3.7%, P = 0.039) nerve palsies was significantly higher for patients in group B compared to group A. Table 3 shows the clinical outcomes during follow-up in relation with the spreading routes.

3.2. Duration of antibiotic use: significant difference in clinical outcomes

The median duration of antibiotic use in the entire cohort was 93.0 days (IQR 36.0–160.0), while the median duration of antibiotic use were 92.0 (IQR 37.0–112.5) and 217.0 days (IQR 90.0–248.0) for groups A and B (P = 0.019). The median duration of antibiotic use was significantly higher for patients who achieved recovery (102.5 days vs 39.0 days, P = 0.0144) and hospitalized patients (217.0 days vs 19.5 days, P = 0.012).
vs 90.0 days, \( P = 0.0073 \). Fig. 2 shows the correlation of different clinical outcomes with the duration of antibiotic use. Furthermore, the duration of antibiotic use did not correlate with diagnostic delay (\( R^2 = 0.04166, P = 0.2005 \)), whereas diagnostic delay was strongly associated with therapeutic delay (\( R^2 = 0.9626, P < 0.0001 \)). Fig. 3 shows the correlation between diagnostic delay with antibiotic use and therapeutic delay. Regarding antibiotic therapy, one patient received a wait-and-see approach due to lack of complaints. Three patients were lost to follow-up due to transfer to another hospital. In 39% of patients who used antibiotics, treatment was stopped because of complete clinical recovery. Furthermore, in 18% of patients the decision to cease treatment was purely based upon decreased metabolic activity on PET scan. The combination of clinical and radiological findings was the reason for discontinuing treatment in another 26% of patients. Other noted reasons for discontinuing treatment (17%) were an allergic reaction, palliative care and patient mortality.

### Table 2

Microbiological characteristics of this cohort.

| Parameter                  | Entire cohort (n = 41) | Group A (n = 27) | Group B (n = 14) |
|----------------------------|-----------------------|-----------------|-----------------|
| Cultured species           |                       |                 |                 |
| * Candida species*         | 11 (26.8)             | 5 (18.5)        | 6 (42.9)        |
| * Staphylococcus aureus*   | 8 (19.5)              | 5 (18.5)        | 3 (21.4)        |
| * Pseudomonas aeruginosa*  | 24 (58.5)             | 15 (55.6)       | 9 (64.3)        |
| * Streptococcus viridans*  | 1 (2.4)               | 0 (0)           | 1 (7.1)         |
| * Aspergillus species*     | 1 (2.4)               | 1 (3.7)         | 0 (0)           |
| * Proteus mirabilis*       | 1 (2.4)               | 1 (3.7)         | 0 (0)           |
| * Citrobacter koseri*      | 1 (2.4)               | 1 (3.7)         | 0 (0)           |
| * No growth*               | 6 (14.6)              | 4 (14.6)        | 2 (14.3)        |
| * Commensal bacteria*      | 4 (9.8)               | 3 (9.8)         | 1 (7.1)         |
| Prescribed antibiotics (n, %) |                     |                 |                 |
| * Amoxicillin*             | 15 (36.6)             | 10 (37.0)       | 5 (35.7)        |
| * Azithromycin*            | 1 (2.4)               | 1 (3.7)         | 0 (0)           |
| * Ceftazidime*             | 3 (7.3)               | 1 (3.7)         | 2 (14.3)        |
| * Ciprofloxacin*           | 25 (61.0)             | 16 (59.3)       | 9 (64.3)        |
| * Clarithromycin*          | 0 (0)                 | 0 (0)           | 0 (0)           |
| * Clindamycin*             | 5 (12.2)              | 3 (11.1)        | 2 (14.3)        |
| * Cotrimoxazole*           | 3 (7.3)               | 2 (7.4)         | 1 (7.1)         |
| * Fluoxacin*               | 5 (12.2)              | 3 (11.1)        | 2 (14.3)        |
| * Fluconazole*             | 2 (4.9)               | 1 (3.7)         | 1 (7.1)         |
| * Gentamycin*              | 4 (9.8)               | 2 (7.4)         | 2 (14.3)        |
| * Meropenem*               | 5 (12.2)              | 3 (11.1)        | 2 (14.3)        |
| * Piperacillin/tazobactam* | 36 (87.8)             | 22 (81.5)       | 14 (100)        |
| * Vancomycin*              | 2 (4.9)               | 1 (3.7)         | 1 (7.1)         |
| Median duration of antibiotic use in days (SD) | 93 (39–192) | 92 (37–112.5) | 217 (90–247.0) |

### Table 3

Clinical outcomes during follow-up. Statistical analysis was performed between group A (simple spread pattern) and B (complex spread pattern).

| Parameter                  | Entire cohort (n = 41) | Group A (n = 27) | Group B (n = 14) | P-value  |
|----------------------------|-----------------------|-----------------|-----------------|----------|
| Median duration of complaints before presentation to ENT in weeks (IQR) | 8.0 (4.0–12.0) | 6.0 (3.0–12.0) | 10.0 (6.0–12.0) | 0.292*   |
| Median diagnostic delay in days (IQR) | 40.0 (29.5–85.5) | 42.5 (31.0–81.0) | 37.5 (25.0–90.0) | 0.839*   |
| Median therapeutic delay in days (IQR) | 42.5 (28.0–85.0) | 37.0 (23.0–66.0) | 37.5 (25.0–90.0) | 0.961*   |
| Mortality (n, %)            |                       |                 |                 |          |
| * Disease-related*          | 5 (12.2)              | 3 (11.1)        | 2 (14.3)        | 0.401*   |
| * Non-disease-related*      | 9 (22.0)              | 7 (25.9)        | 2 (14.3)        |          |
| * Alive*                   | 26 (63.4)             | 16 (59.3)       | 10 (71.4)       |          |
| Recovery (Mardinger et al., 2003), yes (n, %) | 26 (63.4) | 15 (55.6) | 11 (78.6) | 0.147* |
| Recurrence, yes (n, %)     | 3 (7.3)               | 1 (3.7)         | 2 (14.3)        | 0.253*   |
| Complications, yes (n, %)  | 15 (36.6)             | 6 (22.2)        | 9 (64.3)        | 0.008*   |
| Hospitalization, yes (n, %) | 10 (24.4) | 5 (18.5) | 5 (35.7) | 0.251* |
| Disease-related surgery, yes (n, %) | 13 (31.7) | 5 (18.5) | 8 (57.1) | 0.012* |
| Cranial nerve palsy (n, %) |                       |                 |                 |          |
| * VI                       | 1 (2.2)               | 1 (3.7)         | 0 (0)           | 1.000    |
| * VII                      | 10 (22.2)             | 4 (14.8)        | 6 (42.9)        | 0.047*   |
| * IX                       | 5 (11.1)              | 1 (3.7)         | 4 (28.6)        | 0.039*   |
| * X                        | 4 (8.9)               | 1 (3.7)         | 3 (21.4)        | 0.107*   |
| * XII                      | 3 (6.7)               | 1 (3.7)         | 2 (14.3)        | 0.265*   |
| Recovery cranial nerve palsy (n, %) | 3 (27.3) | 1 (33.3%) | 2 (25) | 0.516* |
| * Yes                      | 1 (9.1)               | 0 (0)           | 1 (12.5)        |          |
| Partial                    | 0 (0)                 | 2 (66.7%)       | 4 (30)          |          |
| No                         | 1 (9.1)               | 0 (0)           | 1 (12.5)        |          |
| Median duration of follow-up (months, IQR) | 12.0 (6.0–19.5) | 8.5 (6.0–15.0) | 15.5 (11.0–26.0) | 0.102* |

4 Based on physician global assessment.

* Mann-Whitney U test.

** ANOVA.

* Chi-square test (two-tailed).

* Fischer-exact test (two-tailed).
3.3. Mortality, complications and facial nerve palsy associated with diagnostic delay

The median duration of complaints before presentation to an otolaryngologist was 8.0 (IQR 4.0–12.0) weeks in the entire cohort, no significant differences were found between group A and B (6.0 weeks vs 10.0 weeks, P = 0.292). Furthermore, the median diagnostic delay (first complaints until NEO diagnosis) was 40.0 (IQR 29.5–85.5) days, while the therapeutic delay (first complaints to appropriate antibiotic treatment) was 42.5 (IQR 28.0–85.0). There were no differences in diagnostic and therapeutic delay between group A and B. The majority of patients received antibiotic treatment within 3 days after NEO diagnosis. The median diagnostic delay was significantly associated with mortality (P = 0.0455), complications (60.0 days vs 34.5 days, P = 0.0449) and facial nerve palsy (79.5 days vs 35.0 days, P = 0.0143). Fig. 4 shows the correlation of various clinical outcomes with diagnostic delay.

4. Discussion

This retrospective chart review study investigated the relationship between clinical outcomes and the infectious spreading pattern of NEO. This study demonstrates that the most common spreading pattern is the singular spreading route. Furthermore, it was shown that complex spreading routes were associated with cranial nerve palsies (N. VII and N. IX), surgical interventions, and
longer duration of antibiotic use. Longer duration of antibiotic use was associated with higher rates of clinical recovery and hospitalization. Also, diagnostic delay was found to be associated with higher rates of disease-related mortality, complications, and facial nerve palsies. The most commonly stated claims about NEO were also observed in our study: it mostly affects the elderly patients with diabetes mellitus. It is a fragile population with a high rate of mortality during the disease course, whether or not disease-related. Our patient group mostly presented with complaints of otalgia, hearing loss and otorrhea. This finding is in line with the results of other studies (Glikson et al., 2017; Mardinger et al., 2003). Cranial nerve palsies are relatively common in NEO as 22.2% of patients in our study were affected, a finding corresponding to other studies (Mani et al., 2007; Stern Shavit et al., 2016; Marina et al., 2019; Franco-Vidal et al., 2007; Lee et al., 2008). Disease specific mortality rate has formerly been described as 14% (Stern Shavit et al., 2016). This study found a disease specific mortality of 11.1%, which was not significantly different between spreading pattern groups.

4.1. Relation of symptoms to spreading routes

The clinical manifestations of NEO as reported by the patients were found to correlate with infectious spreading patterns, as the single anterior spreading route was associated with a painful temporomandibular joint region. On the other hand, vertigo (vestibulocochlear dysfunction) significantly occurred more often in the complex spreading route compared to the single anterior spreading route. This implies that cranial nerve or inner ear damage occurs more often in complex spreading patterns. On top of that, patients with a complex spreading route were treated longer than patients with a single spreading route. These findings can guide the otorhinolaryngologist during history taking and may already point to a specific spreading pattern, thus managing patient expectations about disease course and associated treatment duration. Our study found an association between a more extensive NEO spreading route (group B) and an increased incidence of facial palsy (42.9%), as compared to a pure anterior spreading route (group A; 14.8%). This difference between group B and A was also found for the glossopharyngeal nerve (28.6% vs 3.7%, P = 0.039).

4.2. Diagnostic delay

Most patients were first seen by their general practitioner (GP), who treated them with oral antibiotics (mostly amoxicillin) before referring them to a hospital. In this stage, the distinction between a regular external otitis and necrotizing external otitis is difficult to make. The median time between first presentation at the GP and diagnosis of NEO by CT at the hospital is 8.0 weeks. This duration of delay is a gross estimation, because data from the first visit to the GP is not always accurately documented. However, this clearly illustrates the difficulty of distinguishing between an otitis externa and NEO, and this reveals a significant challenge of the disease. In addition, a long treatment duration for otitis externa should always alert the clinician to consider NEO. When the diagnosis is made, appropriate treatment should be started quickly. Finally, we would like to point out our diagnostic and treatment algorithm with suggestions for clinicians with the following flow chart (see supplement 1). In this study, diagnostic delay was associated with a higher rate of mortality, complications, and facial palsies. This suggests that patient or doctor’s delay might affect clinical outcome, as complications (most common was facial palsy) might likely be caused by prolonged exposure to an inflammatory process. Therefore, reducing treatment delays should be necessary to prevent mortality and clinical complications of NEO.

4.3. Antibiotic exposure: importance of tissue penetration

In this study, the majority of patients were using antibiotics for three months or longer, the rationale behind this is to treat the
causative micro-organism. While, the inflammatory process could be caused by different pathogens, the most common cultured micro-organism in this study was *Pseudomonas aeruginosa*, and the most frequently used antibiotic was piperacillin–tazobactam. This antibiotic is known for its bone penetration, achieving bone concentrations up to 40.0 μg/g in literature (Al-Nawas et al., 2008; Incavo et al., 1994), which should be sufficient to achieve the minimal inhibitory concentration of *Pseudomonas aeruginosa* (Thabit et al., 2019). However, there is more need for research in tissue penetration of antibiotics in the skull base, which unfortunately is limited by a few factors (Mouton et al., 2008; Jager et al., 2019). The median duration of antibiotic use was significantly higher for patients that had clinical recovery, which indicates the necessity for prolonged antibiotic exposure as it seems that more patients recovered. However, it must also be noted that a portion of patients in the non-recovery group had a short duration of follow-up, and were still receiving antibiotics. Furthermore, the median duration of antibiotic use was also higher for patients that had a complex spread pattern and for hospitalized patients. Hence, patients who are severely affected by NEO seem to have higher antibiotic exposure, and may therefore be in need for more aggressive and prolonged treatment.

4.4. Strengths and limitations

The strength of this study is that it correlated systematically determined radiological spread patterns with clinical outcomes. Furthermore, a wide-range of antibiotic data was available, allowing this study to make estimates of the duration of antibiotic use. Hence, the median duration of antibiotic use could therefore be related with clinical outcomes. The available data allowed this study to investigate relevant clinical factors that may assist in determining patients’ outcomes. However, the present study is limited due to its retrospective design, its small sample size and single-center experience. The sample size for this rare disease does not significantly differ from most studies (Mardinger et al., 2003; Franco-Vidal et al., 2007). The patients’ records were reviewed for the presence or absence of symptoms and complications. However, if certain symptoms were not mentioned in the patients’ clinical records, they were noted as absent thus possibly causing an underestimation of symptom prevalence. Furthermore, there was also a relatively high extent of missing data, especially regarding clinical symptomology. In addition, the recovery of the cranial nerve palsies was based on medical records, of which it was not always clear to what extend the palsy had recovered. Furthermore, the definition of clinical recovery was also based on the physician’s medical records. Therefore, there was no standardized definition for clinical recovery in this study, which is susceptible to bias.

5. Conclusion

NEO is a severe disease, with significant mortality and morbidity (cranial nerve palsies). The radiological spread pattern may assist in predicting clinical outcome. Furthermore, complex spread patterns are associated with higher rates of clinical nerve palsies (N VII and N IX), complications, surgery rates, and longer duration of antibiotic use. Diagnostic delay was associated with mortality, complications and facial palsies. A long treatment duration for otitis externa should always alert the clinician to be aware of necrotizing otitis externa.

Funding source

There was no funding received for this work from any of the following organizations: National Institutes of Health (NIH), Wellcome Trust, Howard Hughes Medical Institute (HHMI), and others.

Declaration of competing interest

The authors declare no conflict of interests.

Acknowledgment

There are no sources of support that require acknowledgment.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.joto.2022.05.002.

References

Adams, A., Offiah, C., 2012. Central skull base osteomyelitis as a complication of necrotizing otitis externa: imaging findings, complications, and challenges of diagnosis. Clin. Radiol. 67 (10), e7–e16.

Al-Nawas, B., Kinzig-Schippers, M., Soergel, F., Shah, P.M., 2008. Concentrations of piperacillin–tazobactam in human jaw and hip bone. J. Cranio-Maxillofacial Surg. 36 (8), 468–472.

Arya, S., Rame, P., D’Cruz, A., Hathiram, B.T., Khatarr, V.S., 2012. Infratemporal Fossa, masticator space and parapharyngeal space: can the radiologist and surgeon speak the same language? Otorhinolaryngol. Clin. Int. J. 4, 125–135.

Carfae, M.J., Kesset, B.W., 2008. Malignant otitis externa. Otolaryngol. Clin. 41 (3), 537–549 viii-ix.

De Ru, J., Aarts, M., van Benthem, P.P., 2010. Malignant external otitis; changing Faces. J. Int. Adv. Otol. 6, 274–276.

Franco-Vidal, V., Blanchet, H., Bebear, C., Dutronc, H., Darrouzet, V., 2007. Necrotizing external otitis: a report of 46 cases. Otol. Neurotol. 28 (6), 771–773.

Clikson, E., Sagiv, D., Wolf, M., Shapiro, Y., 2017. Necrotizing otitis externa: diagnosis, treatment, and outcome in a case series. Diagn. Microbiol. Infect. Dis. 87 (1), 94–78.

Handzel, O., Halperin, D., 2003. Necrotizing (malignant) external otitis. Am. Fam. Physician 68 (2), 309–312.

Incavo, S.J., Ronchetti, P.J., Choi, J.H., Wu, H., Kinzig, M., Sörgel, F., 1994. Penetration of piperacillin–tazobactam into cancellous and cortical bone tissues. Antibiot. Agents Chemother. 38 (4), 905–907.

Jager, N.G.L., van Hest, R.M., Lipman, J., Roberts, J.A., Cotta, M.O., 2019. Antibiotic exposure at the site of infection: principles and assessment of tissue penetration. Expert Rev. Clin. Pharmacol. 12 (7), 623–634.

Kwon, B.J., Han, M.H., Oh, S.H., Song, J.J., Chang, K.H., 2006. MRI findings and spreading patterns of necrotizing external otitis: is a poor outcome predictable? Clin. Radiol. 61 (6), 495–504.

Lee, S., Hooper, R., Fuller, A., Turfaikow, A., Cousins, V., Nouara, R., 2008. Otopneic cranial base osteomyelitis: a proposed prognosis-based system for disease classification. Otol. Neurotol. 29 (5), 666–672.

Lee, J.-E., Song, J.-J., Oh, S.-H., Chang, S.O., Kim, C.-H., Lee, J.H., 2011. Prognostic value of extension patterns on follow-up magnetic resonance imaging in patients with necrotizing otitis externa. Arch. Otolaryngol. Head Neck Surg. 137 (7), 688–693.

Mani, N., Sudhoff, H., Rajagopali, S., Moffat, D., Alon, P.R., 2007. Cranial nerve involvement in malignant external otitis: implications for clinical outcome. Laryngoscope 117 (5), 907–910.

Mardinger, O., Rosen, D., Minkow, B., Tulzinsky, Z., Ophir, D., Hirshberg, A., 2003. Temporomandibular joint involvement in malignant external otitis. Oral Surg. Oral Med. Oral Pathol. Oral Radiol. Endod. 96 (4), 389–403.

Marina, S., Goutham, M.K., Rajeshwary, A., Vadhida, B., Devika, T., 2019. A retrospective review of 14 cases of malignant otitis externa. J. Otolaryngol. 45 (2), 63–66.

Morris, K., 2013. Revising the declaration of Helsinki. Lancet 381 (9881), 1889–1890.

Mouton, J.W., Theuretzbacher, U., Craig, W.A., Tulkens, P.M., Derendoff, H., Cars, O., 2008. Tissue concentrations: do we ever learn? J. Antimicrob. Chemother. 61 (2), 235–237.

Rubin, J., Yu, V.L., 1988. Malignant external otitis: insights into pathogenesis, clinical manifestations, diagnosis, and therapy. Am. J. Med. 85 (3), 391–398.

Rubin Grandis, J., BFt, Branstetter, Yu, V.L., 2004. The changing face of malignant external otitis. J. Oral Maxillofac. Surg. 62 (8), 472.

Stern Shavit, S., Soudry, E., Hamzany, Y., Nageris, B., 2016. Malignant external otitis: a report of 46 cases. Otol. Neurotol. 28 (6), 771

References
van der Meer, W.L., van Tilburg, M., Mitea, C., Postma, A.A., 2019. A persistent foramen of Huschke: a small road to Misery in necrotizing external otitis. AJNR Am. J. Neuroradiol. 40 (9), 1552–1556.

van der Meer, W.L., Waterval, J.J., Kunst, H.P.M., Mitea, C., Pegge, S.A.H., Postma, A.A., 2022 Mar. Diagnosing necrotizing external otitis on CT and MRI: assessment of pattern of extension. Eur Arch Otorhinolaryngol. 279 (3), 1323–1328. https://doi.org/10.1007/s00405-021-0809-2. Epub 2021 Apr 25. PMID: 33895803; PMCID: PMC8897339.

van Kroonenburgh, A., van der Meer, W.L., Bothof, R.J.P., van Tilburg, M., van Tongeren, J., Postma, A.A., 2018. Advanced imaging techniques in skull base osteomyelitis due to malignant otitis externa. Curr. Radiol. Rep. 6 (1), 3.

von Elm, E., Altman, D.G., Egger, M., Pocock, S.J., Gotzsche, P.C., Vandenbroucke, J.P., 2008. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. J. Clin. Epidemiol. 61 (4), 344–349.