UK consensus definitions for Necrotising Otitis Externa in adults

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ABSTRACT

Background: Necrotising otitis externa (NOE) is an under-recognised, poorly understood, severe infection of the external ear canal and lateral skull base. No established national or international guidelines exist for NOE and the optimal strategy for diagnosis and management remains uncertain. There is no widely accepted case definition for NOE and none have been developed via consensus of multidisciplinary experts. We aimed to established consensus definitions for NOE to facilitate the diagnosis and exclusion of NOE in clinical practice and expedite future high-quality study of the condition.

Methods: The work comprised of a systematic review of the literature, five iterative rounds of consultation via a Delphi process and open discussion within the collaborative. An expert panel analysed the results to produce the final outputs.

Results: Eighty UK clinicians specialising in ENT, Infection and Radiology with a special interest in NOE took part in the work which was undertaken between 2019 and 2021. The minimum response rate for a Round was 76%. Consensus criteria for all proposed case definitions, outcome definitions and consensus statements were met in the fifth round and shared with leading UK specialist bodies for review.

Conclusions: This work distils the clinical opinion of a large group of multidisciplinary specialists from across the UK to create practical definitions and statements to support clinical practice and research for NOE. This is the first step in an iterative process. Further work will seek to validate and test these definitions and inform their evolution.

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INTRODUCTION

Necrotising otitis externa (NOE) is an under-recognised, poorly understood, severe infection of the external auditory canal (EAC) and lateral skull base[1]. If detected late, this condition has a poor outcome with spread of infection to involve the cranial nerves, the base of skull and the central nervous system[2]. Patients affected by NOE are generally frail and elderly with multiple co-morbidities[3,4]. It presents a challenge to Ear, Nose and Throat (ENT) in-patient surgical units, which are generally ill equipped to manage complex, long-stay and commonly frail medical patients. The disease is associated with high mortality; one case-series reported overall survival of 38% at 5 years with disease-specific mortality of 14%[5]. Early diagnosis and treatment may reduce the need for long-term antibiotic therapy and will reduce the risk of serious complications.

No established national or international guidelines exist for the diagnosis and management of NOE[6]. Most published series are limited and of poor quality. Not surprisingly, the optimal strategy for diagnosis and management of NOE remains uncertain[3,4] and there is considerable variability in how this condition is managed[7].

Cohen and Friedman's definition of NOE from 1987 is often cited[8] and modified versions are used in some studies[3]. However, publications often fail to explicitly state their criteria for defining a case of NOE, and for those that do, there is considerable variation in the definitions applied[3]. To date there is no widely accepted case definition for NOE and none have been developed via consensus of multidisciplinary experts. The lack of an accepted definition has impeded progress in developing diagnostic and treatment algorithms.

Why is a consensus definition for NOE needed?

A diagnostic definition has two distinct uses. Firstly and most importantly it provides the non-expert clinician with a clear set of criteria to facilitate diagnosis or exclusion of NOE. Under recognition of NOE results in a delay in diagnosis increasing the risk of serious complications

and poorer outcomes in an already frail population. Conversely, given that NOE is typically treated with prolonged courses of broad-spectrum antimicrobials, unnecessary treatment of individuals without NOE with such regimens exposes frail patients to the serious risks associated with these agents[9] as well as contributing more broadly to antimicrobial resistance[10-12]. Accurate diagnostic processes for NOE are therefore important to optimise outcomes for patients with and without NOE. However, to date, no test with sufficient sensitivity and specificity to definitively diagnose or exclude NOE exists, and a poor evidence base is of little help to inform nuanced clinical decision making[3,4].

Secondly, a major limitation of the published literature on NOE is the lack of a consensus definition for NOE. As a result, publications likely reflect heterogenous populations and robust comparison across datasets is impossible. A consensus definition is needed to facilitate future high-quality study of the condition. For example, studies of new treatment regimens must include a robust case definition so findings can be critically appraised and applied to other patient cohorts.

What are the aims of the definitions/statements?

To be widely used and applied, consensus definitions and statements must be robust but also practical. For example, given that many sites in the UK do not have access to urgent magnetic resonance imaging (MRI), inclusion of this as the sole modality in a diagnostic case definition would be problematic. At the start of the project, the following aims for consensus definitions/statements were therefore defined:

1. They should be implementable in all centres across the UK, from a small district general hospital to tertiary referral centres.
2. They should be highly specific (i.e. describe a typical definite case of NOE and minimise the chances of misclassifying another condition), but not necessarily describe all potential presentations of NOE.
3. They are for guidance only and not prescriptive in terms of practice.
4. They should allow standardised description of cases to facilitate recruitment to clinical trials and comparison of cases across different cohorts.

5. They mark the start of an iterative process – as more, and better quality evidence becomes available these definitions/statements will be revisited and revised.

METHODS

This project comprised of a systematic review of the literature, five iterative rounds of consultation via a Delphi process as well as open discussion within the collaborative. An expert panel analysed the results to produce the final guidance (Figure 1).

(i) Systematic Review

A systematic review of the literature for NOE was performed and reported according to PRIMSA guidelines[13] (*Takata et al, manuscript in preparation).* This revealed 422 publications, representing 16,528 patients. Sixty four percent of these publications were excluded from further analysis as they either included less than six patients and/or did not explicitly state the case definition applied. In the studies that did describe a case definition, the criterion used varied widely. No studies specifically addressing case definition were identified. The detailed results of this review will be published as a separate manuscript.

(ii) Delphi method

A Delphi method was used to reach consensus definitions for NOE, outcome definitions and key consensus statements. The Delphi method is a structured, flexible process of obtaining information from a group of experts by means of a series of questionnaires, each one refined based on feedback from respondents on a previous version[14]. This iterative, multistage process is designed to transform opinion into group consensus, and is characterised by the following features: anonymity, allowing opinions to be expressed free from group pressure, iteration with controlled feedback from one round to the next, aggregation of group responses and expert input until consensus has been achieved[15-17]. The method is ideally suited to amalgamate the opinions of a broad range of stakeholders, which was important given the lack of high-quality published evidence for NOE and the likely heterogenicity in practice across the UK[7].

(iii) Participants

A core group of ENT, Infection and Radiology consultant specialists set-up the UK NOE collaborative (MIA, ES, PP). This group, in consultation with national speciality organisations including the British Infection Association (BIA), the British Society for Otology (BSO) and ENT UK identified individuals with an interest in NOE, who were then invited to participate in the Delphi process by email. The same corresponding email address was used by the collaborative throughout the process and only one email address was used for each participant to ensure only one response was logged for each participant at each round. The core group with other experts (PMD, MMcN, MW) facilitated the Delphi process and analysed the data[17].

(iv) Definitions

After a literature review, the core group proposed definitions for definite, possible and complex NOE as well as definitions for outcomes including cure, non-response to treatment and relapse. They also proposed key consensus statements. These definitions and statements were shared with participants in a survey via email. Participants were asked to rate the extent to which they agreed with each definition/statement (strongly agree, agree, disagree, and strongly disagree) on a Likert scale. The survey included the opportunity for individuals to comment after each definition/statement and at the end of the survey. Participants were encouraged to feed back on their reasons for disagreement or agreement with the proposed definitions/statements.

Following each round, results were shared with participants with explanations for proposed revisions to the definitions/statements from the expert group. The Delphi process comprised of five rounds, all of which were conducted by electronic survey apart from Round 3, which took the form of an in-person meeting.

(v) Predefined consensus criteria

The following criteria were agreed for adoption of definitions/statements[18]:

- Minimum of 70% of respondents in agreement or strong agreement with a definition/statement AND
- <15% of respondents in disagreement or strong disagreement with a definition/statement.

Definitions/statements that met these criteria were accepted. Definitions that did not meet these criteria at each round were modified according to feedback and included in subsequent rounds. The Delphi process continued until consensus criteria were met for all definitions/statements.

(vi) Wider stakeholder review

The consensus case definitions/statements were shared with the British Infection Association, British Society for Neuroradiology, ENT UK and British Society Otology.

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RESULTS

Email invitations explaining the objectives of the project and including the initial survey for Round 1 were sent to ninety-three identified specialists in the UK, of whom seventy-four responded (80%) (Figure 2). Individuals who engaged with Round 1 were invited to participate in Round 2. Three individuals who had not participated in Rounds 1 and 2 attended and participated in the meeting for Round 3. Participants who had engaged in any of Rounds 1, 2 or 3 were invited to participate in Rounds 4 and 5 in addition to three individuals who has not been involved in the process prior to Round 4. The process took more than two years to complete, and some individuals were no longer contactable by initial email, meaning the number of possible respondents decreased for Round 5. The minimum response rate for a Round was 76%. The survey questions for each Round can be viewed in Supplementary Information as well as facilitator communiques with the collaborative. Consensus criteria for all case definitions, outcome definitions and consensus statements were met in Round 5. These are summarised in Tables 1, 2, 3 and 4.

DISCUSSION

This is the first published study which has sought to standardise diagnostic and outcome criteria for NOE, following consultation with experts working in the field from three specialities: ENT, Radiology and Infection. Consensus definitions/statements were obtained for all of the identified areas set out by the expert group at the start of the project.

The Delphi process is an ideal method for the development of diagnostic criteria in the absence of an available gold standard test or a robust evidence base[17], and has been used widely for this purpose[15,19-22]. This method reduces bias, enhances transparency and allows the involvement of individuals from diverse clinical backgrounds and dispersed geographical locations. It also helps ensure that a single influential participant does not have a disproportionate influence on the process. One potential disadvantage of this method is the possible lack of individual responsibility and accountability, however in our work this was addressed in part by in-person discussions and encouragement of feedback from individuals at each round.

A major barrier to the agreement of these definitions/statements was the ongoing SARSCoV2 Coronavirus Disease (COVID-19) pandemic at the time the Delphi process was being conducted. This was a challenging time for all clinicians, especially Infection specialists, and as a result there were delays in engaging some key stakeholders. Similarly, due to widespread physical distancing we were unable to convene a planned in-person meeting to discuss the final results. However, the consistent response rate of ≥76% for all rounds in our study is noteworthy and should afford confidence in the final definitions/statements whilst acting as testament to the commitment of UK specialists to improve outcomes for this neglected condition. For context, response rates to Delphi surveys are usually low; one review reported that a response rate of 35–40% is typical during a first round consultation with 15-18 participants and that surveys with larger pools of participants tend to have lower response rates[23].

Discussion at the in-person meeting confirmed it was not clinically appropriate to have a binary case definition for NOE given that currently available investigations cannot reliably distinguish patients with NOE from those without. For this reason, a decision was made to include a case definition for 'possible' NOE in the study outputs, to describe those patients without definitive evidence of NOE but for whom clinical suspicion is still high. This approach has been applied successfully in other infective conditions involving bone[24,25]. Infection of the EAC is likely a continuum, with otitis externa and NOE extremes of the same disease process. Further work is needed to understand 'possible' NOE, the investigations that reliably distinguish these cases from definite NOE and the variables that determine the outcome of such cases.

The final consensus definitions for NOE adopted by the group include symptoms, signs and radiological changes as obligatory criteria. Specific radiological abnormalities are a relatively objective measure which can be standardised across sites and assessed in future work. Whilst the ideal modality to diagnose NOE is debated[2,26,27], we chose to only include radiological changes on computer tomography (CT) and MRI, given these modalities are most widely available in the UK.

Otalgia and the presence of granulation tissue or inflammation in the EAC were considered essential for diagnosis of a definite case in our definition. In contrast, only 78% and 76% of studies respectively were found to consider these features obligatory criteria in our systematic review (*Takata et al, manuscript in preparation*). It is possible that our definition may be less sensitive and will wrongly exclude 'true' cases of NOE, without visible EAC changes. However, our definition is a starting point, which will evolve as data from a planned UK, multicentre observational study of NOE (Improving outcomes in NOE (IONOE)) and other studies emerge.

The role of the multidisciplinary team (MDT) working in the improvement of patient outcomes is well known[28-30]. In the management of complex orthopaedic infections, time to diagnosis and clinical outcomes have both been shown to improve when MDTs function well[31,32]. The benefits of an MDT approach are multifactorial; patients benefit from care that is co-ordinated,

individualised and delivered by experts; clinicians benefit by having increased exposure to a larger number of cases which improves expertise; and the Unit benefits as the improvements in outcomes build morale. There are sparse data addressing the benefit of MDT working on outcomes for NOE. However, a UK study by Sharma *et al.,* has shown that an MDT approach resulted in a shorter duration of therapy and lower mean hospital length of stay for NOE patients[33]. In our study there was strong support for an MDT model to manage NOE, but concern that this would not be realistically achievable in the absence of dedicated local funding.

The term 'malignant otitis externa' (MOE) was first coined by Chandler in 1968 when reporting the first case series of severe temporal bone osteomyelitis, originating from the EAC, associated with *Pseudomonas aeruginosa* infection[34]. Later the term 'NOE' was introduced[35]. The terms MOE and NOE have since been used interchangeably to describe the condition. Whilst the terms 'necrotising' and 'malignant' convey the aggressive and serious nature of the condition, they are both recognised to be misnomers in that they do not describe the pathophysiology of the condition. It was proposed and accepted that since malignancy is an important differential for this condition, it was preferable to use the term 'NOE.'

Conclusion

This work distils the clinical opinion of a large group of multidisciplinary specialists from across the UK to create practical definitions and statements to support clinical practice and research for NOE. This is the first step in an iterative process. Further work will seek to validate and test these definitions and inform their evolution.

Figure 1. Overview of process to develop consensus case definitions and statements for NOE

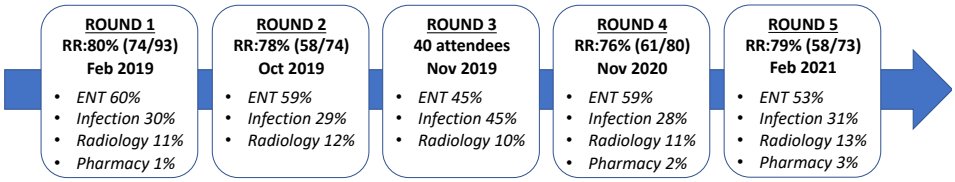

Figure 2. Rounds in Delphi process showing response rate (RR) for each Round and speciality involvement

DEFINITIONS of NOE
DEFINITE NOE **NOE is definitely present if <u>ALL</u> of the following are present:** • Otalgia and otorrhoea OR otalgia and a history of otorrhoea • Granulation OR inflammation of the external auditory canal • Histological exclusion of malignancy in cases where this is suspected • Radiological features consistent with NOE: (i) CT imaging findings of bony erosion of the external auditory canal, together with soft tissue inflammation of the external auditory canal **OR** (ii) MRI with changes consistent with NOE (for example bone marrow oedema of the temporal bone with soft tissue inflammation of the external auditory canal)
POSSIBLE NOE **A severe infection of the external ear canal which <u>does not</u> show bony erosion of the external auditory canal on CT scan OR <u>does not</u> show changes consistent with NOE on MRI if this is performed (for example bone marrow oedema of the temporal bone) AND which has <u>ALL</u> of the following characteristics:** • Otalgia and otorrhoea OR otalgia and a history of otorrhoea AND • Granulation OR inflammation of the external auditory canal AND • Any of the following features (i) Immunodeficiency (ii) Night pain (iii) Raised inflammatory markers (ESR/CRP) in absence of other plausible cause (iv) Failure to respond to >2 weeks of topical anti-infectives and aural care

Table 1: Consensus definitions for NOE. *CRP = C reactive protein; ESR = erythrocyte sedimentation rate.*

COMPLEX NOE
Patients meeting the criteria for 'definite' NOE* may be classified as 'complex' (or severe) IF ANY of the following are present: • Facial nerve or other lower cranial nerve palsy • Cerebral venous thrombosis seen on MRI or contrast enhanced CT • Extensive bone involvement as demonstrated by any of the following; (i) CT showing bone erosion in other skull base locations in addition to the external ear canal wall (for example around stylomastoid foramen, clivus, petrous apex, temporomandibular joint) (ii) MRI showing bone marrow oedema extending to central skull-base (iii) CT or MRI showing extensive soft tissue oedema or inflammation or fluid collection below the skull base (iv) Intracranial spread of the disease (for example dural thickening, extradural or subdural empyema, cerebral/cerebellar abscess) *Patients may present with complex NOE after local signs and symptoms have resolved

Table 2: Definition of complex disease.

OUTCOME DEFINITIONS
CURE A case of NOE is considered treated and cured if a patient has no pain or otorrhoea for a minimum period of 3 months after completing antibiotic therapy.
RELAPSE OF DISEASE Relapse is recurrence of disease after the patient has been treated and cured i.e. at least three months after stopping antibiotic therapy. A relapsed case of NOE is a serious, invasive infection which occurs **after the initial infection was considered to be treated and cured** and is characterised by: ***Recurrence of local disease*** - Recurrent otalgia OR recurrent otorrhoea AND - Recurrent granulation OR inflammation AND - Unchanged or progression of bony erosion of the external auditory canal on CT OR unchanged or progression of MRI changes such as bone marrow oedema of the temporal bone and soft tissue changes of the external auditory canal **AND/OR** ***Development or recurrence of complex disease*** - Development or worsening of a lower cranial nerve palsy, base of skull osteomyelitis or development or worsening of other intracranial complication deemed a consequence of NOE and supported by radiological imaging
NON RESPONSE TO THERAPY A case of NOE is defined as non-responsive to therapy if there is no improvement in otalgia or otorrhoea or inflammation or granulation tissue in the EAC after 14 days of optimum analgesia, anti-infective therapy, aural care and optimisation of immune state.

Table 3: Consensus definitions for treatment outcomes

CONSENSUS STATEMENTS
FIRST LINE IMAGING CT Scan is the initial imaging modality of choice for a suspected case of NOE
MULTIDISCIPLINARY APPROACH Once a diagnosis of definite NOE has been made, specialist review as part of a multidisciplinary team approach should be arranged
NOMENCLATURE 'Necrotising Otitis Externa' is the preferred name for this condition over 'Malignant Otitis Externa'

Table 4: Consensus statements

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