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Necrotising Otitis Externa: Multidisciplinary consensus definitions

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Necrotising Otitis Externa: multidisciplinary consensus definitions

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Keywords: Necrotising, malignant, otitis externa, Pseudomonas, antimicrobial

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ABSTRACT

Objective: To establish consensus definitions for NOE to facilitate the diagnosis and exclusion of NOE in clinical practice and expedite future high-quality study of this neglected condition.

Design: 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 which were shared with and endorsed by national speciality bodies.

Setting: Secondary care in the United Kingdom (UK).

Participants: UK clinical specialists practising in Infection, Ear Nose and Throat Surgery or Radiology.

Main Outcome Measures: Definitions and statements meeting the following criteria were accepted: (a) Minimum of 70% of respondents in agreement or strong agreement with a definition/statement AND (b) <15% of respondents in disagreement or strong disagreement with a definition/statement.

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.

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

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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.

Strengths and Limitations

- First consensus definitions for NOE from a large number of experts working in the three different specialist areas (ENT, radiology, infection) involved in the management of this condition
- These definitions are both pragmatic and useful clinically, but also stringent enough to support further research
- Limitation is that these definitions are based on expert opinion. This work will provide the basis for data generation to support an evidence based approach to definition development in the future.

Key words: Necrotising, malignant, otitis, externa, Pseudomonas, antimicrobial

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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

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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.

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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).

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(i) Systematic Review

A systematic review of the literature for NOE was performed and reported according to PRIMSA guidelines[13] (*Takata et al, submitted).* 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].

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(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), ENT UK and the British Society for Otology (BSO) 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.

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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 BIA, ENT UK, BSO and the British Society of Neuroradiologists (BSNR).

(vii) Ethical Approval

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The approval of an ethics committee(s) or Institutional Review Board was not required as this Delphi study does not involve human subjects research. No patient data were collected for this study, which was completely based on the feedback provided by experts regarding NOE.

(viii) Patient and Public Involvement

There was no patient or public involvement in this study.

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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 as well as facilitator communiques with the collaborative can be accessed in Figshare. 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. The final consensus definitions and statements were endorsed by the BIA, ENT UK, BSO and BSNR.

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

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UK Definitions for NOE

DEFINITIONS of NOE
DEFINITE NOE **NOE is definitely present if ALL 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 does not show bony erosion of the external auditory canal on CT scan OR does not show changes consistent with NOE on MRI if this is performed (for example bone marrow oedema of the temporal bone) AND which has ALL 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

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Table 2: Definition of complex disease

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COMPLEX NOE
Patients meeting the criteria for 'definite' NOE may be classified as 'complex' (or severe) <u>IF ANY</u> 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)

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Table 3: Consensus definitions for treatment outcomes

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UK Definitions for NOE

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.

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Table 4: Consensus statements

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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'

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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.

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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

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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, submitted*). It is possible that our definition may be less sensitive and will wrongly exclude 'true' cases of NOE, without visible EAC changes or without pain. 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[28]. 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.

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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 'necrotising otitis externa'.

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.

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CONFLICT OF INTEREST/DISCLOSURES

Nil to disclose.

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FIGURE LEGENDS

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

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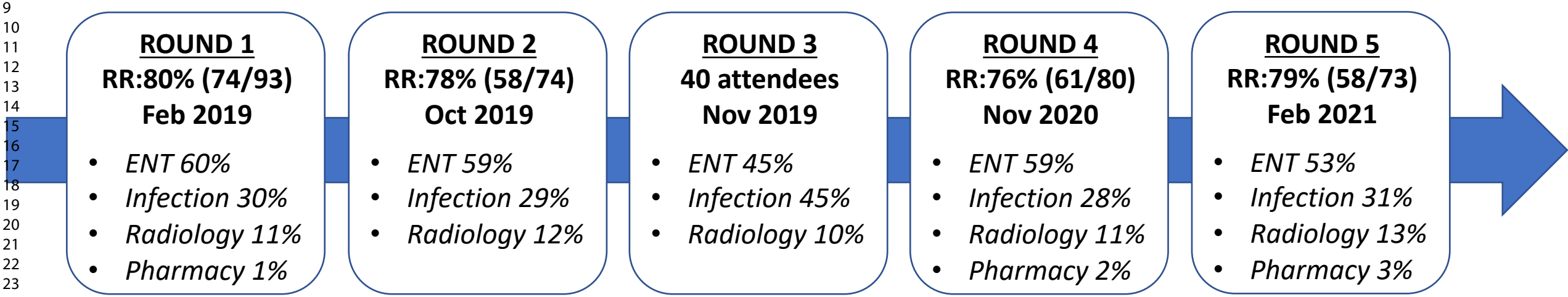
ROUND 1
RR:80% (74/93)
Feb 2019
ENT 60%
Infection 30%
Radiology 11%
Pharmacy 1%
ROUND 2
RR:78% (58/74)
Oct 2019
ENT 59%
Infection 29%
Radiology 12%
ROUND 3
40 attendees
Nov 2019
ENT 45%
Infection 45%
Radiology 10%
ROUND 4
RR:76% (61/80)
Nov 2020
ENT 59%
Infection 28%
Radiology 11%
Pharmacy 2%
ROUND 5
RR:79% (58/73)
Feb 2021
ENT 53%
Infection 31%
Radiology 13%
Pharmacy 3%

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UK consensus definitions for Necrotising Otitis Externa: a Delphi study

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ABSTRACT

Objective: To establish consensus definitions for NOE to facilitate the diagnosis and exclusion of NOE in clinical practice and expedite future high-quality study of this neglected condition.

Design: 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 which were shared with and endorsed by national speciality bodies.

Setting: Secondary care in the United Kingdom (UK).

Participants: UK clinical specialists practising in Infection, Ear Nose and Throat Surgery or Radiology.

Main Outcome Measures: Definitions and statements meeting the following criteria were accepted: (a) Minimum of 70% of respondents in agreement or strong agreement with a definition/statement AND (b) <15% of respondents in disagreement or strong disagreement with a definition/statement.

Results: Seventy four 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

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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.

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.

Key words: Necrotising, malignant, otitis, externa, Pseudomonas, antimicrobial therapy

Strengths and Limitations:

- *This Delphi process has engaged a large group of respondents - 74 UK-based clinicians across the key three specialities expert in managing patients with NOE (ENT, Infection and Radiology).*
- *The response rate to each of the Rounds is considered high for a Delphi study (>75%).*
- *A broad recruitment strategy was employed, but we may have missed UK clinicians who are experts in this field.*
- *We have only recruited clinicians based in the UK.*

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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. 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(1). Patients affected by NOE are generally frail and elderly with multiple co-morbidities(2, 3). This condition 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%(4). 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(5). Most published series are limited and of poor quality(2, 3) . Not surprisingly, the optimal strategy for diagnosis and management of NOE remains uncertain(2, 3) and there is considerable variability in how this condition is managed(6).

Cohen and Friedman's definition of NOE from 1987 is often cited(7) and modified versions are used in some studies(2). 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(2). To date there is no widely accepted case definition for NOE and none have been

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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 the 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 extended regimens exposes frail patients to the serious risks associated with these agents(8) as well as contributing more broadly to antimicrobial resistance(9-11). 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(2, 3).

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.

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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, with UK specialists, expert in managing NOE as well as open discussion within the collaborative. An expert panel analysed the results to produce the final

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guidance (Figure 1). Consent from participants was implicit in their taking part and their support for publication.

(i) Systematic Review

A systematic review of the literature for NOE was performed and reported according to PRISMA guidelines(12) (*Takata et al, submitted).* The systematic review was registered on PROSPERO (PROSPERO ID: CRD42020128957). The search identified all English language clinical papers published on NOE. 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. Of note, 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(13). 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

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and expert input until consensus has been achieved(14-18). 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(6).

(iii) Participants

A core group of ENT, Infection and Radiology senior consultant specialists with a special interest and expertise in NOE, set-up the UK NOE collaborative (MIA, ES, PP). This group, in consultation with national speciality organisations including the British Infection Association (BIA), ENT UK and the British Society for Otology (BSO) 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 questionnaire was set up and analysed on Google Forms. It was possible for the core group to identify if participants had replied, but not how they had replied ensuring the anonymity of the process. All participants consented to publishing the results. The core group with other senior experts (PMD (ENT consultant), MMcN (Bone and Joint Infection Surgeon), MW (Infection specialist)) facilitated the Delphi process and analysed the data(16).

(iv) Definitions

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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(19):

- 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.

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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 BIA, ENT UK, BSO and the British Society of Neuroradiologists (BSNR).

(vii) Patient and Public Involvement Statement

There was no public/patient involvement in this study.

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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 and raw data can be viewed in Supplementary Information which includes facilitator communiques with the collaborative (See Supplementary files 1-9). 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. The final consensus definitions and statements were endorsed by the BIA, ENT UK, BSO and BSNR.

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

DEFINITIONS OF NOE
DEFINITE NOE NOE is diagnosed if ALL 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 does not show bony erosion of the external auditory canal on CT scan OR does not show changes consistent with NOE on MRI if this is performed (for example bone marrow oedema of the temporal bone) AND which has ALL 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 2: Definition of complex disease

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).

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Table 3: Consensus definitions for treatment outcomes

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 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 4: 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'

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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(16), and has been used widely for this purpose(14, 20-23). 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

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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(24).

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(25, 26). 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(27-29), we chose to only include radiological

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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, submitted*). It is possible that our definition may be less sensitive and will wrongly exclude 'true' cases of NOE, without visible EAC changes or without pain. 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(30-32). In the management of complex orthopaedic infections, time to diagnosis and clinical outcomes have both been shown to improve when MDTs function well(33, 34). 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(30). 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(35). 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.

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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(36). Later the term 'NOE' was introduced(37). 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 'necrotising otitis externa'.

This is the first published study which has sought to standardise diagnostic and outcome criteria for NOE, following consultation with experts. However, the results should be interpreted in the context of the limitations of the methods used. We tried to recruit broadly, but may have inadvertently missed some specialists. The data is collected from UK based clinicians which may limit broader application of results. The decisions by the core group were led by the results of each round, which including comments by the participants, so reducing any risk of bias.

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

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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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FIGURE LEGENDS

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

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a) CONTRIBUTORSHIP

The conception and design of the work was done by SHH, MK, PM-D, ES, MW, PP, MAM, MIA. The data collection was done by SHH, MK, MPS, MIA, UK NOE Collaborative. The data analysis and interpretation was done by SHH, MIA, MK, ES, PMD, MW, PP. The first draft of the paper was done by SHH, MIA. The article was critically reviewed and revised by SHH, MK, MPS, PMD, ES, MW, PP, MAM, MIA and the UK NOE Collaborative

b) FUNDING STATEMENT

The authors declare that this study has not received any financial support

c) **COMPETING OF INTERESTS** T

The authors do not have any conflict of interest to declare

d) ETHICS APPROVAL

We sought advice from the chair of the Oxford University Hospitals Joint Research Office Study Classification Group who considered that the Delphi panel did not require formal ethical approval.

e) DATA SHARING

Raw data from the study are supplied as Supplementary files.

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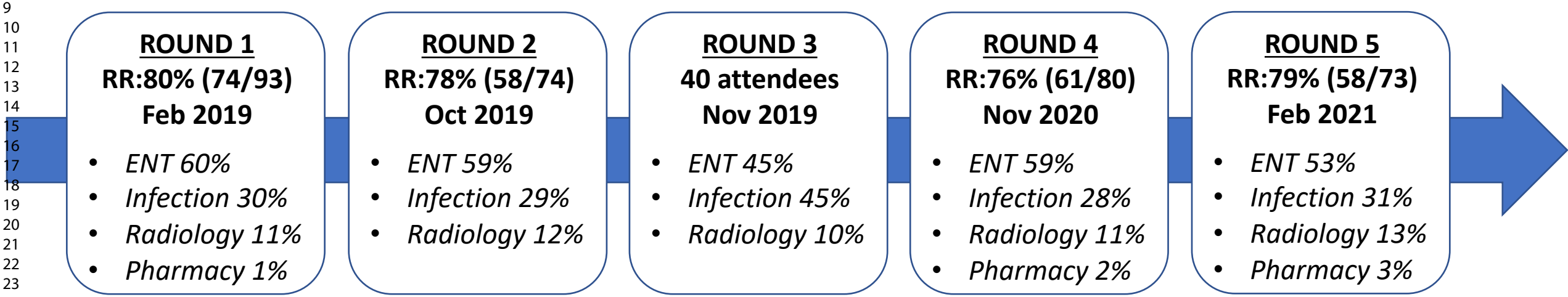
Evidence
Literature search
Core group
Proposed definitions agreed
Invitation
UK specialists invited to participate
Delphi Process
5 rounds of iterative consultation and expert analysis
Stakeholder Consensus
Review by national specialty groups

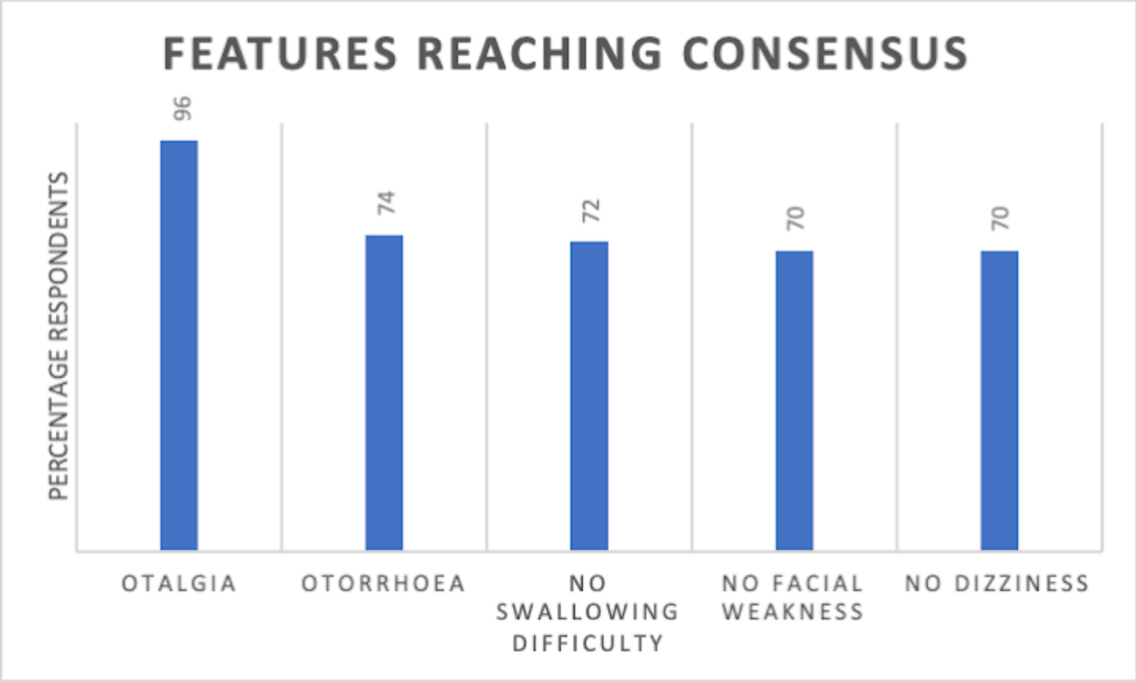

ROUND 1
RR:80% (74/93)
Feb 2019
ENT 60%
Infection 30%
Radiology 11%
Pharmacy 1%
ROUND 2
RR:78% (58/74)
Oct 2019
ENT 59%
Infection 29%
Radiology 12%
ROUND 3
40 attendees
Nov 2019
ENT 45%
Infection 45%
Radiology 10%
ROUND 4
RR:76% (61/80)
Nov 2020
ENT 59%
Infection 28%
Radiology 11%
Pharmacy 2%
ROUND 5
RR:79% (58/73)
Feb 2021
ENT 53%
Infection 31%
Radiology 13%
Pharmacy 3%

DELPHI ROUND 1 – RESULTS
FEBRUARY 2019
Response Rate: 84% (74/93)

Part 1: DEFINITE NOE

A true case of DEFINITE NOE will have the following features

1a. Symptoms: MAJOR symptoms - necessarily present for all definite cases of NOE: *



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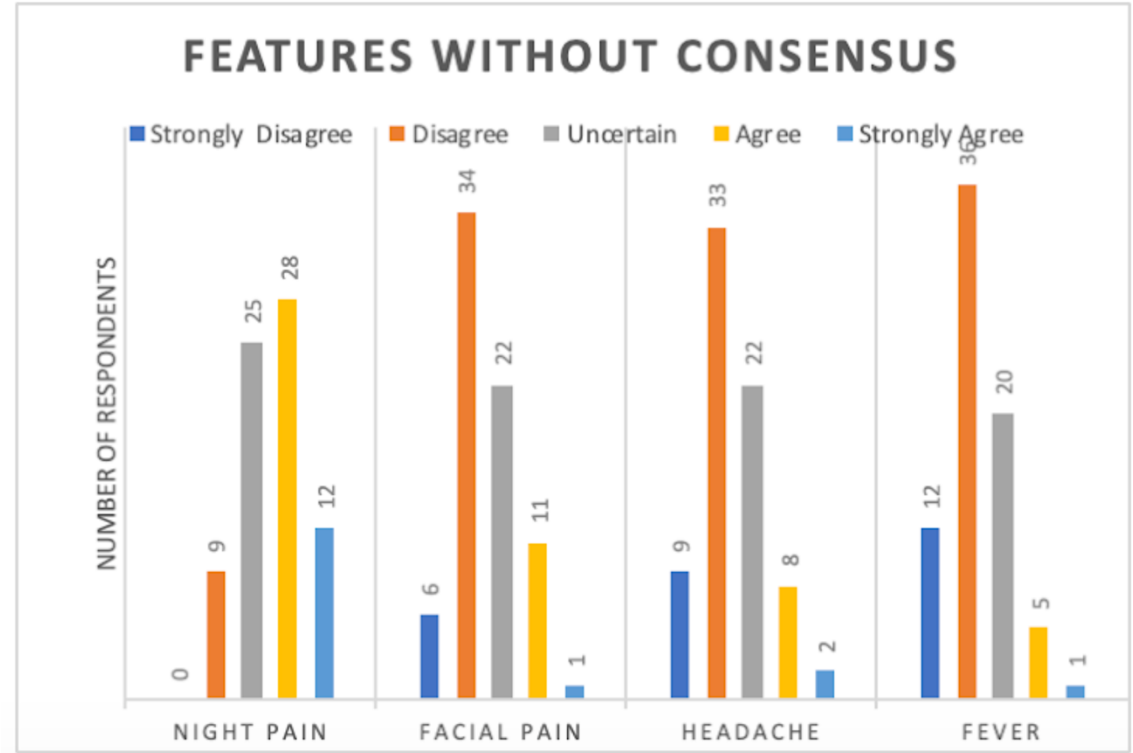
1b. Symptoms: MINOR symptoms - which MAY be present for all definite cases of NOE: *



2. A true case of DEFINITE NOE will have the following clinical signs: *

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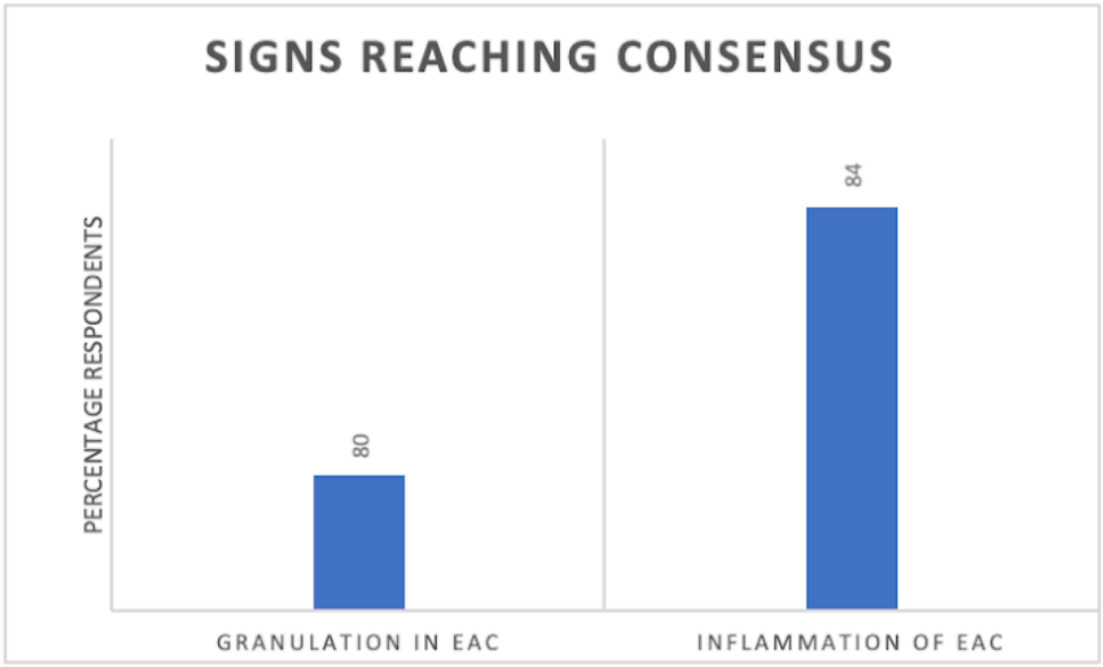

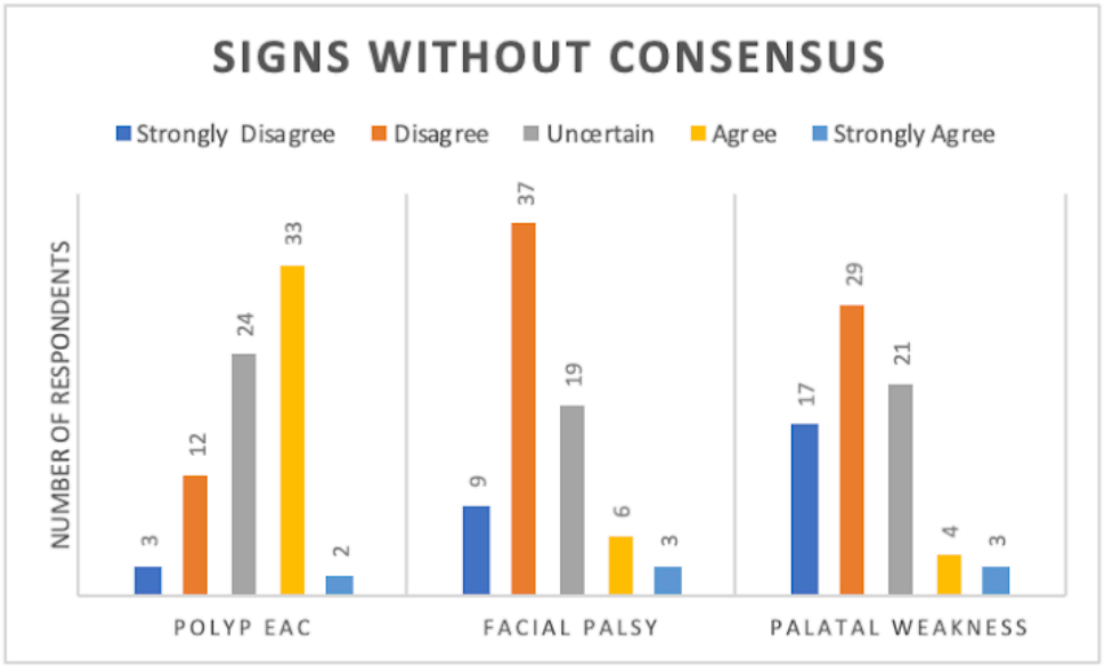

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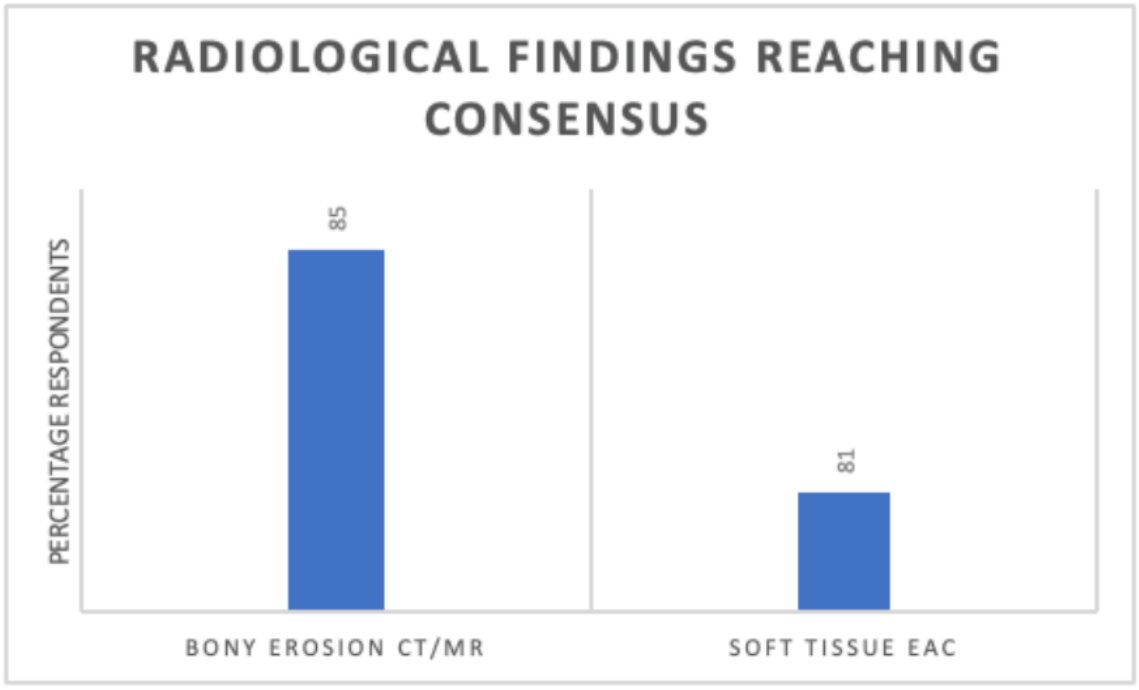
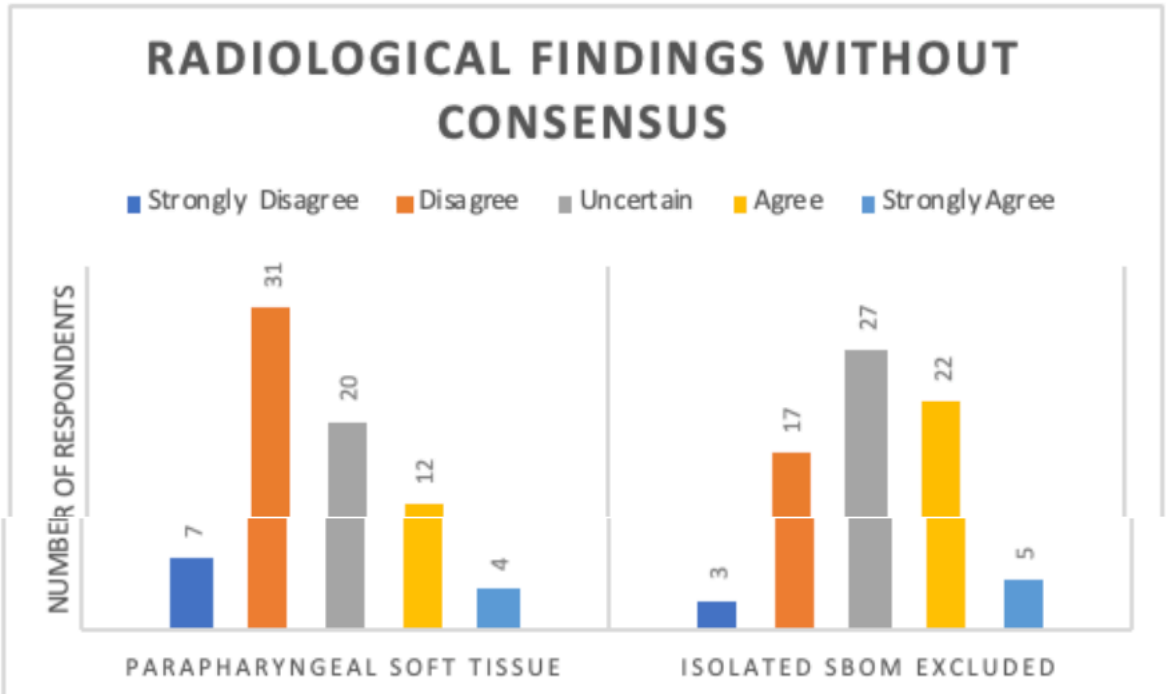
3. A true case of DEFINITE NOE will have the following findings on imaging: *





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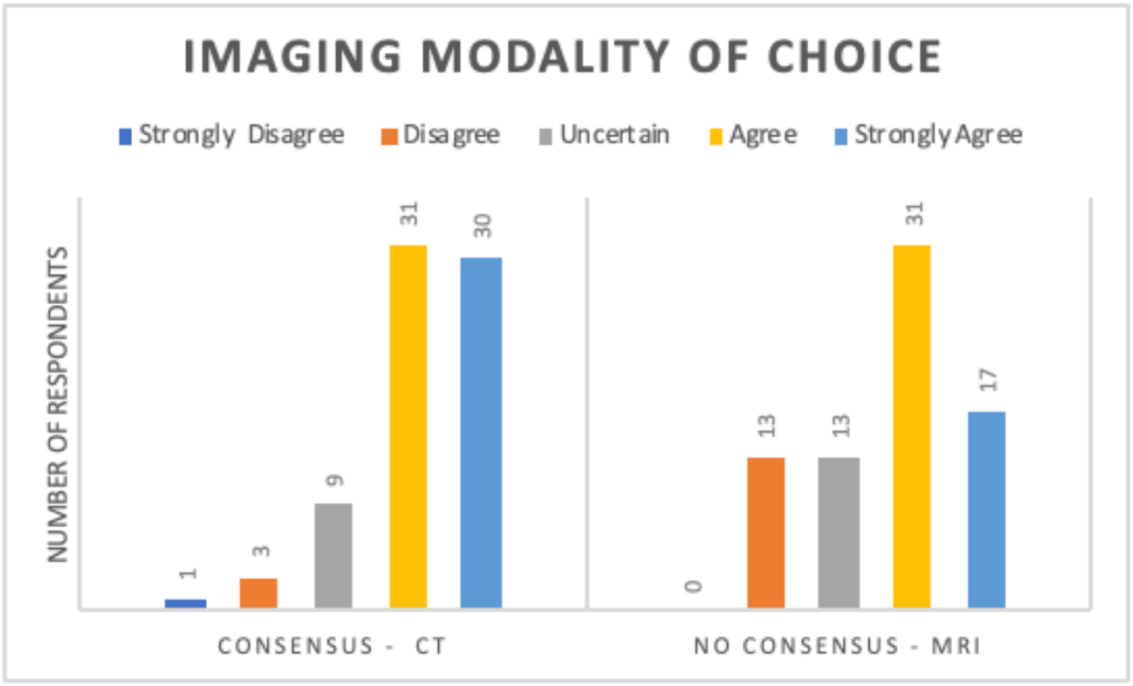
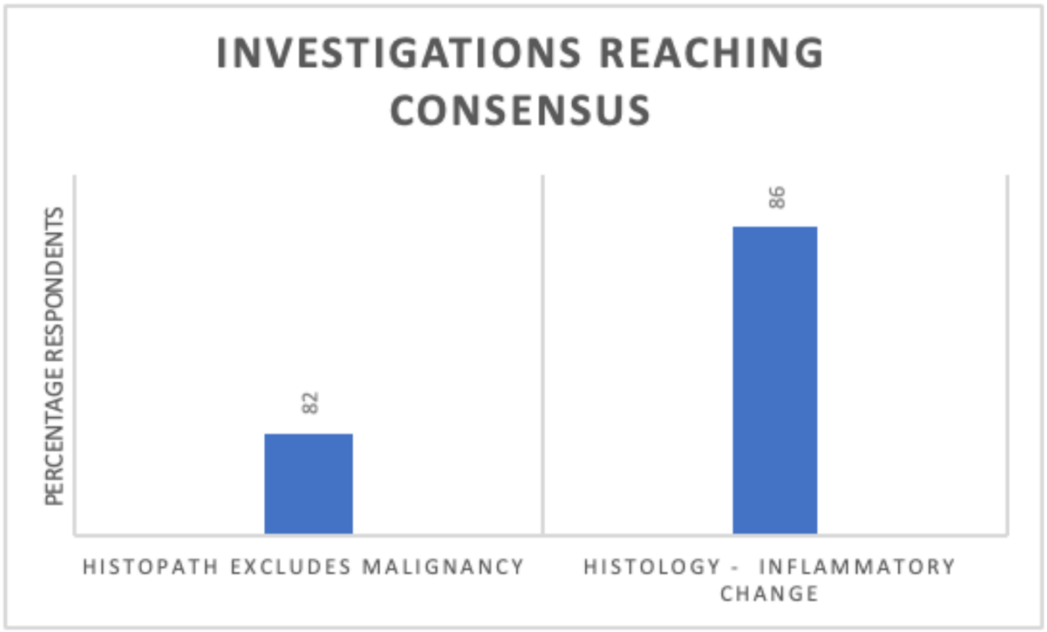


4a. INVESTIGATION: A true case of DEFINITE NOE will have the following findings on histology: *



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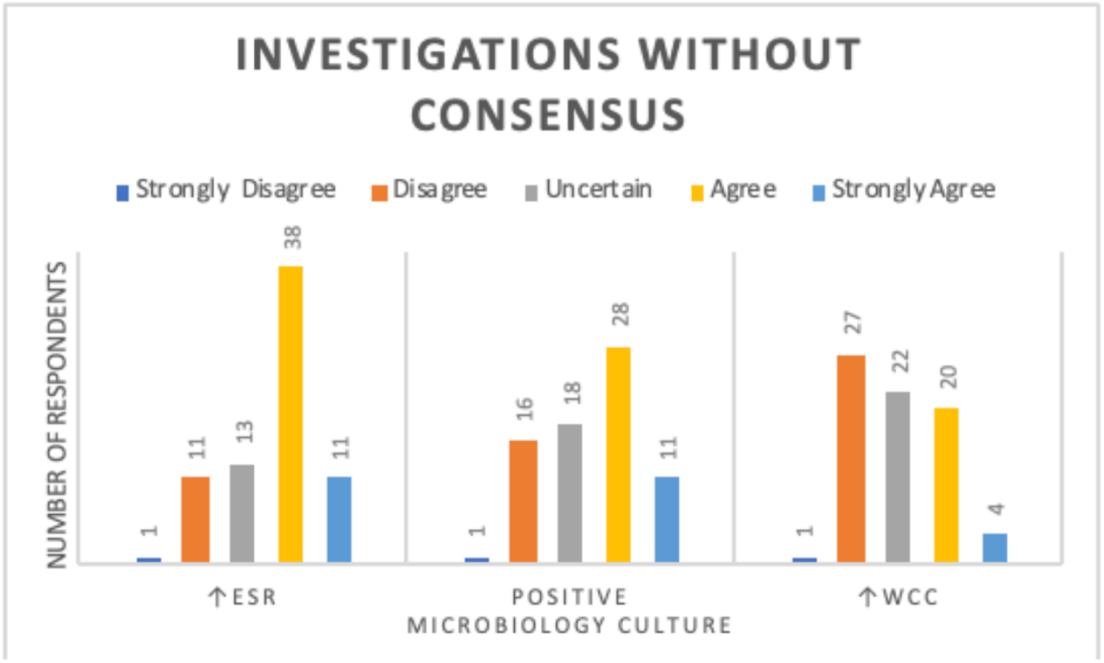
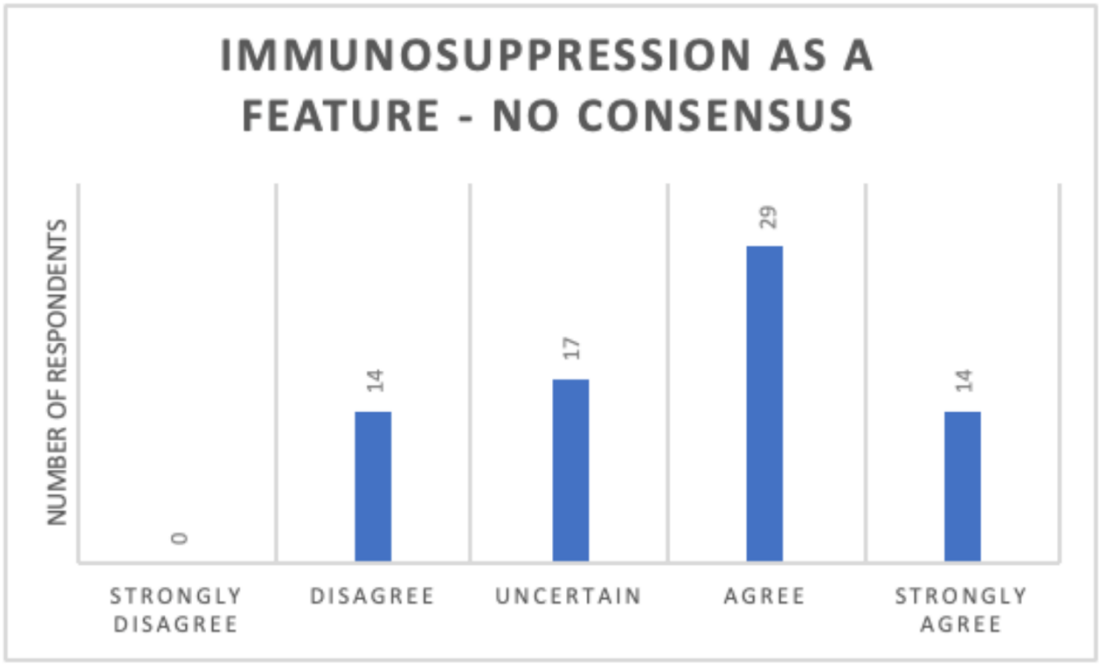
4b. INVESTIGATION: A true case of DEFINITE NOE will have the following biochemistry/haematology findings: *



5. Regarding risk factors for DEFINITE NOE: *



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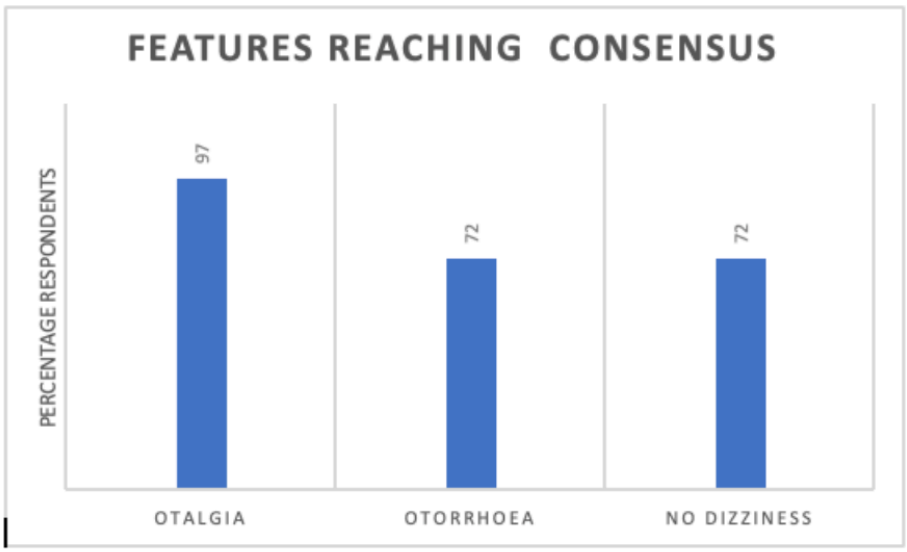
Part 2: Clinical Diagnosis & Investigation of Cases of PROBABLE NOE

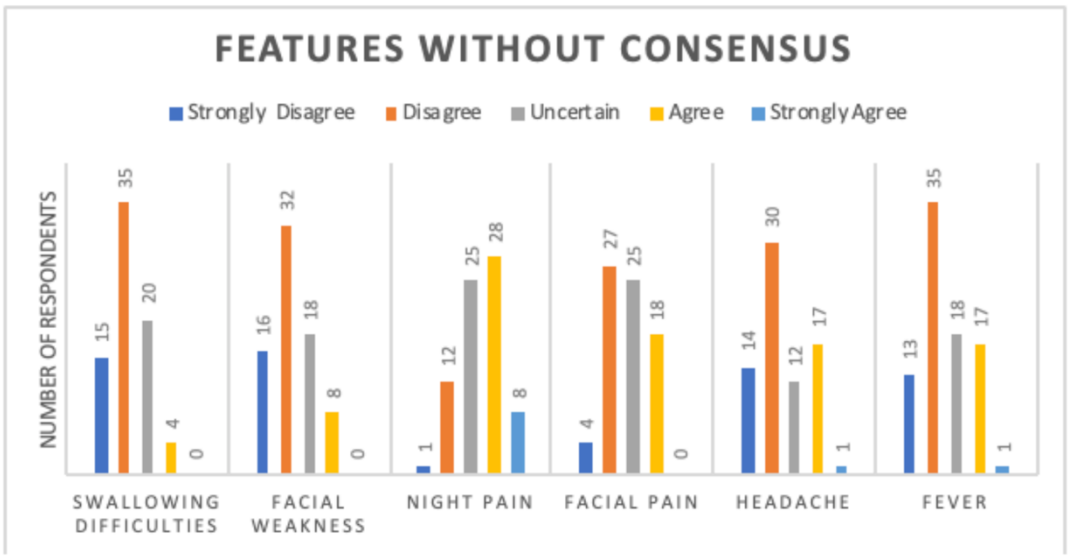
This definition covers those cases that do not meet ALL the criteria for definite NOE, but needs to be differentiated from severe OE. They are not the cases in whom further testing is awaited, but this constitutes a final diagnosis. This definition is important because it will impact antibiotic management.

A true case of probable NOE will have the following features:

13. 1a. Symptoms: MAJOR symptoms - necessarily present for all probable cases of NOE: *



1b. Symptoms: MINOR symptoms - which MAY be present for all probable cases of NOE: *



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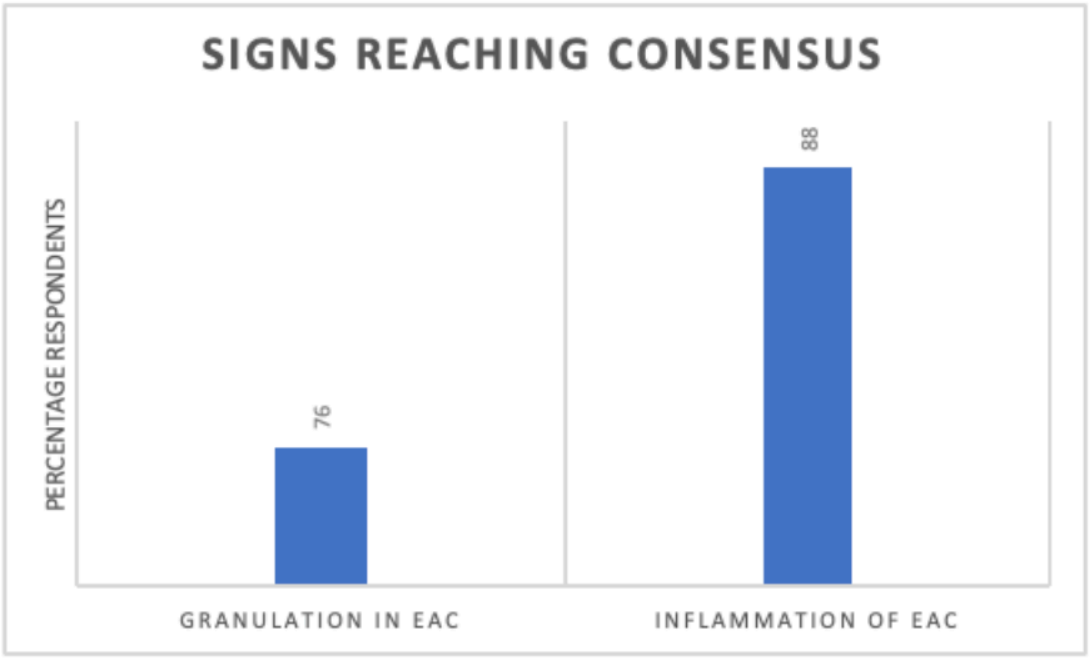
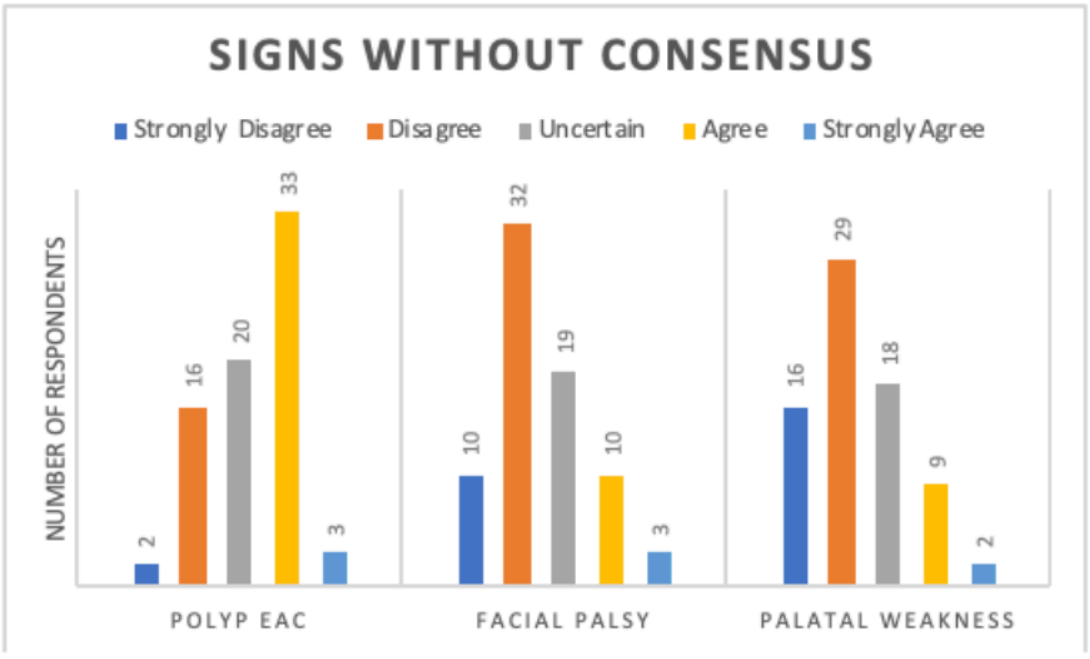
2. A case of PROBABLE NOE will have the following clinical signs: *





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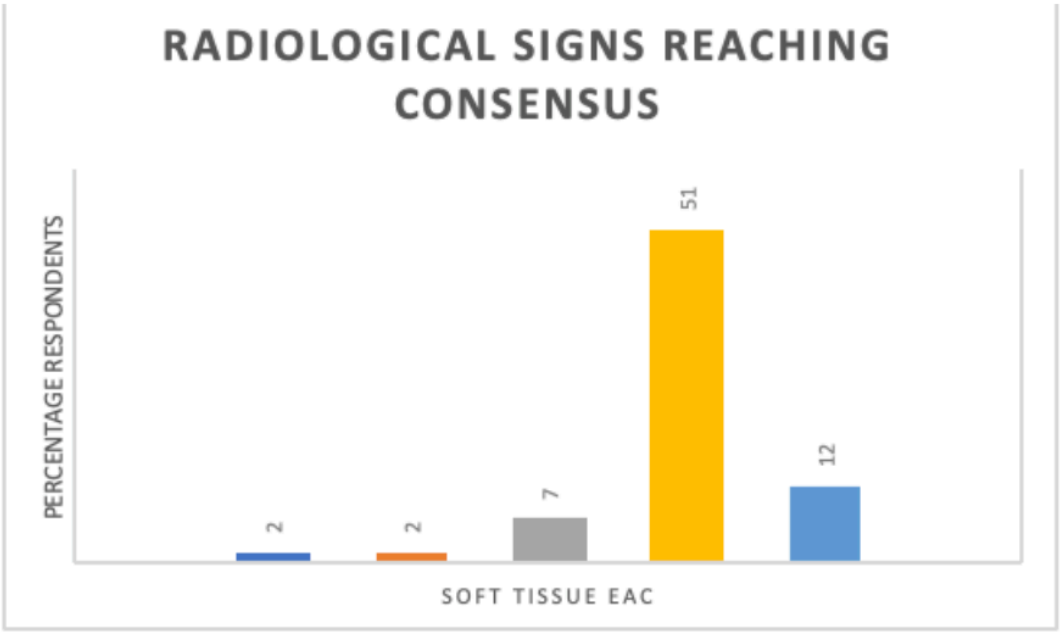
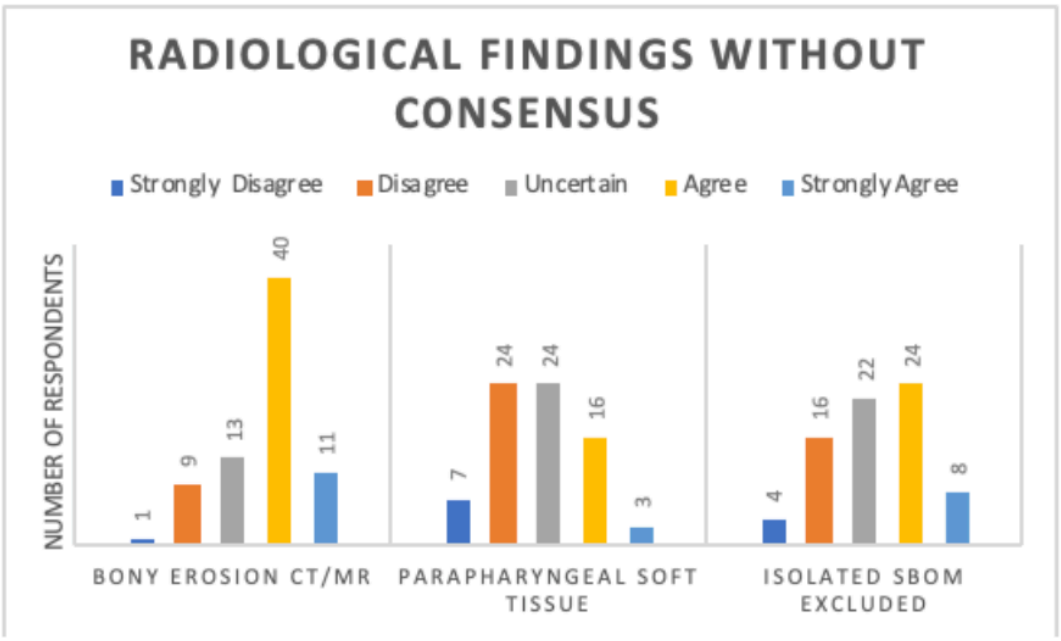
3. A case of PROBABLE NOE will have the following findings on imaging: *





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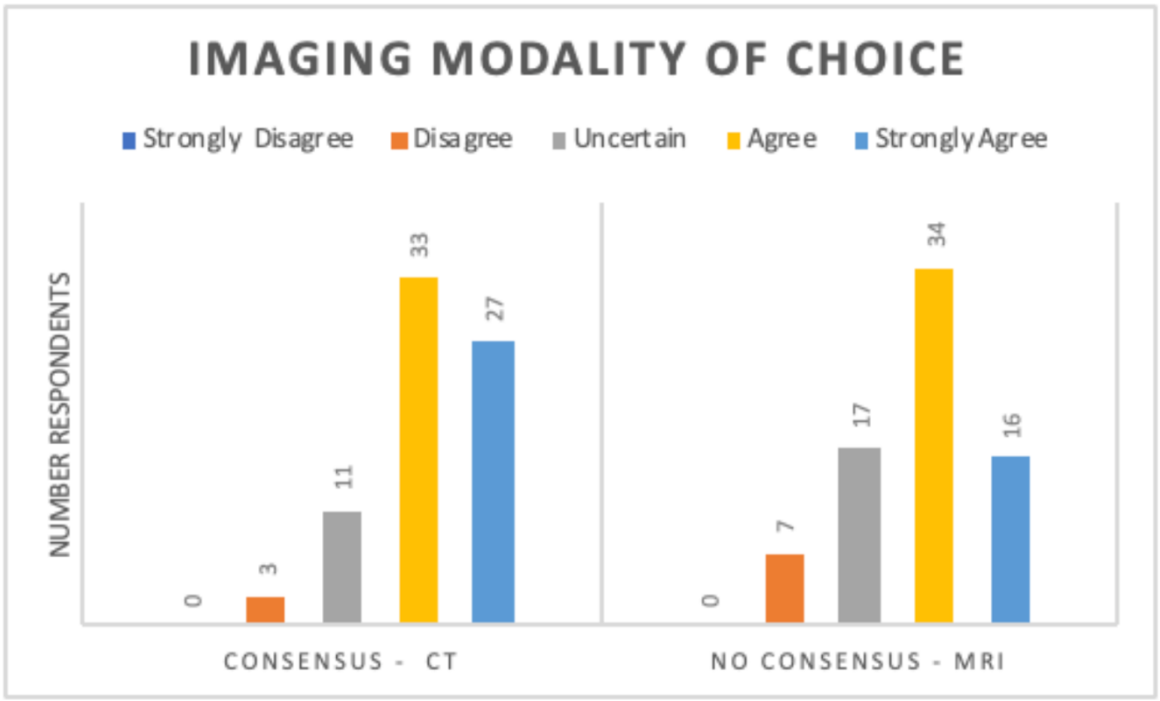
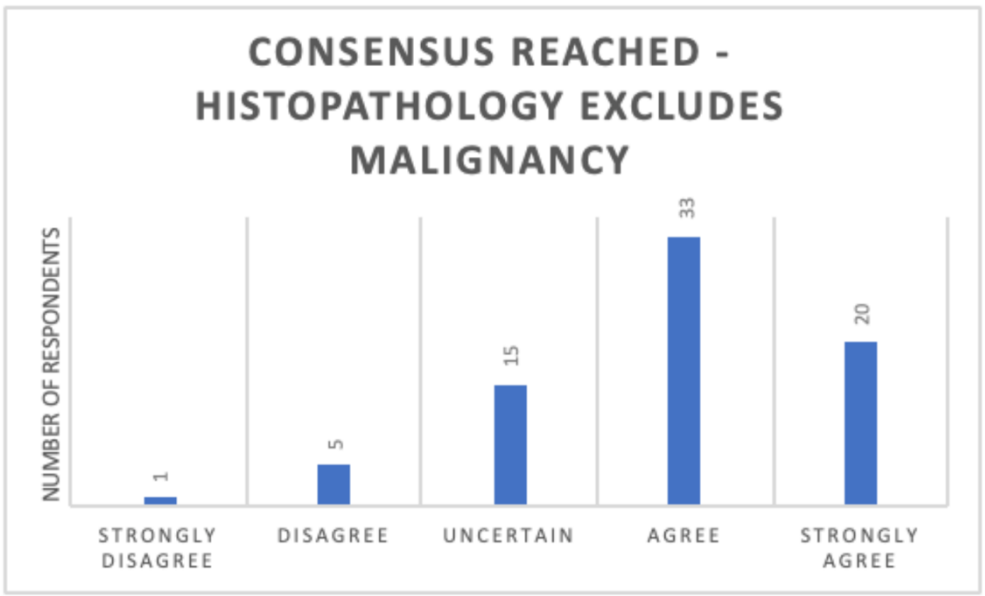


4a. INVESTIGATION: A case of PROBABLE NOE will have the following findings on histolog



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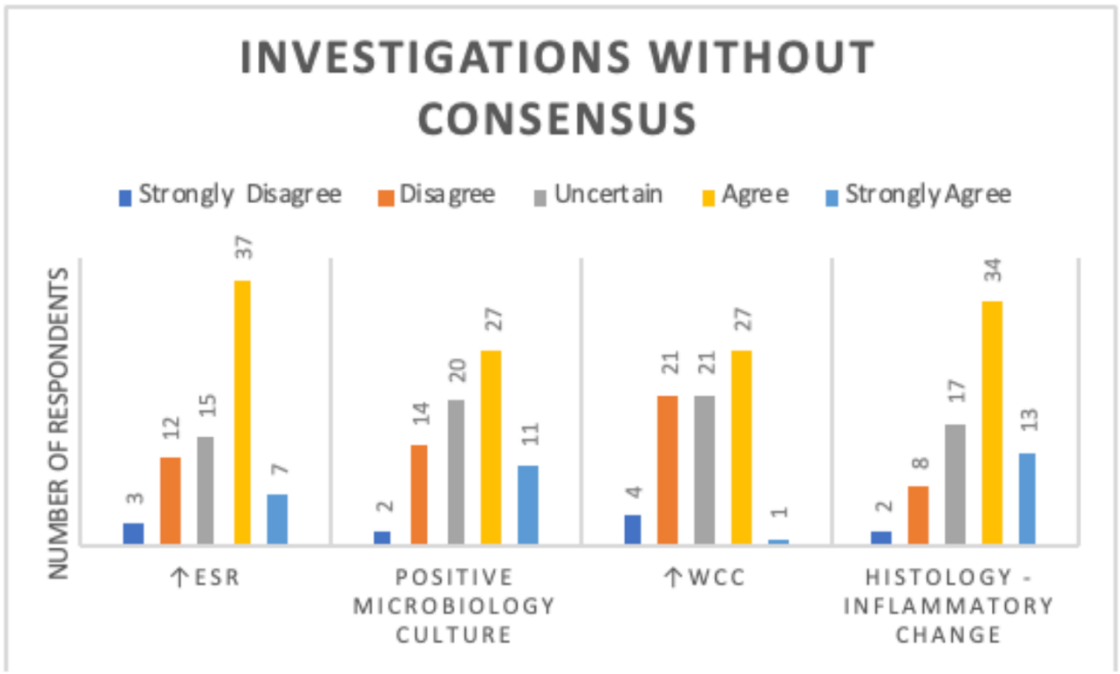
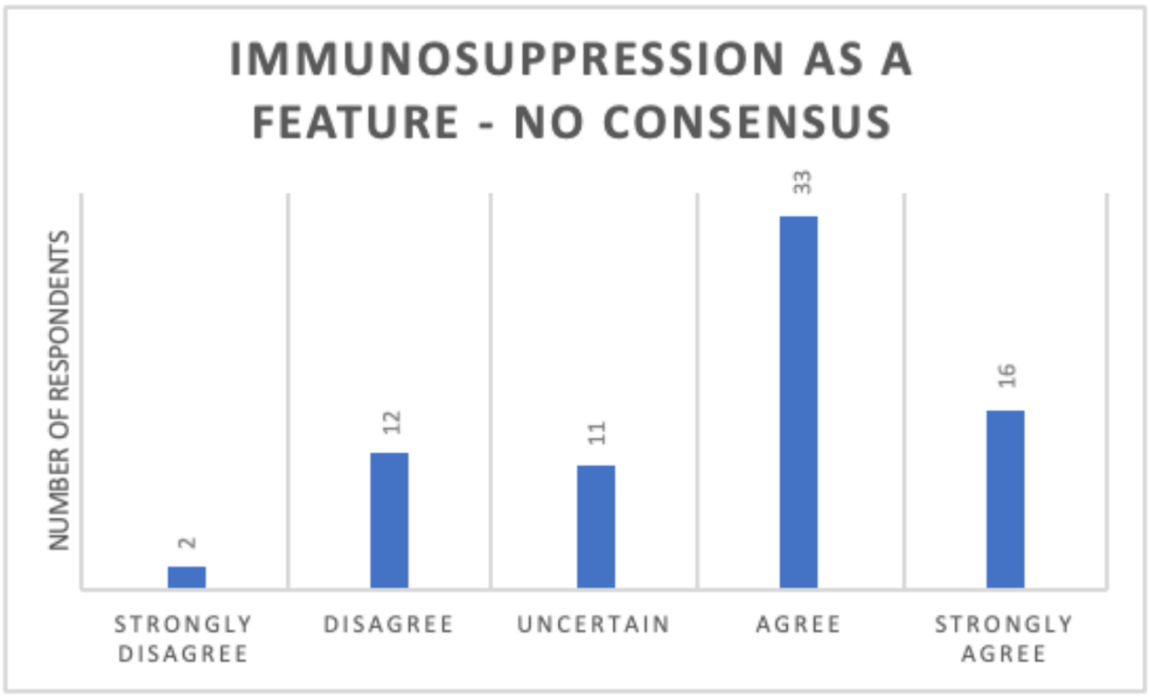
4b. INVESTIGATION: A case of PROBABLE NOE will have the following biochemistry/haematology findings: *



5. Regarding risk factors for PROBABLE NOE: *



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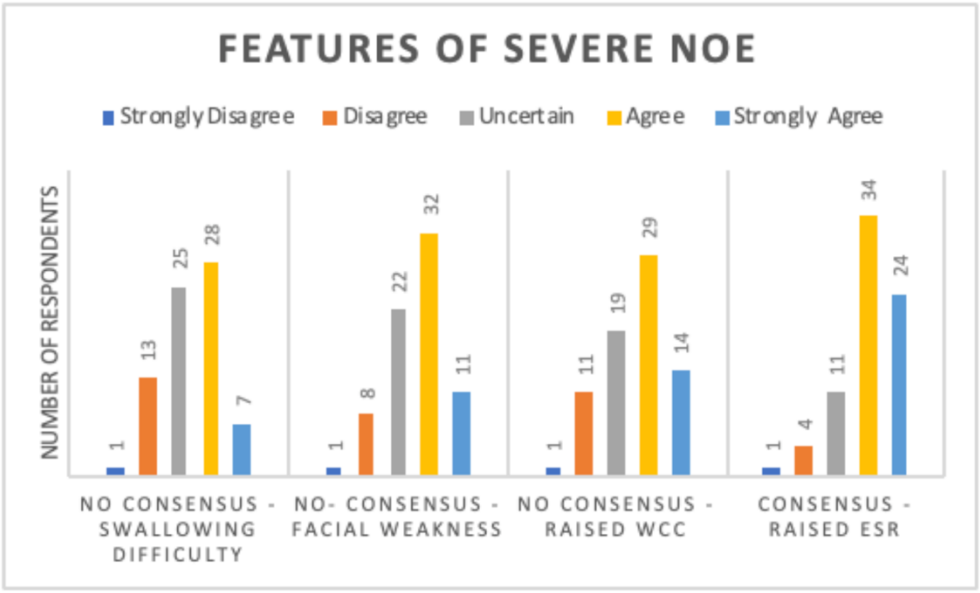
1. Which of the following features present in a definite case of NOE would meet criteria fc severe disease? *



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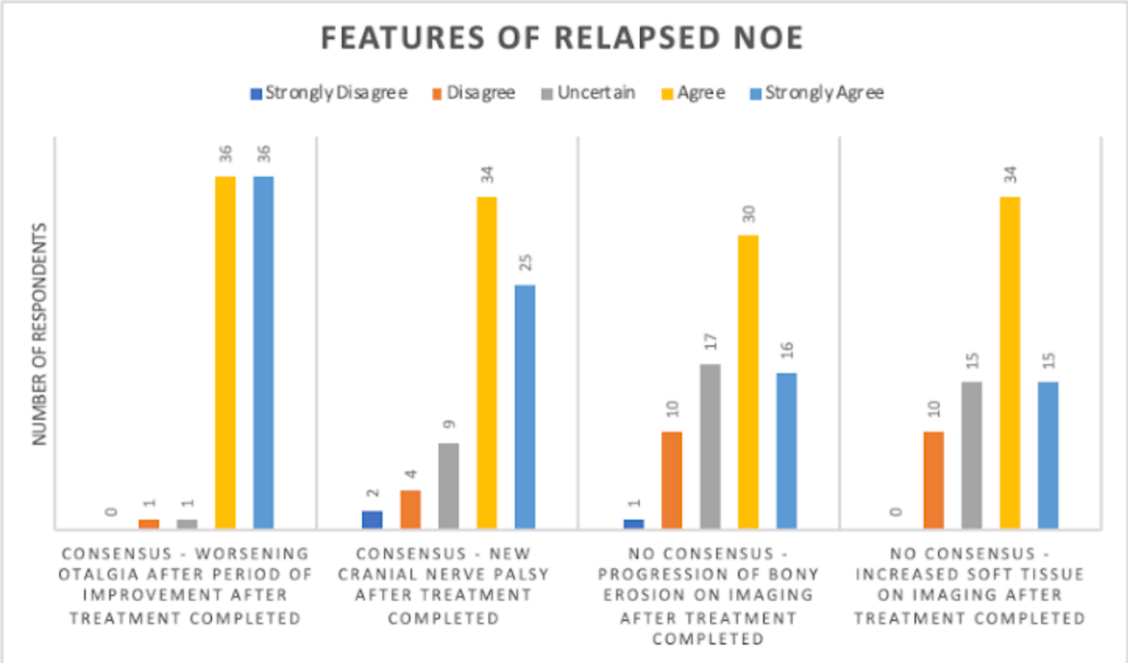
Part 4: Diagnosis of RELAPSED NOE

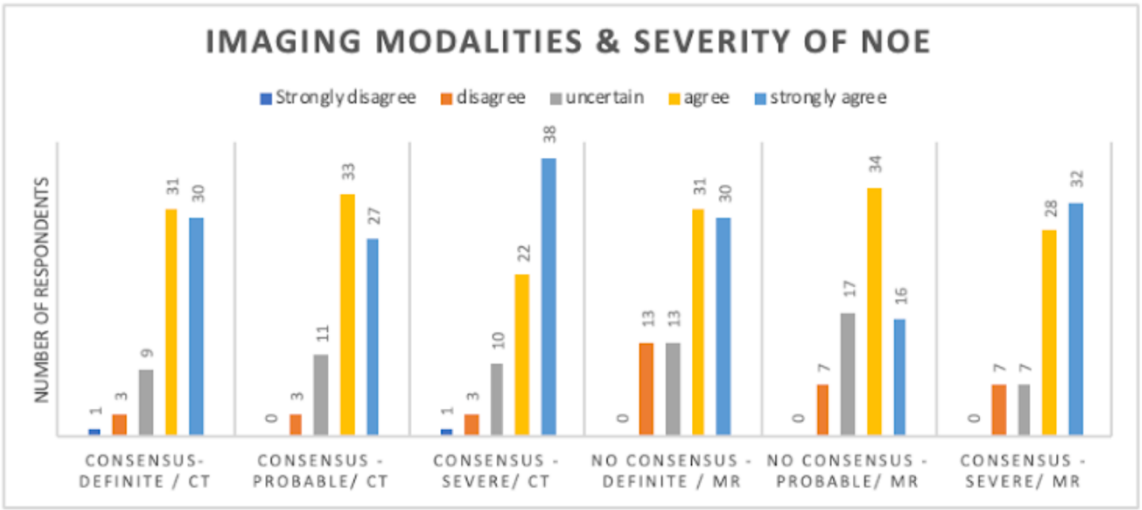
In order to better understand treatment failure, we need to understand what constitutes a true relapsed case. This should be differentiated from 'a case with progressive disease'. A relapsed case is a case where the patient has responded to treatment and the treatment course has been completed.

The following questions will try to ascertain what should define a relapsed case of Necrotising Otitis Externa

1. The following SYMPTOMS suggest a relapsed case: *



3. Regarding imaging: *



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Diagnostic Criteria for Necrotising Otitis Externa: Setting The Foundations

Thank you for your participation in Round 1. Respondents from Round 1 will be invited to take part in Round 2. Please use the same email address used in Round 1, to which this second round survey has been sent.

For Round 2 we have analysed the results of Round 1 in accordance with commonly accepted criteria[1], and incorporated your comments to design a set of questions which we hope will bring us closer to achieving consensus for a case definition for definite NOE. Relevant results from Round 1 are presented prior to the corresponding questions below; you may and the charts helpful when responding to these second round questions.

In addition, we aim to define: probable NOE, severe NOE, relapsed NOE and non-responding NOE

The case definition of NOE should include every true case of NOE and exclude every case that may have some features of, but is not truly NOE.

We have included one question on indications for imaging as this is a likely to be key variable in classifying cases.

At the end of the survey we have given you the opportunity to add any questions that you think should have been included or to make any general comments.

We aim to publish this Delphi process and the conclusions of this process. Everyone who completes both Round 1 and 2 will be credited as a collaborator.

[1]. Diamond IR, Grant RC, Feldman BM, Pencharz PB, Ling SC, Moore AM, et al. DeQning consensus: a systematic review recommends methodologic criteria for reporting of Delphi studies. J Clin Epidemiol. 2014;67:401–09]

nly

Outcomes from Delphi Round 2: NOE Case Definition

DEFINITE CASE

1a. Symptoms: MAJOR symptoms - necessarily present for all definite cases of NOE:

Consensus	No Consensus
Otalgia AND otorrhoea INCLUDE (86%)	Otalgia OR otorrhoea Otalgia alone Otorrhoea alone

1b. Symptoms: MINOR symptoms - which MAY be present for all definite cases of NOE:

Consensus	No consensus
Night pain – INCLUDE (81%)	Facial pain Trismus Headache Fever

1c. What number of minor symptoms should be present , together with major symptoms, to define a true case:

0 – 35.7%
1 – 25.7%
2 – 22.9%
3 – 14.3%
4 – 1.4%

2. A true case of DEFINITE NOE will have the following clinical signs:

Consensus	No consensus
EAC granulation AND inflammation – INCLUDE (80%) **EAC granulation OR inflammation – INCLUDE (79%)** **No signs – EXCLUDE – 89%**	Inflammation alone Granulation alone

3. A true case of DEFINITE NOE will have the following findings on imaging:

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Consensus	No consensus
Bone erosion EAC CT – INCLUDE (87%) **Soft tissue EAC CT – INCLUDE (81%)** **Bone erosion AND soft tis EAC – INCLUDE (79%)** **CT soft tis – T1 MR – INCLUDE (81%)** **Normal CT/MR – EXCLUDE (87%)**	Bone erosion OR soft tissue Isolated SBOM from source other than EAC excluded

4a. INVESTIGATION: A true case of DEFINITE NOE will have the following findings on histology:

Consensus	No consensus
Malignancy excluded – INCLUDE (87%) Inflammation confirmed – INCLUDE (83%) Malignancy excluded AND inflammation confirmed – INCLUDE (93%)	Excludes malignancy or confirms inflammation Histo always sent

4b. INVESTIGATION: A true case of DEFINITE NOE will have the following biochemistry/haematology findings:

Consensus	No consensus
	Raised CRP Raised ESR

5. Regarding risk factors for DEFINITE NOE: NO CONSENSUS The patient will be always frail or immunosuppressed (diabetic, steroid therapy, malignancy, biologic therapy, HIV infected etc.)

COMMENTS

- CT alone may lags behind actual bony destruction
- Changes in time are also useful in confirming or refuting definite NOE - e.g. Improvement with treatment on serial imaging
- As a radiologist who has seen many cases of NOE, I believe that even streakiness to the parapharyngeal fat in the appropriate clinical context is sufficient to diagnose NOE and we have had many cases treated as such
- There may be no signs in the ear and the patient has got skull base Osteomyelitis, if the patient had been treated before hand but not adequately.
- minor criteria don't necessarily need to be present, but might be helpful in the absence of definite radiological features eg no bone erosion but soft tissue swelling present, having multiple minor criteria present +/- immunosuppression could be sufficient for a definite diagnosis.
- Certain criteria together make it a DEFINITE NOE. For example a facial palsy AND granulation tissue (even without evidence of bony erosion on CT). We should incorporate that somehow ideally.
- T1 enhanced imaging is an important modality in the diagnosis of NOE

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- Granulation tissue is inflammatory tissue, it is formed in response to inflammation, I don't see how one can have granulation tissue without inflammation in the canal.
- Regarding immunosuppression, advancing age is an important risk factor in itself without necessarily implying frailty.

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PROBABLE CASE

1a. Symptoms: MAJOR symptoms - necessarily present for all probable cases of NOE:

Consensus	No Consensus
Otalgia AND otorrhoea INCLUDE (81%)	Otalgia OR otorrhoea Otalgia alone Otorrhoea alone

1b. Symptoms: MINOR symptoms - which MAY be present for all probable cases of NOE:

Consensus	No consensus
Night pain – INCLUDE (71%)	Facial pain Facial weakness Trismus Headache Fever

1c. What number of minor symptoms should be present , together with major symptoms, to define a probable case:

0 – 22.9%
1 – 32.9%
2 – 30%
3 – 11.4%
4 – 2.9%

2. A case of PROBABLE NOE will have the following clinical signs:

Consensus	No consensus
EAC granulation OR inflammation – INCLUDE (81%) **No signs – EXCLUDE – 81%**	EAC granulation AND inflammation – Inflammation alone Granulation alone

3. A case of PROBABLE NOE will have the following findings on imaging

Consensus	No consensus
Soft tissue swelling of external ear canal will be visible on CT or MRI – INCLUDE - 87%	CT scan excludes bony erosion

4a. INVESTIGATION: A case of PROBABLE NOE will have the following findings on histology

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Consensus	No consensus
Inflammation confirmed – INCLUDE (86%) **Malignancy excluded AND inflammation confirmed – INCLUDE (80%)**	Excludes malignancy or confirms inflammation Histo always sent

4b. INVESTIGATION: A case of PROBABLE NOE will have the following biochemistry/haematology findings:

Consensus	No consensus
CRP MAY be raised – 83% **ESR MAY be raised – 86%**	Raised CRP Raised ESR

5. Regarding risk factors for PROBABLE NOE: NO CONSENSUS The patient will be always frail or immunosuppressed (diabetic, steroid therapy, malignancy, biologic therapy, HIV infected etc.)

COMMENTS

- Bony erosion on CT would confirm NOE in the correct setting but a lack of bone erosion does not exclude it. If there are risk factors, marked soft tissue changes and/or persistent clinical concern I would advocate baseline MRI to assess for bone oedema and serial imaging to assess response to treatment. My concerns would be either missing NOE if we image early in the course but also missing malignancy if we box patients into NOE diagnosis.
- Repeated ear trauma (eg in-ear headphone use) is risk factor in immunocompetent/ non-frail individuals, ear syringing and hearing aid use
- Probable NOE in my mind is the group of patients where the clinical symptoms and signs are compatible but the imaging may not be complete (CT without MRI for example) or unable to tolerate MRI all sequences. They do not need to have an immunosuppression risk factor to meet a case definition.
- I'm not confident that I understand how you will use these answers e.g. Symptoms: MINOR symptoms - which MAY be present for all probable cases of NOE - I don't see how something can be MAY and present in ALL. Also ...A case of PROBABLE NOE will have the following findings on imaging: CT scan excludes bony erosion - you mean WILL -they may because its not perfectly sensitive...?
- the length of duration of symptoms also important
- Also I have disagreed with facial weakness for probably NOE because I think it is more of an indicator of definite NOE!
- Probably diagnosis still shouldn't just be oedema of external canal, should show some evidence of tissue of the external ear and beyond otherwise this is simple otitis externa at that point. Doesn't have to show bone erosion. CRP and ESR May be raised but I don't believe it always has to be, have seen patients with limited raised blood serological marker

SEVERE CASE

1. **Which of the following features present in a definite case of NOE would meet criteria for severe disease?**

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Consensus	No consensus
Cerebral venous thrombosis – INCLUDE – 89% **Lower cranial nerve palsy INCLUDE 99%** **Disease spread contralaterally INCLUDE 81%**	Elevated Inflammatory markers (ESR or CRP)

2. **One or a combination of how many of these features in a definite case of NOE should meet criteria for severe disease?**

Consensus	No consensus
1 – INCLUDE – 70%	>1, >2, >3

3. **The following features on MR are suggestive of severe disease (MR as imaging modality reached consensus):**

Consensus	No consensus
Soft tis/fluid collection below skull base - INCLUDE – 70% **Intracranial involvement - INCLUDE– 91%** **Central SBOM – INCLUDE – 88%**	

4. **The following features on CT are suggestive of severe disease (CT as imaging modality reached consensus):**

Consensus	No consensus
Bone erosion of stylomastoid foramen walls – INCLUDE – 73% **Intracranial involvement – INCLUDE – 93%** **Central SBOM – INCLUDE – 91%**	Soft tissue below skull base

COMMENTS

- Facial weakness should be included in the list of features
- Are we delineating between NOE and Skull base osteomyelitis? Whilst they ay be part of the same spectrum, they can appear and act as separate diseases.
- Skull base osteomyelitis is a different disease entity to NOE and should be investigated and managed on its own merits.
- Central skull base without obvious clinical history to support an ear cause I believe is a separate entity to NOE, though in the same family per se.
- I would regard any complication (facial nerve involvement, collection, TMJ involvement/septic arthritis, thrombosis, intracranial spread) as severe, or extensive skull base involvement
- would consider broader terms used for bony erosion on CT as may be variable distributions not just around the SMF e.g. EAC alone, TMJ, extension into mastoid and/or petrous apex

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- I would have thought that severe disease we more of a clinical severity rather than radiological, the neurology and physical impairment being most prominent.
- I am struggling to know without a radiological grading score which of these changes on CT or MRI I would classify as severe versus non severe but definite NOE that is why we need a way of grading the imaging
- for some of the radiology I would rely on specialised radiologist input

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RELAPSED CASE

1. **The following SYMPTOMS suggest a relapsed case:**

Consensus	No consensus
Worsening otalgia after improvement after treatment completed – INCLUDE 96% **Worsening otorrhoea after improvement after treatment completed –INCLUDE 71%** **Worsening otalgia AND otorrhoea after improvement after treatment completed –INCLUDE – 77%** **Worsening otalgia OR otorrhoea after improvement after treatment completed –INCLUDE – 74%**	

2. **The following SIGNS suggests a relapsed case**

Consensus	No consensus
Recurrent granulation after resolution and tx completed – INCLUDE – 87% **Recurrent inflammation after resolution and tx completed – INCLUDE – 77%** **Recurrent granulation AND inflammation after resolution and tx completed – INCLUDE – 77%** **Recurrent granulation OR inflammation after resolution and tx completed – INCLUDE – 74%**	

3. **The following IMAGING findings suggest a relapsed case**

Consensus	No consensus
Progression bony erosion or bone marrow oedema after improvement – INCLUDE – 93% **Increased soft tissue after improvement – INCLUDE – 89%** **No role for imagine – EXCLUDE – 82%**	

4. **The following INVESTIGATION results suggest a relapsed case:**

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Consensus	No consensus
Rising ESR after treatment completed - - INCLUDE – 70%	Rising CRP after treatment completed

5. Regarding the duration off from treatment prior to diagnosis of relapse (not treatment failure) – NO CONSENSUS: 1 week, 2 weeks, 2 months

COMMENTS

- Variable times commented from 1 week to 3 months based on frequency of imaging
- We find gallium scans are useful for monitoring for treatment response and relapsed disease, or for disease progression. It is the only imaging that gives "real time" data. CT erosive finding are late. MRI oedema takes a long time to resolve. Is there any point in defining the difference between incompletely treated and relapsed disease? if the patient is worsening (at any stage), they need more treatment.
- is there enough evidence to define this between 2 weeks and 2 months post treatment
- unless antibiotic treatment is standardised, the definition for 'relapse' is subject to bias/ Would nee ID guidance on the duration of treatment completion to be able to confidently answer Q5
- Any signs or symptoms after treatment cessation has been agreed should constitute a relapse.
- I think relapse is when the patient 's condition mainly pain/headache deteriorates after a period of being asymptomatic as patient can still be down graded to oral AB and can get a recurrence of symptoms.
- It is technically a "relapse" of that infection. Better to use the term recurrence of NOE instead of relapse? and then define relapse as return of symptoms/signs at any point after Completion of treatment and recurrence as having to have a minimum gap of one month off treatment?
- I don't think inflammatory markers are reliable markers of active infection but would worry if raised.
- It depends how we define 'cure' or cessation of treatment
- If a patient reaches 2 months post-diagnosis is it another (new) infection?
- increase in time after treatment completed adds to the confidence in the diagnosis of relapse

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NON-RESPONSE TO TREATMENT

1. Symptoms

Consensus	No consensus
Worsening otalgia on treatment – INCLUDE 91% **Worsening otorrhoea on treatment – INCLUDE 70%** **Both – INCLUDE 76%** **Either/or – INCLUDE 73%**	

2. Signs

Consensus	No consensus
Worsening granulation on treatment – INCLUDE 70% **Worsening inflammation on treatment – INCLUDE 77%** **Either or – INCLUDE 71%**	Both – IGNORE? – 66%

3. Imaging

Consensus	No consensus
Progression bony erosion whilst on treatment – INCLUDE 77% **Progression bone erosion to other parts skull base except EAC – INCLUDE 84%** **Progression bone marrow oedema/enhancement skull base MR – INCLUDE 77%**	Increased soft tissue

4. Investigations

Consensus	No consensus
	Rising CRP on treatment Rising ESR on treatment Exclusion malignancy on histology

5. Duration on treatment prior to diagnosis of non-response:

Consensus	No consensus
Min 3/7 – EXCLUDE – 79%	5 7 10 14

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IMAGING

Imaging in Otitis Externa

Consensus	No consensus
No role in severe/persistent – EXCLUDE – 87% **Imaging in severe/persistent when abx failed – INCLUDE 80%** **Severe pain INCLUDE – 74%** **Night pain INCLUDE – 74%** **Lower CN palsies INCLUDE – 100%** **Immunosuppression – include – 76%**	Imaging is only indicated in severe/persistent OE where there has been failure of antibiotic therapy AND risk factors* (diabetes, Immunocompromise etc) for NOE are present Polyp

Imaging in NOE

Consensus	No consensus
CT 1st line – INCLUDE – 87%	MR 1st line If CT shows swelling of external auditory canal but no bone erosion then MRI should be performed If CT shows no swelling of external auditory canal or bone erosion then MRI should be performed PET-CT should be performed if CT and MRI are normal

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NOV
21

UK NOE Collaborative Inaugural Meeting & Case Definition Workshop

by UK NOE Collaborative

Follow

Free

Description

We would greatly appreciate your presence at the UK NOE Collaborative Inaugural Meeting. A key aim of this meeting will be to agree a case definition for NOE. It is hoped this definition will be endorsed by ENT UK and the British Infection Association and used in subsequent work in the UK.

Prior to the meeting, outputs from the online Delphi process will be circulated for review.

The venue (in central Oxford) will be confirmed and details circulated once number of attendees are known. We would therefore be grateful if you could confirm attendance asap.

Provisional Programme:

1200 - 1300: Lunch

1300 - 1400: Introduction to Collaborative & Future Plans

1400 - 1500: Case Definition Workshop 1

1500 - 1530: Tea & Coffee

1530 - 1630: Case Definition Workshop 2

1630 - 1700: Closing Remarks

Date and time

Thu, 21 November 2019
12:00 – 17:00 GMT
Add to calendar

Location

Oxford. Venue TBC.
Oxford
View Map

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The first UK NOE Collaborative meeting took place on the 21st November 2019 at St. Peter's College, Oxford.

The aim of the meeting was to discuss the UK NOE Collaborative Delphi process to date and to carry out a third round of the Delphi survey, continuing work on the definition for definite, probable, relapse, severe cases and agreeing indications for imaging.

Presentations

The programme started with an informative presentation by Professor Martin McNally, Head of Limb Reconstruction, Oxford. He presented two previous Delphi processes for case definition development with which he had been involved: fracture related infections and prosthetic joint infections. Both of these processes involved groups of international collaborators and required an extended, iterative process to resolve. The notable difference for these conditions compared to NOE, was the existence of published data to inform the process. Whilst the challenges of the method were undeniable, the benefit of being able to agree guidelines and plan studies based on widely agreed definitions was evident.

Dr Pieter Pretorius, Consultant Neuroradiologist, Oxford provided clear succinct insights into the advantages and disadvantages of different scanning modalities and illustrated the difficulties of making a radiological diagnosis of NOE. A discussion followed on what modality should be used to follow cases and diagnose relapsed cases. MRI and CT are widely used, however the usefulness of other modalities including gallium scans and PET scans have yet to be shown.

Ms Maha Khan, ENT Specialist Registrar, Manchester presented an overview of the principles of the Delphi process, the rationale for the questions used to date in the NOE Delphi process and results from Round 2.

Dr Susanne Hodgson, Academic Clinical Lecturer in Infection, Oxford presented the proposed NITCAR prospective study protocol. The discussion focussed on whether definite cases or definite and possible cases of NOE should be included in the study design. The choice between a thorough research study and a more limited national service evaluation was also reviewed and the group were in favour of a definitive study. Discusssions are ongoing with INTEGRATE and it is hoped that this study will prove to be a successful collaborative effort between the two groups.

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Delphi Process Discussion

The discussion of case definitions was the main focus for the day. This session was facilitated by Professor McNally and Ms Emma Stapleton, ENT Consultant, Manchester. During the first half of the session the discussion was left open to allow attendees to discuss a range of the different aspects of NOE. The second half of the discussion was more focussed, in order to address items from Round 2 of the Delphi Process which had not yet reached consensus.

It was agreed that the term 'malignant otitis externa' should not be used. It was pointed out that the term 'necrotising otitis externa' is not accurate due to the absence of true necrosis. This point was discussed and it was agreed that although a misnomer, there was no support for a proposal to rename the condition.

The chronology of symptoms was raised and it was agreed that whilst otalgia and otorrhoea had met consensus as essential features for a clinical diagnosis of NOE, the otorrhoea may have subsided by the time a diagnosis of NOE was made. It was therefore agreed that clinical diagnosis of NOE requires the inclusion of the phrase 'or a history of recent otorrhoea'. The group agreed that adding minimum durations of symptoms/signs prior to imaging or escalation of treatment would be important in defining an investigative algorithm. Professor McNally's past experience advised against pursuing the suggestion of a scoring system for predicting the liklihood of a case from a consellation of findings.

There was discussion about the meaning of the term 'probable NOE'. Professor McNally supported the concept of having a term to define those cases which may not fulfil all the criteria for a definite case. It was agreed that the term 'possible NOE' might be a more appropriate term to define these cases.

It was agreed that CT is the intial imaging modality of choice, and if normal in the presence of a clinical suspicion of NOE, it would be reasonable proceed to MRI. The need to explore the role of gallium/SPECT/labeled scans was repeatedly raised and agreed that data is needed to inform the role of each of these modalities.

It was agreed that non-response is defined as no reduction in symptoms after two weeks of effective therapy; relapse involves worsening of symptoms or signs following a period of improvement, and a list of features indicating severe NOE had previously met consensus. Relapse, non response and severe infection were difficult to clearly define and for future clarity, will benefit from wider consultation addressing specific questions around timing of diagnosis, role of histology/laboratory markers and imaging modality. It was acknowledged that there is little data to support these definitions other than expert opinion, and that there should be a careful review once the evidence becomes available.

INTEGRATE are currently undertaking a Delphi process to establish a case definition for otitis externa. It was acknowledged that this process, once completed should link to and inform the Delphi process for NOE so that the definitions from these two processes will reflect the continuum of disease.

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It was agreed that a definite case of NOE has a history of otalgia and otorrhoea with evidence of unequivocal bone erosion on CT. It was agreed that this condition is most likely in an elderly frail, diabetic or otherwise immunocompromised person.
It was agreed that a MDT approach including ENT, radiology and infection specialists should be promoted.

Conclusion

The aims for the day were ambitious and although clear definitions of all conditions were not agreed, important progress was made. Consensus definitions were reviewed and supported and the direction of the next round of the Delphi process was agreed. Important decisions were made regarding design of the planned, national prospective study. Perhaps most importantly, the network was strengthened with great enthusiasm and clear commitment to support future work.

Next steps

The definitions agreed at this meeting will be circulated in another round in the Delphi process to the UK NOE Collaborative email group. Once consensus is reached, the agreed definitions will be circulated more widely through the supporting organisations including BIA, BSO, ENT UK and BSAC for wider consultation before these are finally agreed. Members will be invited to participate as contributing sites in the planned prospective national study of the epidemiology, risk factors, management and outcomes.

Monique Andersson
On behalf of UK NOE Collaborative

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Delphi Round 4

Dear Colleagues,

Thank you for your contribution to this NOE Delphi process. We apologise for the major delay in the process, which was somewhat unavoidable. We are now entering Round 4, having had two electronic rounds of questions and one face to face meeting.

In this current round there is only one section, with a total of 5 questions with opportunity for comment. There may appear to be repetition from previous rounds. This is to ensure that we have consensus. Should consensus be reached on all definitions the next step will be that the agreed definitions will be circulated to a wider group including all the organisation stakeholders including BSO, ENT UK, BIA and BSAC for consideration and comment. If there are other organisations who you think should be involved please let us know. If we do not reach consensus we will need to engage in another round of questions.

We have used a number of terms in the definitions that themselves need defining. As was discussed at the Oxford meeting knowing how we are using certain words is critical to agreeing or disagreeing with the proposed definitions. *Please be aware of these definitions as you reply to the questionnaire. They can be viewed here or by following the link at the top of each page.*

Thank you again for your contribution.

Kind regards,

Monique Andersson, Consultant in Infection Oxford

Martin Williams, Consultant in Infection Bristol

Pablo Martinez-Devesa, Consultant ENT Surgeon Oxford

Emma Stapleton, Consultant ENT Surgeon Manchester

Pieter Pretorius, Consultant Neuroradiologist Oxford

DEFINITIONS

It was clear from Round 3 that having a clear understanding of terms used in definition is important. Please find below the key definitions used in this document.

Otorrhoea – discharge from the EAC. This may be a symptom or a sign.

Otalgia – pain originating in the ear.
Note a patient may not always complain of pain (eg. in severe dementia) but there are signs suggestive of severe pain (eg. irritability, groaning, holding ear and others). It is acknowledged that in very rare cases eg. in diabetics with severe neuropathy this symptom may be absent.

Granulation tissue - specialised tissue that is formed during the process of healing. It comprises a proliferation of fibroblasts and vascular endothelial cells (angiogenesis), which impart a soft, granular, reddish appearance to the wound and hence the term "granulation". Histologically, it is seen as a proliferation of small capillaries set in oedematous, loose fibroblastic stroma that contains a variable number of acute and/or chronic inflammatory cells.

Inflammation in EAC – presence of erythema and oedema in the EAC.

CT – Non-contrast enhanced, high-resolution acquisition with 1 or less mm slice thickness bone and soft tissue algorithm reconstructions. If intracranial complications are suspected and MRI not availible, contrast enhanced CT can be performed.

MRI- High resolution axial and coronal T1 weighted images as well as T2 and/or STIR images + DWI. This is can be performed without gadolinium but a gadolinium enhanced scan with fat-saturated post-gadolinium T1-weighted images should be considered in patients with an eGFR > 30 , particularly if intracranial complications are suspected or if the differential diagnosis includes malignancy.

Possible NOE – this is a diagnosis made on presenting clinical features and is an indication to proceed to imaging to enable a definite diagnosis of NOE. This definition answers the question; 'who should progress to intial imaging?'

Severe NOE – the reason for defining this as a separate entity is because it may impact duration of therapy and there may be indication for deep sampling or operative intervention. Unless it is defined we will not know how to manage it or whether it needs to be managed differently to NOE which is not considered severe.

Histology – sampling of the external ear canal, showing features of inflammation. The key outcome of investigation is to exclude malignancy and other differential diagnoses eg. cholesteatoma, keratosis obturans, langerhans cell histiocytosis.

Immunocompromise – this refers to any state which may compromise an individal's immune system. It may be the result of frailty/HIV/malignancy/ diabetes/biological drug therapy/others.

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Frailty – a condition or syndrome which results from a multi-system reduction in reserve capacity to the extent that a number of physiological systems are close to, or past, the threshold of symptomatic clinical failure. As a consequence the frail person is at increased risk of disability and death from minor external stresses[1]

Optimisation of immune state – where possible interventions should be put in place to improve immune function eg. improving diabetic control, reducing/stopping immunosuppression, improving compliance with ARVs.

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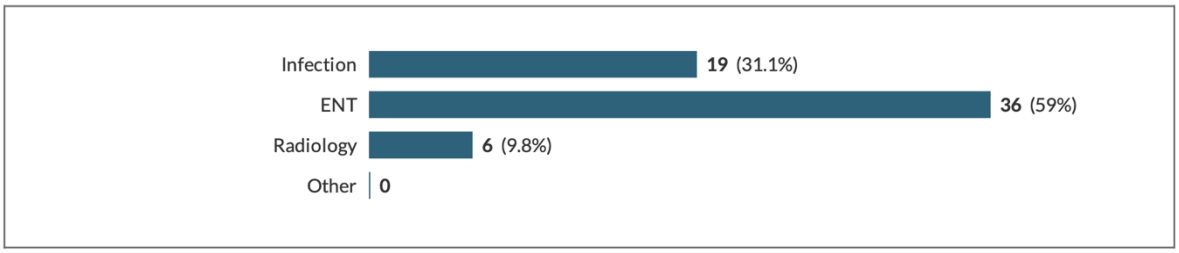
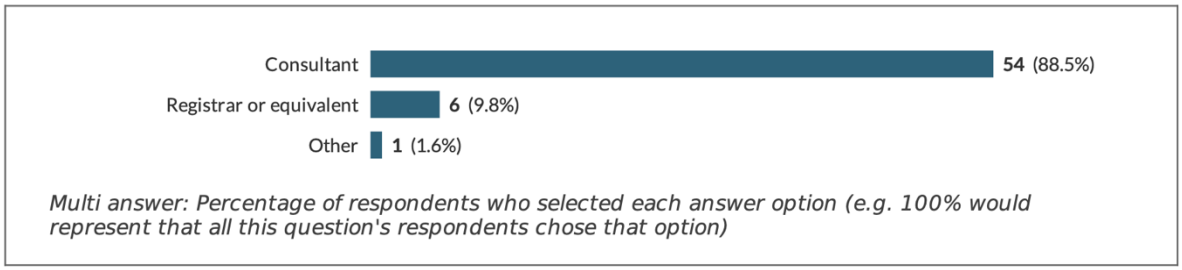
[1] https://www.bgs.org.uk/sites/default/files/content/resources/files/2018-05-23/fff_full.pdf

DELPHI ROUND 4 – RESULTS
NOVEMBER 2020
Response Rate: 76% (61/80)

Specialty



Grade



Multi answer: Percentage of respondents who selected each answer option (e.g. 100% would represent that all this question's respondents chose that option)

If you selected Other, please specify:

Showing 1 response	
Senior Otology and Implant Fellow	662153-662144-67468810

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The following definitions have already received consensus:

I. Defining a true case of Necrotising Otitis Externa (NOE)

NOE is an invasive infection of the external ear canal which has the following characteristics:

- Otalgia and otorrhoea OR otalgia and a history of otorrhoea

AND

- Granulation OR inflammation of the external auditory canal

AND

- CT imaging findings of bony erosion of the external auditory canal, together with soft tissue inflammation of the external auditory canal

AND

-is confirmed by exclusion of malignancy on histology

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Comments:

Showing all 33 responses Show less
I agree apart from the final one. If there is no granulation tissue, no biopsy will be taken. Generalised swollen ear canal would not be biopsied but would be NOE so I think this needs to at least have a qualifying footnote to say (if granulation tissue/polyp present)
I would say that you don't just have to have bone erosion, you need soft tissue invovlement beyond the external auditory canal (TMJ/skull base)
Entirely agree
Agreed
Should 'a history of otorrhoea' be defined as 'a recent history'? (If so, then we need to define 'recent', but this could be reasonably broad/vague). I think the imaging should be defined as CT or MRI - if the patient happens to have had MRI as first line (without a CT) they shouldn't be excluded from the case definition.
'is confirmed by exclusion of malignancy on histology' in practice is aspirational. Our ENT surgeons very rarely send histology samples
Agree
We have seen a few cases of little or no pain, but with clear bony destruction of EAC bone. We are not certain why these are painless. Diabetic neuropathy has been suggested.
'confirmed by exclusion of malignancy on histology' although correct in my experience occurs <50% time.
Not all cases have samples sent for histology. Whilst it is preferable to have malignancy excluded if possible, I don't think this is a requisite for making a diagnosis fo NOE.
in our institute 40% CT false negative in early NOE. MRI with contrast far more sensitive and specific
Agree
Bony erosion may not be evident on CT in early cases so this needs to be highlighted
I think this is good that we have opted for a gold standard definition albeit in practice histology is rarely performed in my experience
not all cases can get a biopsy
The last point suggests that ALL patients must be biopsied and also raises the question as to where to biopsy from as the superficial inflammatory appearances may mask a deeper seated neoplasm. I am not sure biopsy is mandatory in all cases?
Agree with above definition.
Agree
Agree
Imaging - if CT normal but MR shows inflammation of marrow I would still deem that to be a true case.
Does a biopsy HAVE to be done to call it a true case. If so I am going to struggle to include the majority of our cases!
Seems reasonable, but where does this leave the patient with a persistent area of exposed bone in the floor of the external ear canal, but no bone erosion confirmed by CT. Can we say 'ideally CT imaging findings of bony erosion'?
Severe intractable pain not responding to topical treatment, not just otalgia, is a key symptom. Sometimes there is just soft tissue involvement on MRI without bony erosion on CT. it may be better to make this AND/OR. The presence of diabetes or immunocompromisr is not pathognomic but if present certainly makes NOE much more likely.
We have a problem of cases where the patient presents with complications of NOE eg. cranial nerve palsy but does not have bony erosion of the temporal bone. How should these cases be classified?
Very reasonable
agreed
Agree
Does it have to have bone erosion. What if there is extensive inflammatory soft tissue change and marrow signal change on MR?
yes
"true case" or confirmed case?
Patients will often present with a normal ear canal, local infection there having resolved as it spread medially
Tissue biopsy for histology is not commonly done in my centre, rather only done if poor response to antibiotic or relapse. It isn't always easy to do a biopsy.
Agree, but CT finding can be subtle in terms of bone erosion, in which case if clinically NOE, treat as such if CT equivocal / soft tissue only

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II. Defining a case of severe NOE

A case of NOE may be classified as 'severe' if any of the following are present;

- Facial nerve palsy 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;
    - CT showing bone erosion in other skull base locations in addition to the external ear canal wall, e.g: around stylomastiod foramen, clivus, petrous apex.
    - MRI showing bone marrow oedema extending to central skull-base.
    - CT or MRI showing extensive soft tissue phlegmon below the skull base.
- Intracranial spread of the disease (dural thickening, extradural or subdural empyema, cerebral/cerebellar abscess)

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Comments:

Showing all 25 responses Show less
agree
Entirely agree
Agreed
I agree with these as severe local/anatomical features. I am not certain, but wanted to raise whether any systemic features should be considered (new onset delerium, renal impairment etc, without another cause). On balance, these are probably 'complex' rather than 'severe' disease, and therefore are reasonably left out?
happy with this
Something about unresponsive cases (culture -ve cases) would be helpful here
Agree
Agree
Happy with this
Agree
about right
Agreed
Agree with above definition.
Agree
What about to TMJ - seen several cases of this
Agreed
It isn't just erosion of bone marrow. I would just say bone and leave out the marrow. It's inflammation that is seen on the MRI and not necessarily oedema. Not sure I like the term phlegmon. It's a bit 18th century. Perhaps better to say extensive soft tissue involvement of the skull base. Other complications such as Gradenigo's would also be classified as severe. Similarly one occasionally sees abscess formation within the skull base.
as per the comment above - only a definite cases of NOE can have severe NOE
Instead of 'severe NOE' perhaps it should be call 'complicated NOE' people use the term 'Severe' to describe anything that is painful. A change in nomenclature will prevent clinicians using the term 'severe' as descriptor of symptoms, when in NOE (as is currently proposed) it is used as a descriptor clinical and radiological signs
agreed
Agree
yes
fair enough
Agree!
agree

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III. CT scan is the first choice of imaging modality for a suspected case of NOE

Comments:

Showing all 26 responses Show less
happy with this but feel that MRI should be completed as it picks up the odd cases (recently had an inflammatory condition and have exclude malignancy). plus I also feel it is more useful for follow up.
Entirely agree
yes
yes
happy with this
Agree
Agree
Agree
No if I had a choice it would be post contrast MRI but this is not always possible due to availability (rare today) metal foreign bodies, implants and claustrophobia. CT/PET may then need to be considered
This was extensively discussed at the Oxford meeting but if we have agreed from the experienced radiologists that this is the case can we make it more specific ie. a FLAIR SEQUENCE WITH CONTRAST. For example
Agreed
Agree with CT as first choice of imaging because not all units have access to MRI.
Agree
Yes
Yes
Definitely not. It is very important to do both CT and MRI.
I'm becoming less convinced about this as I see more and more cases. CT is the most easily accessible imaging modality but MR is better, both for diagnosis abs as a baseline for monitoring.
CT is the first choice imaging modality while an MRI is also done at the same time to assess soft tissue invovement
Not controversial
agreed
Yes
I wouldn't be too didactic, CT and MR are both good tests for NOE, MR is more sensitive to soft tissue and marrow changes.
yes
Changes often more obvious on MRI once disease has spread medially - I would not specify modality
Agree
agree

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IV. Defining a case of 'possible'[1] NOE

Possible[1] NOE is a severe infection of the external ear canal which has 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

- immunodeficiency
- night pain
- raised inflammatory markers (ESR/CRP) in absence of other plausible cause

failure to respond to >2 weeks of topical anti-infectives and aural care

---

[1] See definition section

eview only

Comments:

Showing all 28 responses Show less
agree
Entirely agree
This is a good definition
yes - is there a need to specify how immunodeficiency is defined? important to make sure this term is regarded broadly enough to include diabetes. Does being very old and frail with co-morbid problems count as being 'immunodeficient'? (for the purposes of this definition, I would say yes).
happy with this
failure to respond is divisive as might be used as easy get out clause. Nominally this includes all diabetics with otitis which is quite a big patient group and a definition like this may open the floodgates for referrals.
agree
This very similar to the Friedmann and Cohen obligatory and possible criteria of definite NOE. I think if the and was changed to or for the last 4 criteria (immunodeficiency, night pain, raised markers and failure to adequate treatment) would be more non-specific. As it stands its very specific
Agree
This is a very clinical definition which for possible is appropriate. Are we able to define the population better. Does this ever present like this is under 18 year olds or even in young adults. I feel it may not
seems ok
An alternative term could be 'severe OE'
Agree with above definition.
Agree
Agree
So essentially "possible" becomes anyone without imaging and "true" becomes only those ones who get a biopsy? I am not sure this quite works, for us the true would be the top criteria but without mandating it is CT, occasionally might jsut have had MR and often no biopsy.
Seems reasonable. Do we need a category of 'Probable NOE'?
A lot of the criteria for possible NOE are not in the definition of true NOE. That doesn't seem logical (see comments above re: immunosupression and intractable, non-responding pain)
is the failure to respond part of the any features? I think it should be definitely in the definition as this moves it from severe OE to possible NOE
Possible is the same as definite according to previous Delphi rounds.
NICE definition of Acute Otits externa is below 3 weeks. Any failure to respond after 3 weeks of treatment should be investigated for NOE
not controversial
agreed
ok
What about not responding to appropriate and or repeated courses of oral abx
fair enough
"Immunodeficiency including diabetes mellitus"
agree

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V. Defining a NOE case of non-response to therapy

A case of NOE is defined as non-reponsive 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

Comments:

Showing all 24 responses Show less
agree
Entirely agree
OK
Does 'anti-infective therapy' need to be further defined? eg does topical therapy count? oral amox for 2 weeks meets the case definition stated above, but most of us wouldn't be surprised if not much response in a classic NOE case. Should the definition say something more specific, e.g. 'appropriate systemic (oral or IV)' anti-infective therapy?
agreed
I would suggest a longer time period of 4 weeks.
Agree
Fine
Agree
I think this is fair
consider in absence of immunosuppression /diabetes - if the purpose of this definition is to alter antibiotic therapy without culture results
Agreed
Agree with above definition.
Agree
Should we state what anti infective treatment ie systemic? Cipro flocs in orally or taxocin
yes
It would need at least a month of appropriate treatment before a case of NOE is classed as non-responsive to therapy. Once NOE is diagnosed the minimum period of therapy we use is 6 weeks.
perhaps define 'improvement'. (using a visual analalogue scale?)You may not expect a resolution in pain. ottorrhoea or granulation in this period
agreed
yes
Effective and optimised antimicrobial therapy?
should it be specified whether the anti-infective therapy is systemic?
Agree.
agree

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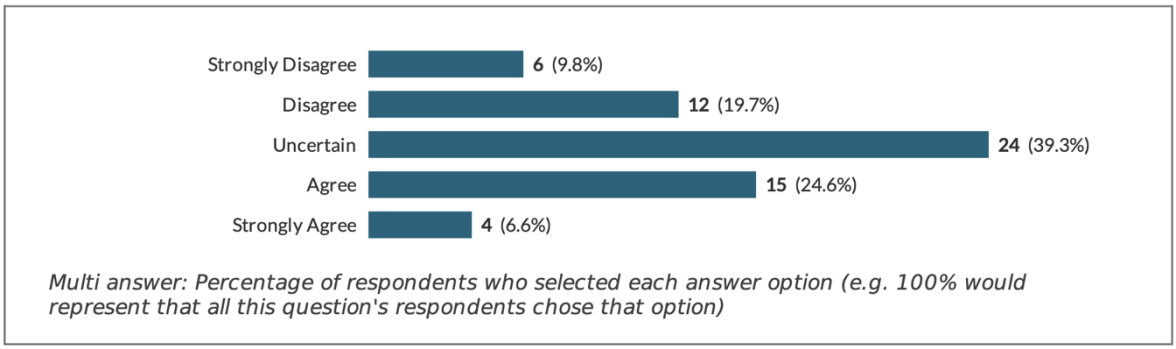
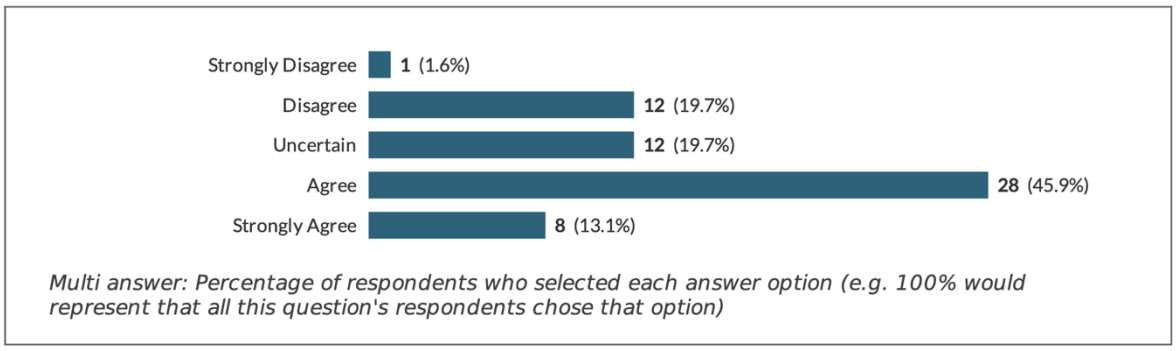
The following definitions have not yet reached consensus

I. Defining a case of relapsed NOE

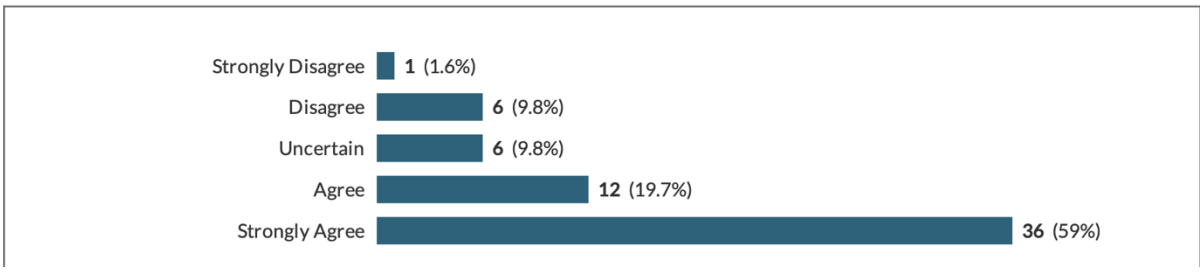
A case of NOE is considered to be treated and cured if a patient has no pain nor otorrhoea for a minimum period of *1 month* after completing antibiotic therapy



A case of NOE is considered to be treated and cured if a patient has no pain nor otorrhoea for a minimum period of *2 months* after completing antibiotic therapy



A case of NOE is considered to be treated and cured if a patient has no pain nor otorrhoea for a minimum period of *3 months* after completing antibiotic therapy



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Comments:

Showing all 25 responses Show less
have seen cases of relapse follwoing a period of up to 6 months where they were reportedly asymptomatic. I think higher chance of this occuring in elderly immunocompromised individuals
None
It is difficult to give a time frame as all cases are different.
I routinely get follow up scans to check changes/inflammation not worsening
I am not involved in the treatment of patients with NOE
Treatment failure is defined after 14 days of therapy - 1 month is probably too soon, whereas 3 months would give more confidence that relapse is unlikley. Is it worth defining early and late relapse (e.g. <1 month and > 3 months) as the cause of relapse may be different - early may indicate inadequate duration of treatment whereas late relapse may indicate the evolution of resistance or persisting nidus?
Defining cure on basis of pain/otorrhoea resolution alone is concerning as most of us will have seen late relapses. Imaging would be an additional factor.
If CRP changes were evident during the active infection, this can be another useful marker or resolution (ie remains low).
3 months
Do we have any good data on mean time to relapse.
The highest incidence of recurrence is in the first 4 weeks but there is a steady tail off thereafter. 1 month is too short to claim a cure
I guess this depends on at what stage you complete antibiotics. I usually treat for an additional 2-3 months once the EAC skin is normal.
Relying on pain as a marker for cure can be dangerous as with recurrence of pain, patients can develop cranial neuropathy
Deep seated bacterial infections can take time to represent such as in dis it is and pji this may be indolent and take time to present
For me, 6 weeks would be the cutting point to consider it treated and cured.
would a repeat imaging have any role for the above if compared with baseline scans
I think the term cured requires a longer period of time of being symptom free and so I have chosen 3 months. It also takes time for MRI findings to show improvement.
Most relapses occur within a few weeks to a month of stopping antibiotic. Most recurrences of infection occur within 3 months and can often be predicted by the underling comorbidities and/or anatomical defects of the patient concerned.
Depends how long the course of antibiotics is. If it is at least 6 weeks then I opt for 2 months. If shorter then 3 months
For me, the minimum cut off would be 6 weeks.
Like that it is clinical"cure" not radiological but time post treatment is trickier- i think 2 months feels long enough to wait but not 3 months...
Normalised inflammatory markers and lack of progression on the MRI are also critical indicators of cure
I would rely on MRI imaging too
Again I'd say appropriate and dose optimised antimicrobial therapy. I'd change all antibiotic to antimicrobial
Difficult, I haven't seen many relapsed cases to have a feel, I recall two who I think relapsed fairly quickly.

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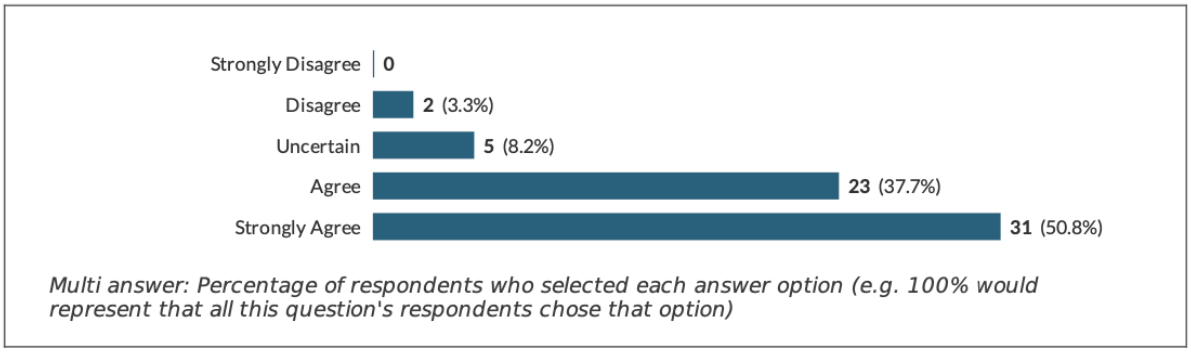
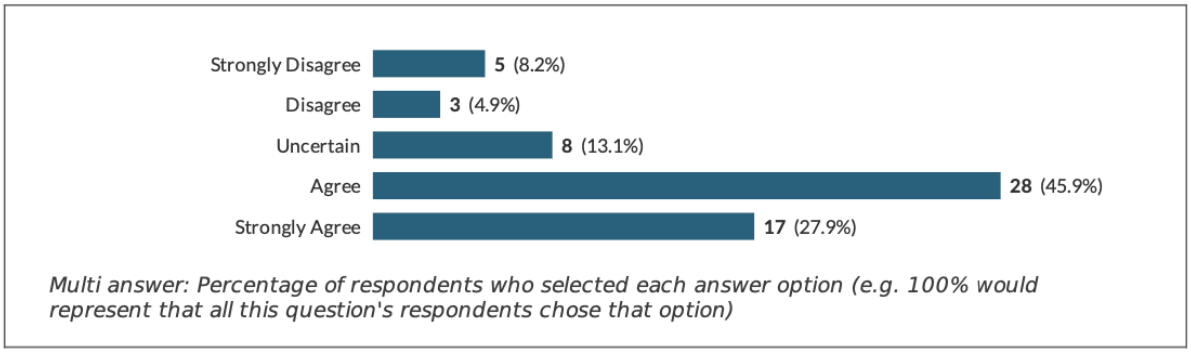
II. Imaging in NOE

If the original CT scan does not show any bony changes, then if clinical suspicion is high MRI scan is indicated



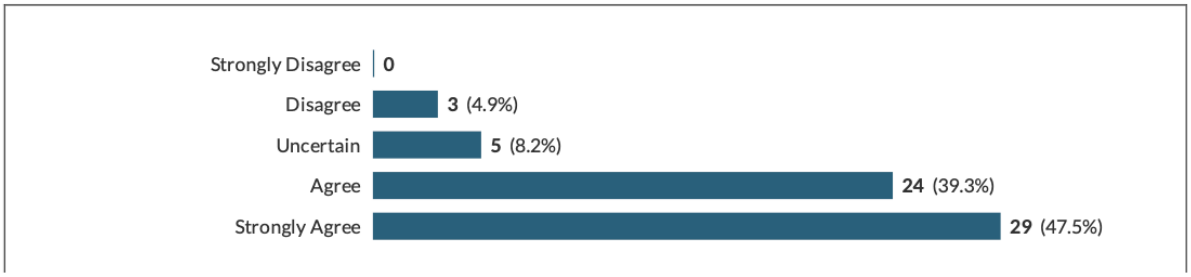
Multi answer: Percentage of respondents who selected each answer option (e.g. 100% would represent that all this question's respondents chose that option)

If there is suspicion of relapse of NOE a repeat CT scan is indicated



Multi answer: Percentage of respondents who selected each answer option (e.g. 100% would represent that all this question's respondents chose that option)

If there is suspicion of relapse of NOE and the repeat CT scan does not show any bony changes, then MRI scan is indicated



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Comments:

Showing all 21 responses Show less
personally I feel that MRI's are better are looking at changes over time including relapse as it is often the soft tissue invovlement extent that changes. Only severe case tend to get further bone destruction.
I am unclear about the utility of MRI for diagnosing relapse as the bony oedema may persist for weeks/months (?) and a repeat MRI scan may only be helpful if the patients have interval MRI imaging and at the end of therapy. This would have a resource implication, and potentially drive further treatment as the MRI changes are likely to lag behind CT and clinical parameters
Unlikely to be no bony changes in a true relapse case as that was part of the criteria for original NOE diagnosis.
CT changes typically occur several weeks after the osteitis. Can therefore be late signs. CT is rarely performed AFTER resolution of NOE, therefore we have no baseline scan for comparison. Comparing to the initial diagnostic CT does not tell us when these changes occur. Gallium scan is a more time sensitive imaging modality.
MR is sufficient if there was a previous CT (from first diagnosis)
often more time efficient to repeat both CT and MRI as only one may not give the answer
bony changes can remain so for beyond a year therefore CT may be difficult to interpret. More work needs to be done with PET/CT for the above
they all should have basline MRI scans and in case of suspicion of relapse, MRI should be performed rather than CT and compared to the original MRI. MRI is much more sensitive to detect changes compared to CT
I think a pet ct would be better as further bony change is likely to be seen even when healing if the relapse is close to the initial event. A ct one year later would be acceptable but not two months after disease
I do not feel a second CT is required. MRI is better at tracking flare-ups.
The imaging modalities CT and MRI identify different tissue involvement. CT will pick up bone erosion. MRI will pick up soft tissue involvement. Bacterial infection and fungal infection also behave differently with fungal infection being more frequently associated with extension of infection into the skull base i.e. skull base osteomyelitis.
If the original CT scan does not show bony changes, I would only consider MRI if the clinical suspicion was dubious and was considering other differentials. If there was a high clinical suspicion such as CN VII palsy and granulation/otorrhea in a diabetic then I'd treat as NOE without MRI.
after discussion with consultant radiologist. You could have a scenario where the CT settings were not perfect for the purpose of the scan
CT is a poor means of monitoring NOE. Contrast enhanced T1 MRI is the gold standard
Relapse is a clinical diagnosis, there will not have been time for radiological changes to subside to make a diagnosis on imaging.
I would tend to use MRI 1st line looking for relapses
We do an MRI scan as routine on all proven or suspicious cases of NOE.
CT should be the first port of call for suspected recurrent NOE, even if the original CT was normal. Advantages due to speed, availability and difficulty of optimising and interpreting subtle cases on MRI, especially in non-specialist centres.
We use MRI for monitoring reponse to treatment/relapse
MR and Ct are complementary - MR changes are long-lived and may not reassure despite clinical improvement, CT may be less sensitive! MDM discussion would be great if it can be funded/supported
I think this neglects the very useful role on Nuclear medicine imaging (Gallium/technetium scan

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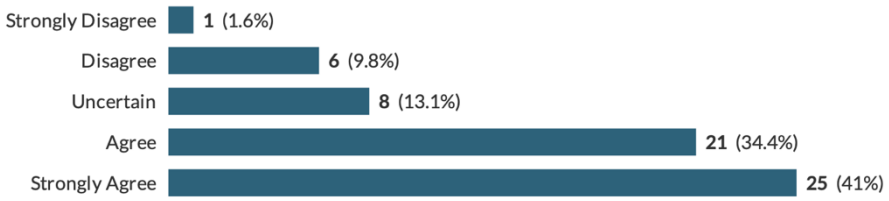
III. MDT

Cases of definite and possible NOE should be discussed in a MDT forum ideally involving ENT, infection and radiology



Multi answer: Percentage of respondents who selected each answer option (e.g. 100% would represent that all this question's respondents chose that option)

Any further comments?

Showing all 32 responses Show less
I think this is the ideal to aim for but it is difficult with such small numbers and fluctuations in numbers across the year.
May not need to be a formal MDT meeting but rather one that involves all disciplines by email or virtually
In an ideal world (well resourced) then strongly agree. Is this a UK approach, or intended to be applicable in other settings? for a global audience, this would not be possible and perhaps should be an aspiration rather than essential.
Only complex / recurring cases
There are resource issues to address but this would be a desirable practice.
Difficult to convene as cases are relatively sporadic even in large centres. A monthly/bimonthly meeting might be worthwhile (case numbers wise) but is too infrequent to inform management plan of case seen the next day.
These teams should agree protocols and work together, but a formal MDT is not required. We do not have ID on site in our unit.
So much resources. difficult to justify efficiency.
Ideally but unclear if resources to support this. Is there a role for a national MDT for difficult cases as for TB and fungal infections?
MDT working while ideal should not be mandated as it is impractical for a low volume condition and in the majority of simple cases not required.
This is a complex pathology therefore it needs an MDT approach particularly as there is the emergence of microbial resistance and multiple problems with therapy - rash, deranged LFT, neutropaenia as well as the ongoing debate about imaging to diagnose and monitor treatment response
In an ideal world - but this does not happen here
MDt may also be needed for potential ambulatory management of these cohort of patients using continue infusion devices for administering antibiotics

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The MDT approach brings early care from relevant specialties to the patient thus improving outcome.
If this is feasible depending on the size of the unit and availability of specialists.
I agree in theory that this would be ideal. Practically, with relatively low numbers annually (albeit anecdotally rising), I'm not sure there would be enough cases to justify a formal MDT. I would STRONGLY agree with a national cross-specialty protocol, however.
I have a number of patients who are treated with a good pathway however if there are issues then I discuss at teleconference with skull base surgeons
You may not have a microbiologist attending, but still useful to discuss
I don't think microbiology have to be in the MDT but should certainly be involved in the decision making. Radiology and ENT are mandatory. Some centres may also mange these patients through infectious diseases
Concept is good but will need to think about how this is funded
Definite and possible NOE are the same thing according to previous Delphi rounds! Not all centres have access to an MDT.
Not necessarily a formal meeting though.
If there is a standard pathway for management, only the unresponsive ones need to be discussed.
A discussion should occur but is there a requirement for all cases of NOE to be discussed in a formal MDT???
If support/funding available though.
may not be possible in all cases
MDT can happen virtually or via e mail discussions
I'd suggest they also need to include infection pharmacy / antimicrobial pharmacy particularly around the dose optimisation angle
likely to involve discussion on a case by case basis rather than a regular MDT
MDT is advisable for any uncommon and potentially serious condition in principle.
Utilise each specialty, but a formal MDT is not essential. I would be concerned if the outcome said it can only be managed by MDT
we have done this by joining up a series of two way conversations in the past. virtual platforms it will facilitate mdts within and between centres

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NOE DELPHI ROUND 5

Setting the Foundations

Thank you so much for your Round 4 replies and very helpful comments. The response rate was 75% (61/81), with 59% of these replies from ENT, 31% from Infection and 10% from Radiology specialists.

We have consensus (>70% respondents agreeing or strongly agreeing) for all of the statements included in the Round 4 questionnaire. However, some very useful points were raised, which will help to improve these definitions and their utility moving forward. For this reason, we have modified the definitions and would like to re-confirm consensus before they are finalised. Once we have your agreement, we will circulate a manuscript which will form the basis of a proposal for adoption by ENT, Infection and Radiology bodies in the UK.

When considering these definitions, we would like to emphasise the following aims:

1. They can be implemented in all centres across the UK, from a small DGH to a tertiary referral centre.
2. They aim to be highly specific (i.e. describe a typical 'definite' case of NOE and minimise the chances of misclassifying another condition), but do not necessarily describe **all** potential presentations of NOE.
3. They are for guidance only and are not prescriptive in terms of practice.
4. They allow standardised description of cases which will facilitate recruitment to clinical trials and comparison of cases across different cohorts.
5. This is the start of an iterative process. The lack of quality data is making it difficult to propose clear recommendations for some definitions. As more information becomes available these definitions will be revisited and revised.

We have been using a Delphi method in order to achieve these aims. A Delphi method is a group of facilitation techniques which employs an iterative multistage process, designed to transform opinion into a group consensus. It is a flexible approach which was developed in order to systematically synthesise expert opinion. Currently there are no universally accepted criteria for using this technique, but it has the following features: anonymity, iteration with controlled feedback from one round to the next, aggregation of group responses and expert input until consensus has been achieved.

We have highlighted the changes to the definitions from Round 4 in red. Where necessary, a brief explanation of the change(s) is given. We have included 4 questions in the same format as previously.

Thank you again for your contribution.

Monique Andersson	Pablo Martinez-Devesa	Martin Williams	Emma Stapleton	Pieter Pretorius
Infection	ENT Surgeon	Infection	ENT Surgeon	Neuroradiologist
Oxford	Oxford	Bristol	Manchester	Oxford

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I. DEFINITE CASE OF NECROTSING OTITIS EXTERNA (NOE)

Discussion following Round 4:

i) Imaging: Some respondents highlighted that radiological changes suggestive of NOE may be detected by CT and/or MRI and that some centres use both modalities in the early investigation of these cases. For this reason, both modalities will be included in the definition of a definite case of NOE. There is a caveat however, namely that MRI is essentially a more sensitive modality than CT to detect early changes which might be ascribed to this diagnosis. Changes like bone marrow oedema of the temporal bone or other features may be visible on MRI when bony erosion is not yet discernible on CT. Further studies are planned to understand what changes are associated with NOE on MRI, how this compares with findings on CT and whether this difference impacts the management and outcome of NOE. We are proposing a pragmatic approach to dealing with this discrepancy until we have more data.

ii) Histology: Many respondents commented that samples are not routinely sent for histological analysis and so histology excluding malignancy should not be required to make the diagnosis of a definite case of NOE.

QUESTION 1.

A definite case of NOE is an invasive infection of the external ear canal which has the following characteristics:

- Otalgia and otorrhoea OR otalgia and a history of otorrhoea

AND

- Granulation OR inflammation of the external auditory canal

AND

- Histological exclusion of malignancy in cases where this is suspected

AND

- Radiological features consistent with NOE

(This refers to EITHER CT imaging findings of bony erosion of the external auditory canal, together with soft tissue inflammation of the external auditory canal **OR** MRI with changes consistent with NOE, for example bone marrow oedema of the temporal bone with soft tissue inflammation of the external auditory canal).

Strongly disagree Disagree Uncertain Agree Strongly Agree

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Comment: _____

II. DEFINING SEVERE NOE

Discussion following Round 4:

i) **Nomenclature: Some participants commented that the term 'severe' used in medicine is commonly used to describe severity of symptoms rather than complexity of disease. Indeed patients with severe NOE e.g. cranial nerve palsy may have mild pain. The term 'severe' has therefore been changed to 'complex'**

ii) **Anatomical spread: Temporomandibular joint (TMJ) involvement is commonly seen in complex disease and has been added to the common sites of disease extension from the EAC.**

iii) **The term 'phlegmon' has been changed to 'soft tissue oedema or inflammation or fluid collection'**

QUESTION 2.

A case of NOE may be classified as 'complex' if any of the following are present:

- Facial nerve palsy 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;
  - CT showing bone erosion in other skull base locations in addition to the external ear canal wall, e.g: around stylomastoid foramen, clivus, petrous apex, temporomandibular joint.
  - MRI showing bone marrow oedema extending to central skull-base.
  - CT or MRI showing extensive soft tissue oedema or inflammation or fluid collection below the skull base.
- Intracranial spread of the disease (dural thickening, extradural or subdural empyema, cerebral/cerebellar abscess)

Strongly disagree Disagree Uncertain Agree Strongly Agree

Comment: _____

III. DEFINING 'POSSIBLE NOE'

Discussion following Round 4:

i) **'Possible NOE' describes a case that does not meet the criteria for a definite case of NOE, but where a high degree of clinical suspicion exists. Having this category was strongly supported at Round 3. These cases may represent atypical presentations or**

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may represent severe OE/early NOE. A number of participants suggested that the definition of possible NOE should include reference to the absence of radiological changes typical of a definite case of NOE, since this is a key part of the investigation of these cases.

QUESTION 3.

Possible NOE is a severe infection of the external ear canal which does not show bony erosion of the external auditory canal on CT scan OR does not show changes consistent with NOE on MRI if this is performed (for example bone marrow oedema of the temporal bone) AND which has 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

- immunodeficiency
- night pain
- raised inflammatory markers (ESR/CRP) in absence of other plausible cause
- failure to respond to >2 weeks of topical anti-infectives and aural care

Strongly disagree Disagree Uncertain Agree Strongly Agree

Comment_____

IV. **DEFINING 'RELAPSED NOE'**

Consensus was reached in Round 4 that a case of NOE is considered treated and cured if a patient has no pain nor otorrhoea for a minimum period of 3 months after completing antibiotic therapy.

Relapse is recurrence of disease after the patient has been treated and cured i.e. at least three months after stopping antibiotic therapy.

Discussion following Round 4:

i) Symptoms: Whilst relapse may present with EAC symptoms, patients may also present with no EAC signs or symptoms, but with progression of base of skull osteomyelitis or other deep-seated complications. The definition of relapse has therefore been modified to reflect this.

ii) Follow up Scanning: It was noted that the definition of relapse included the need for progression of radiological changes after demonstration of radiological improvement. Since it is not routine for many centres to perform follow-up imaging

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after resolution, the definition includes the terms 'unchanged or progression'.

iii) **Modality: Centres differ in their choice of modality to investigate relapse and so the definition now includes changes on CT and/or MRI.**

QUESTION 4.

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.

Strongly disagree Disagree Uncertain Agree Strongly Agree

Comment_____

Any additional final comments about the 'NOE: Setting the foundations' process/any specific issues_____

_____

Thank you for your contribution.

We plan to circulate the first draft of the manuscript detailing the process and outcome of this project in the next 6-8 weeks for your further input.

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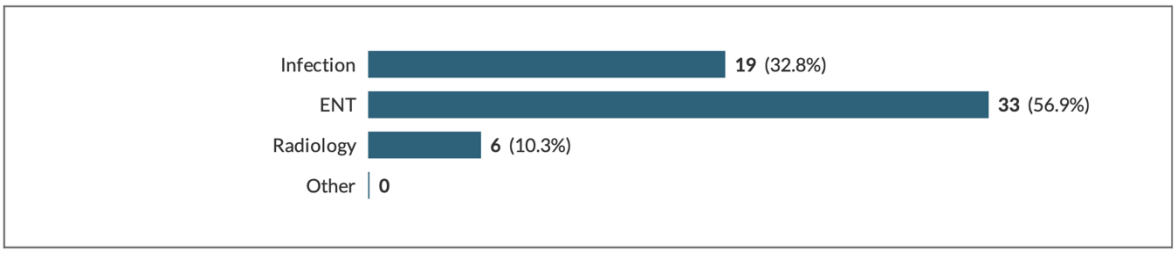
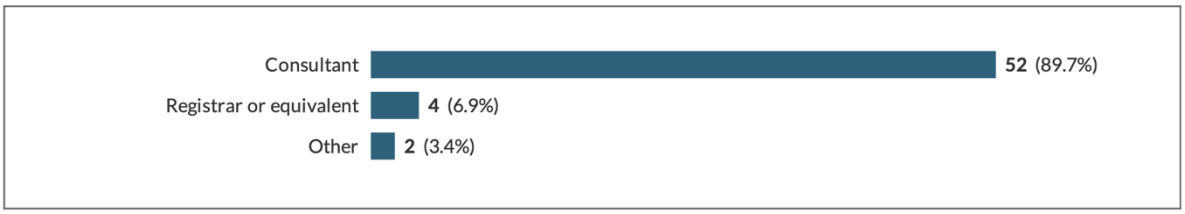
DELPHI ROUND 5 – RESULTS
FEBRUARY 2021
Response Rate: 79% (58/73)

Specialty



Grade



If you selected Other, please specify:

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senior otology fellow	708126-708117-73888958
Specialty Doctor	708126-708117-73952284

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Question 1

A definite case of NOE is an invasive infection of the external ear canal which has the following characteristics:

- Otalgia and otorrhoea OR otalgia and a history of otorrhoea

AND

- Granulation OR inflammation of the external auditory canal

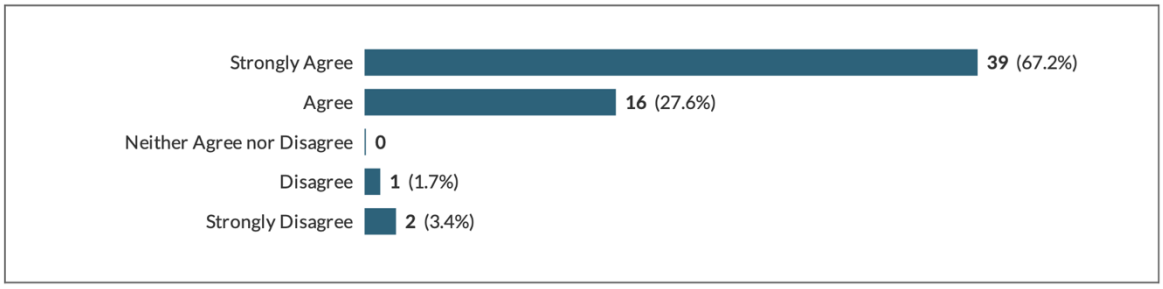
AND

- Histological exclusion of malignancy in cases where this is suspected

AND

- Radiological features consistent with NOE

(This refers to EITHER CT imaging findings of bony erosion of the external auditory canal, together with soft tissue inflammation of the external auditory canal **OR** MRI with changes consistent with NOE, for example bone marrow oedema of the temporal bone with soft tissue inflammation of the external auditory canal).



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This definitely works for me. These are the 4 things that would seal a diagnosis of NOE for me, and more so if patient was diabetic.
CT scans in early NOE can be very misleading due to the lag of bony demineralization. MRI far more helpful in particular BM oedema and oedema around the TMJ and soft tissue of the infratemporal fossa structures therefore should read CT and/or MRI
if granulation/ inflammation is part of the diagnostic criteria why would you not biopsy this?
Until excluded malignancy can cause same symptoms - histological exclusion is the only definitive way of proving it.
Soft tissue oedema of the ear canal is a common finding in just OE. I think perhaps it should say something like: evidence of soft tissue inflammation extending beyond and including the external auditory canal. For me extension into retrocondylar fat is very classic for NOE.
addition of "in cases where this is suspected" makes this a workable CD
I would say that the histological exclusion of malignancy is a must if there is granulation tissue in the canal. As the symptoms and signs of NOE is sufficient to suspect malignancy.
I have found opacity in mastoid cells without gross bony erosion
should we consider having something around presdisposing factors - or do you think that is covered with the "histological exclusion of malignancy". essentially NOE without underlying immunosuppression of some sort is vanishingly rare
There are often no signs in the ear canal at the time of presentation
good.
For both CT and MRI after soft tissue inflammation of the external auditory canal.. Also consider adding ... or adjacent soft tissues outside the EAC (caudal to the lateral and central skull base/TMJ etc.)
Whilst otorrhoea occurs in many cases it is not universal and I don't think this needs to be part of the diagnostic criteria. I think that malignancy needs to be excluded in all cases. It should be suspected in every case. MRI features of NOE aren't just about bone marrow oedema. There is often oedema of the soft tissues around the skull base, especially the masticator space

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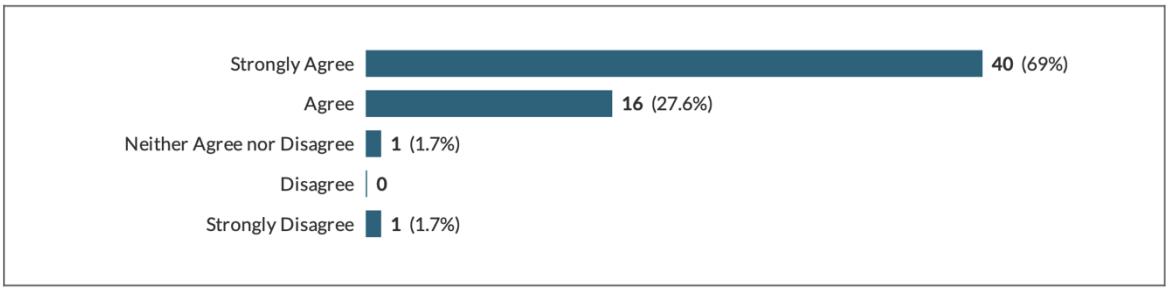
Question 2

A case of NOE may be classified as 'complex' if any of the following are present:

- Facial nerve palsy 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;
    - CT showing bone erosion in other skull base locations in addition to the external ear canal wall, e.g: around stylomastoid foramen, clivus, petrous apex, temporomandibular joint.
    - MRI showing bone marrow oedema extending to central skull-base.
    - CT or MRI showing extensive soft tissue oedema or inflammation or fluid collection below the skull base.
- Intracranial spread of the disease (dural thickening, extradural or subdural empyema, cerebral/cerebellar abscess)



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No issues here. Agreed.
CT or MRI showing extensive soft tissue oedema or inflammation or fluid collection. Its very common in almost all of our NOE to see oedema/inflammation in the soft tissue below the skull base. This is not necessary a poor prognostic indicator or sign of complex disease. I agree totally once disease involves neurovascular structures or crosses the mid-line then it is severe and more complex
I think "extensive soft tissue oedema" is inexact. How do you define "extensive2. I would have thought that soft tissue changes below skull base around the tympanic ring or at the osseocartilagenous junction would be common in 'simple' NOE. What about clarifying by stating that the soft tissue changes have progressed BEYOND the tympanic ring?? I am sure better answered by a neuroradiologist.
I would suggest using the word "Advanced" or "Complicated". The word complex does not necessarily indicate progression of the original disease.
I don't like the term phlegm on at all!
good definition.
I'm not keen on the term 'complex'. Perhaps 'advanced' would be better. With regards to imaging definition of 'advanced' disease, how do you define 'extensive'?
Not sure how 'extensive' soft tissue oedema under the skull base will be defined - would definitely agree re collection though.

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Question 3

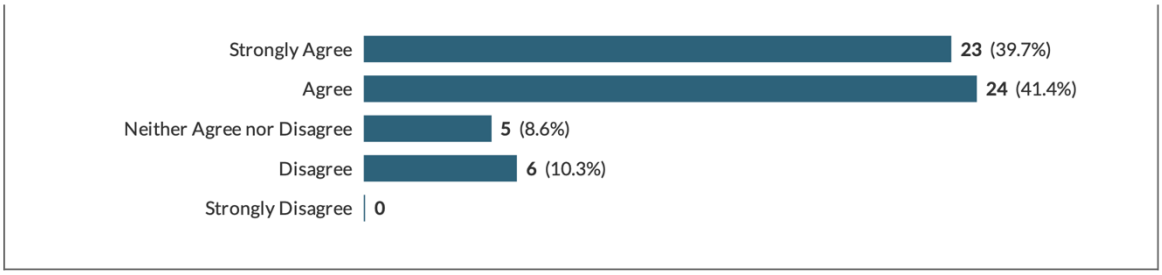
Possible NOE is a severe infection of the external ear canal which does not show bony erosion of the external auditory canal on CT scan OR does not show changes consistent with NOE on MRI if this is performed (for example bone marrow oedema of the temporal bone) AND which has the following characteristics:

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:

- immunodeficiency
- night pain
- raised inflammatory markers (ESR/CRP) in absence of other plausible cause
- failure to respond to >2 weeks of topical anti-infectives and aural care



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is this not severe otitis externa
I agree with this but for some reason not as strongly as with the definite case, though I cannot really add anything to the definition that would strengthen it in my mind. Overall, it is a more than fair definition for a possible case.
NOE is either present or not so it is NOE or severe AOE. AOE left unchecked in the right patient profile is probably a continuum and may lead to NOE. If CT and or MRI shows no extension of inflammation beyond the auditory canal then it is severe AOE not a possible NOE this is too ambiguous and will lead to heterogenicity in future studies
Night pain and raised inflammatory markers could still be an issue in severe otitis externa
I would think MRI would show early changes of NOE so I disagree with this statement.
I would prefer to see this definition in the last section as "AND and 2 or more of the following features" as the definition above with just raised inflammatory markers is not enough in my opinion
I think chronicity or failure to respond should be and AND nont just included in any of the follwoing features
I really think that key population needs to be in this group. Will this definition include that immunodeficiency includes frail or elderly patients. For example simple OE is extremely painful and many younger fit patients present at night with severe pain so I think there needs to be something to reflect this otherwise the definition will not be very 'specific' at all. I think in the 'possible NOE' group it is even more important to ensure this reflects our clinical suspicion that NOE does not occur in the young and healthy.
Note - some also consider this as severe OE and will admit patients for symptom control.
failure to respond to oral cipro and drops as many severe OE's take longer than 2 weeks to settle.
If an MRI scan is performed and does not show any evidence of bone marrow oedema I would not consider it possible NOE since lack of bone marrow oedema on MRI has a higher negative predictive vallue in my view than lack of bone erosion on CT
I would consider if immunodeficiency needs any definition - is is worth specific mention of diabetes? does extreme age/frailty count as 'immunodeficiency'?
immunodeficiency -Clearly that is easy if present but NOE is often seen in those with multiple morbidities (DM, obesity, Heart failure etc etc) and might be worth considering having 'multiple medical morbidities' as a feature

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If a patient has severe Otalgia, Otorrhea, Granulations, Immunodeficient, Night pain, raised ESR and failing to respond to AB for 2 weeks, would the patient still be a possible NOE!!. I think not having the radiological features while fulfilling the rest of the criteria should be an early NOE.
2 weeks is a short time frame to consider a case of OE non-responsive. I would suggest 4-6 weeks.
need histology to rule out other causes in absence on imaging evidence.
good.
If immunodeficiency includes DM
See above re: otorrohoea
night pain is not a feature I have traditionally related specifically to NOE. happy to be outvoted on this point

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Question 4

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

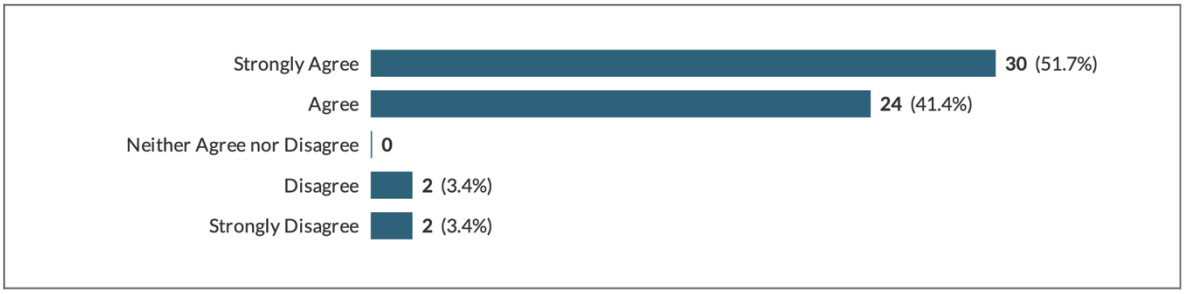
AND

- 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.



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Yes, agreed.
That is fine
I am unclear how the radiological component of 'unchanged' in the definition of recurrence would allow differentiation between a case of O.E. following resolved NOE versus recurrence of NOE. This part of the definition may give rise to an overdiagnosis of recurrent NOE when in fact the patient may have a resolved NOE followed by simple OE.
But you need to define what is "treated" or "cure" before you define relapse- I would define a relapse as one within 6 months of start of first infection and recurrence as reoccurrence of symptoms beyond 6 months.
Some cases will relapse without Ear canal signs (granulations) so stipulating the re-appearance of granulations by using "and" will exclude the most serious cases of relapse, which relapse with CN palsy. Also, most radiological changes of NOE especially the CT ones tend to last for long time and some of them will never re-mineralize or normalise so adding unchanged picture of radiology is not helpful. I would suggest relapse to be recurrence of Otalgia and any of the other 3 (granulations, Progression of Radiology or complications e.g. CN palsy etc...)
CT and MRI findings often remain "unchanged" for many months even in treated cases (although we don't really know the natural history of these changes).
Not so happy with insistence on primary ear symptoms - some of these patients have their ear symptoms cured by initial treatment and this represents skull base disease.
unchanged bone erosion requires a timeframe to be meaningful - even if treated radiological resolution lags by several months
good, includes all relevant considerations.
What's the definition of cure? is it symptoms gone only or does it require change/reversal on radiology?
My only difficulty is the unchanged appearance on CT/MRI
I would remove 'serious and invasive' from the definition of 'relapsed NOE' as all types of NOE are serious and invasive and, if they have been defined as having NOE previously then by definition they must have NOE as the cause of the relapse. I think you need a time scale in the definition of 'relapsed NOE' ie. if they had NOE 10 years ago and they have another episode now that would not be regarded as the same infection. I would say 'within 6 months' of the original infection being regarded as settled. See above re: otorrhoea

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Any additional final comments about the 'NOE: Setting the foundations' process / any specific issues?

Showing all 10 responses
The additions are all valuable and pertinent
see Q3 - I think this is v important so that you dont include lots of patients with simple OE.
These definitions have improved a great deal through this iterative process - well done!
I agree the diagnostic criteria is much tighter with these additions to the definitions.
the definitions nearly make it compulsory to perform both CT and MRI
well done - thank you!
So need a definition of cure! and then define difference between a relapse versus a reoccurrence. well done though nearly there !
Well done, a difficult challenge but we have succeeded in achieving a solid consensus that works in the clinical setting. Thank you, Fiona.
These are good definitions

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