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REVIEW ARTICLE

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The diagnostic conundrum in necrotizing otitis externa

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Abstract

Necrotizing otitis externa (NOE) is an aggressive and fast-evolving infection of the external auditory canal. Late diagnoses and untreated cases can lead to severe, even fatal consequences and so early diagnosis and treatment are paramount. NOE is a notoriously challenging diagnosis to make. It is therefore important to understand what diagnostic modalities are available and how otolaryngologists can use them to accurately treat such an aggressive disease. This review aims to evaluate the different diagnostic options available in NOE and discuss their advantages and limitations, thus, providing an up-to-date picture of the multimodal approach required in the diagnosis of this disease.

KEYWORDS
diagnostic, malignant otitis externa, necrotizing, osteomyelitis, skull base osteomyelitis, temporal bone osteomyelitis

Key points

This study evaluates the current evidence available in diagnosing necrotizing otitis external (NOE). It summarizes the key advantages and disadvantages of the available diagnostic modalities. All diagnostic modalities play a complementary role in diagnosing NOE, tracking its progression, its prognosis, and its resolution. Ultimately a combination of modalities will be required in safely treating NOE.

INTRODUCTION

Necrotizing otitis externa (NOE) is an aggressive and fast-evolving infection of the external auditory canal (EAC).[1] Also known as malignant otitis externa, it can rapidly spread to involve the adjacent soft tissue and lateral skull base and progress to skull base osteomyelitis, intracranial complications, and death.[2] Those most at risk of NOE are elderly patients with comorbidities. These include diabetes mellitus, immunosuppressive conditions (including HIV/AIDS), and those undergoing immunosuppressive treatments such as chemotherapy.[3] Higher rates of complications occur in those with diabetes mellitus.[2] Diabetic microvascular disease alongside infective vasculitis contributes to reduced blood supply resulting in poorer perfusion at the site of infection. This, combined with impaired immune cells and a higher aural canal pH, contribute to poorer defense mechanisms.[4]

The term NOE can be used interchangeably with temporal bone osteomyelitis and skull base osteomyelitis. It is characterized by severe, deep-seated otalgia out of proportion to the clinical signs often despite strong analgesia. There can be persistent otorrhea despite previous treatment with topical antibiotic drops, and a sensation of aural fullness. Clinical examination can reveal EAC debris

as would be expected in otitis externa, but it may also show granulation tissue, polyps, significant edema, and even bony erosion.[5,6] These otoscopic findings are not necessarily present in all cases. The most common bacterial cause is *Pseudomonas aeruginosa*, although rarer cases have isolated causative agents including *Staphylococcus epidermidis* and fungi.[6,7] Differentiating between these can be challenging and may require biopsies to isolate the organism.[8] Effective management involves targeted antibiotic treatment (usually a combination of intravenous and topical therapy), analgesia, and in some cases, surgery.[9] Strict optimization of blood sugar in diabetics is a vital part of ongoing management and correction of immunosuppressive conditions where possible is also vital.

NOE is uncommon but can carry a significant patient burden in terms of morbidity and mortality. Late diagnoses and untreated cases can lead to cranial neuropathies often involving the facial and lower cranial nerves (glossopharyngeal, vagus, accessory, and hypoglossal). Involvement of the abducens nerve has also been reported.[10] The mechanism of this is thought to be primarily from the effect of neurotoxins released by the pathogen. Critical cases involve bone destruction due to osteomyelitis which indirectly contributes to facial palsy.[11]

Given the destructive nature of NOE, with its propensity for complications and mortality, early diagnosis and treatment are paramount. However, NOE is a notoriously challenging diagnosis to make due to the inconsistencies with diagnostic investigations.[12] In addition, its clinical picture and complications can mimic nasopharyngeal and other EAC malignancies as well as cholesteatoma and persistent otitis externa.[13,14] It is therefore important to understand what diagnostic modalities are available and how otolaryngologists can use them to accurately treat such an aggressive disease. This narrative review aims to evaluate the different diagnostic options available in NOE (specifically otogenic skull base osteomyelitis from an otitis externa) and discuss their advantages and limitations.

DISCUSSION

Diagnostic options

A thorough history and clinical findings are important to create a high index of suspicion for NOE. Further diagnostic investigations often give varied results, such as infective blood markers, imaging, and tissue sampling (biopsy of EAC granulation/polyps).[12] If patients are incorrectly treated with high-strength and high-dose intravenous antibiotics in the absence of NOE, this can also cause unpleasant and damaging side effects.[15] Conversely, misdiagnosis or delayed treatment can lead to irreversible damage to surrounding structures and death.[16]

Due to the life-threatening nature of NOE, imaging is recommended to not only exclude differential diagnoses but to also aid in prognostication and measurement of treatment response.[5] The most commonly used modalities are computerized tomography (CT) and magnetic resonance imaging (MRI). More recently there has been an emergence of radionucleotide scans and positron emission tomography (PET) 2-deoxy-2-[fluorine-18] fluoro-D-glucose with CT (18F-FDG-PET/CT), although these are less widely accessible. Biopsies are also invaluable in confirming the presence of inflammation and establishing specific antibiotic therapy for the responsible organism.[17] Where these diagnostic tests are not always available, or time is limited; infection markers in the blood can also help clinicians further strengthen their suspicion of NOE. Erythrocyte sedimentation rate (ESR) has been found to be one of the most specific markers correlating to the progression of NOE.[18]

CT scans

CT scans are readily available in most hospitals and so offer quick solutions. They can demonstrate changes to bone, soft tissue, and blood vessels. Specifically to NOE, contrast CT scans are effective at localizing and characterizing the extent of the spread of the infection. This can be from spreading osteomyelitis at the skull base and the infection in the adjacent soft tissue. They also are useful in visualizing air spaces in the temporal and surrounding bones.[19] Cranial nerve function can also be judged based on images of the various exiting foramina and severity of any surrounding inflammation, correlating well with the clinical picture.[20] CT scans are also sensitive in picking up small cortical erosions and minuscule differences in bone density.[21–23] This was found by a prospective study of 18 patients with NOE.[23] The main limitation of this study was the small sample size which has been a limitation in this field given the rarity of this disease. In studying 18 patients, four were lost to follow-up, one died of the infection, and another died of a different condition. This meant the sample size was further reduced to 12 cases. This meant other factors were not considered. For example, no patients had immunosuppressive disease (such as HIV) and facial nerve palsies were only present in four patients. This may somewhat limit the ability to translate these results across other NOE patients. Despite this, the data obtained from this study did support the role of CT in the initial diagnosis of NOE. Figure 1 demonstrates the use of CT and its findings in a patient who presented with a right aural polyp and subsequently was diagnosed with NOE.

Due to the relative ease of obtaining a CT scan, there is a robust evidence base with multiple studies for their utility in diagnosing NOE.[19–24] Despite individual studies having small population groups, the cumulative sample size of data from a variety of studies is large, and the results of unrelated reports corroborate the effectiveness of CT scans. Another invaluable advantage of CT scans is their role in differentiating between NOE and malignancies. CT images can highlight nasopharyngeal masses and distinguish this from the spread of NOE following the facial nerve plane preserving the architecture (which is not seen in nasopharyngeal malignancy).[25] This could prove to be a valuable tool in cases where there is a high index of suspicion for nasopharyngeal malignancy.

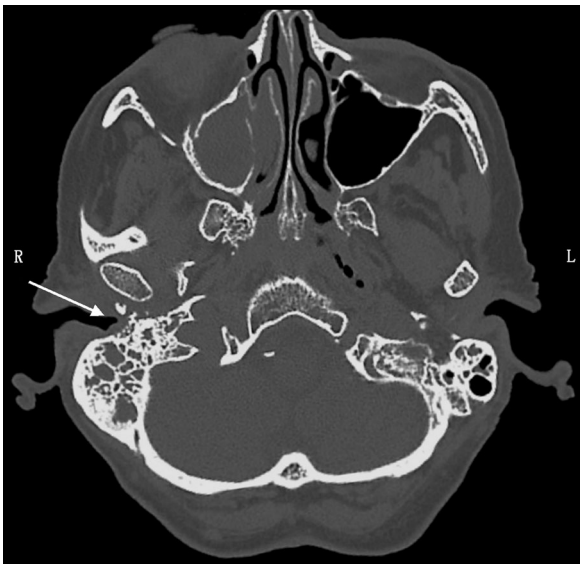

FIGURE 1 Axial computed tomography (CT) scan of the temporal bones and head showing focal bone destruction of the anterior aspect of the external auditory canal (arrow). There is also extensive opacification of the right mastoid air system.

While CT imaging is useful in diagnosis, its main limitations are in the ability to follow-up on the resolution of skull base involvement.[26] Their role as the predictive value in disease progression is limited.[27] CT imaging is also not as sensitive in earlier phases of the infections. This is because CT images can only detect changes in the bone after one-third reduction in mineralization.[4] This has the potential to delay diagnosis and miss earlier osteomyelitis. If used as part of serial scans, they can be efficacious in demonstrating progression and disease resolution.[28] However, this exposes the patient to repeated radiation and is resource intensive.

CT scans are less useful than other modalities in monitoring for therapeutic effect as they do not correlate well with the clinical picture once treatment has begun. It is also important to remember that degree of remineralization is not directly proportional to treatment; this continues after the infection has been cleared which would not be reflected on CT imaging.[26,29] This limits its use in follow-up care. Furthermore, the inability to delineate soft tissues in CT images can create difficulties in distinguishing between NOE and other differentials such as carcinoma.[27]

Taking these findings into account, it is prudent to consider the clinical picture when choosing which CT scan to order. Different imaging techniques should be considered based on clinical concerns. In the acute setting, a CT brain pre- and postcontrast with 1 mm thickness slices would give adequate information on the temporal area and details of the ossicles to assess the osteomyelitis. However, if the investigation of the temporal bone is required in further detail, then CT of the temporal bones with 0.5 mm thickness of slices should be requested.

MRI scans

MRI can also be used in the workup of NOE. One benefit is clear imaging of soft tissue, enabling accurate visualization of the extent of intracranial infection.[30] This includes the investigation of meningeal enhancement and effect on the osseous marrow cavities.[21] MRI was shown to be better than other modalities at detecting complications such as carotid artery occlusion, nasopharyngeal and intracranial extension, and abnormalities of the dura.[30] In addition, bone changes can be detected as early as 3 days from the onset with MRI due to their excellent quality in anatomical localization and identification of soft tissue involvement in skull base osteomyelitis.[31] The sensitivity of this in diabetic patients has been shown to be as high as 90%. Therefore, MRI scans can predict outcomes more accurately than other imaging techniques.[32] This hypothesis was echoed across three separate studies looking into the usefulness of different imaging modalities in NOE.[21,30,32] Despite this, it is important to consider these results in the context of their small sample sizes.

When compared to CT, MRI has been shown to be more useful than CT scans in determining disease progression; however, neither was very accurate for monitoring therapeutic effects once antibiotics had been started.[32] This study only looked at four cases in which all patients had diabetes mellitus. Therefore, further research is required to investigate patients with a wider range of factors known to affect infection and disease progression to draw more reliable conclusions. An additional prospective study concluded that MRI and CT play complementary roles in the diagnosis of NOE.[23]

Diffusion-weighted MRI scans have also been demonstrated to be more useful in monitoring response to treatment than conventional MRIs.[33] A retrospective evaluation reported that diffusion-weighted MRIs had a role in using apparent diffusion coefficient to differentiate between NOE and tumors of the head and neck. Like CT and nasopharyngeal malignancy, MRI can have a role in excluding differentials. However, this study was limited by the small number of patients, the use of different MRI scanners between patients, and the fact that researchers analyzed soft tissue as opposed to bone to come to conclusions due to the ambiguous images of bone. These factors need further research to come to more robust conclusions.[34]

Based on these discussions, MRI brain pre- and post-gadolinium would be the most useful scan in the acute setting. This would exclude complications such as an intracranial abscess or empyema whilst simultaneously providing information on the spread of infection. Figure 2 demonstrates an MRI scan with gadolinium enhancement showing evidence of NOE and extension to the masticator space and TMJ. There was no intracranial involvement in this case. MRI internal auditory meatus should be considered if a more detailed view is required. Standard protocols would involve either a CT brain or MRI brain in the first instance before deciding whether more targeted scans are required.

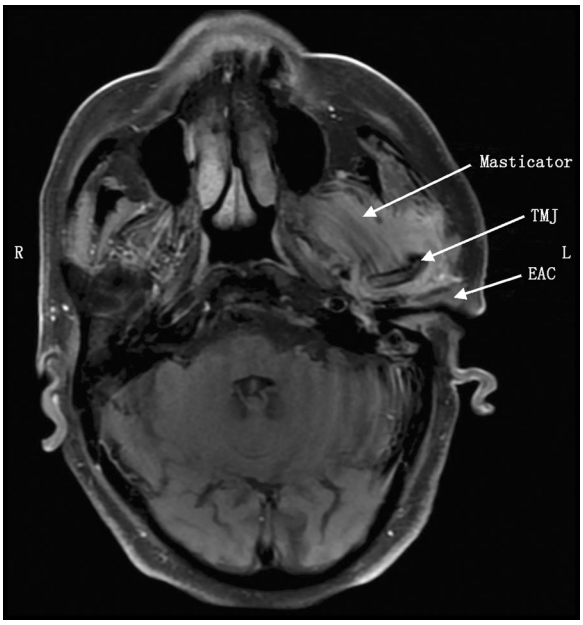

FIGURE 2 Axial magnetic resonance (MR) scan of the head with gadolinium enhancement demonstrating changes consistent with left necrotizing otitis externa (NOE) and extension into the masticator space (labeled masticator) and temporomandibular joint (labeled TMJ). There is extensive thickening and opacification of the external auditory canal (EAC) and mastoid opacification.

Radionucleotide scans

Radionucleotide scans involve the ingestion or injection of a radioactive tracer substance. This tracer is chosen according to the target organ where it accumulates and emits gamma rays which are recorded on a camera and analyzed to produce an image.[35] Evidence suggests that radionucleotide scans can accurately diagnose skull base osteomyelitis and can aid in differentiating between acute infections, chronic infectious processes, and neoplasms.[36] Specific tracers such as ^{67}Gallium Citrate (Ga67), Technetium-99m methyldisphosphonate (^{99m}Tc), and ^{111}Indium (111In) scans have a role in the diagnosis and monitoring treatment response in NOE.[37,38]

Ga67 can highlight the difference between inflammation and infection in NOE, thus, monitoring the progress once antibiotics have been started.[35,36,39] This is also evidenced by the fact that immune cells absorb Ga67, providing an accurate picture of ongoing infectious processes. It was the only tracer documented in the literature which dropped in uptake consistently with improvement in the infection.[38,40] 111In works similarly to Ga67 by binding to leucocytes and accumulating in inflammatory tissue making it a useful marker in skull base osteomyelitis.[29,41] There is limited available evidence on its use in the resolution of infection and so further research is required to investigate whether it would be as useful as Ga67 in the follow-up of NOE. Due to this level of detail, two separate studies found Ga67 radionucleotide scans are more sensitive in the early detection of NOE when compared to CT and MRI.[40,42]

^{99m}Tc can be used to characterize skull base osteomyelitis. It is sensitive in highlighting increased osteoblast activity so can detect early pathogenesis of NOE.[43] However, the ^{99m}Tc tracer scans remain positive during bone repair processes, disregarding their use in follow-up (unlike Ga67).[43] In addition, its usefulness may be limited in excluding differentials that have high bone turnover such as malignancy and postoperative inflammation.[44] ^{99m}Tc can also accumulate in white blood cells of the bone marrow which could lead to false positive results.[44] Therefore, its usefulness is mainly in treatment response and detecting early evidence of skull base osteomyelitis in cases where a diagnosis of NOE is already established.

Despite this, a recent meta-analysis assessed 20 articles with 608 patients and looked at the pooled sensitivities for ^{99m}Tc and Ga67. They concluded results of 85.1% and 71.2% respectively and therefore did not recommend radionucleotide scans in initial investigations of NOE due to poor specificity in characterizing the anatomic extent of infection.[45] Moreover, radionucleotide scans are not commonly available and given their utility over other scans, are debatable in initial management and prognostication; most clinicians principally favor conventional CT or MRI scans.[45]

18F-FDG-PET/CT

18F-FDG-PET/CT scans are a novel imaging method that can illustrate pathologies by identifying the location of metabolically active areas by superimposing PET images onto the anatomic images of the CT scan.[46] The ability to detect leukocyte activity can give very accurate localization of infection and inflammation in metabolically active tissue.[47] For this reason, it is argued in the literature that 18F-FDG-PET/CT scans are the investigation of choice for sensitivity when detecting and localizing NOE as well as in measuring resolution with antibiotic treatment.[48] It has a reported sensitivity of 96% and specificity of 91% in addition to being the most accurate modality for excluding osteomyelitis.[48]

This was demonstrated in a report of a case series that found that patients with full resolution on 18-FDG-PET/CT scans after completing antibiotics had no further recurrence. Indicating that the scan was useful in confirming adequate treatment.[48] However, there are limited studies to support this and so further research is warranted to confirm this finding. Another drawback with these scans is their limited availability. Additionally, these scans require highly trained nuclear physicians to interpret them correctly due to the level of detailed information produced.[49]

Laboratory tests

Laboratory tests are vital in assessing patients with suspected NOE. These include white cell counts (WCC), inflammatory markers including ESR and C-reactive protein (CRP), creatinine, glucose, and ear swab cultures. These tests alongside clinical presentation can aid

clinicians in coming to a diagnosis of NOE. In particular, blood markers can be obtained very quickly when compared to radiological investigations. Furthermore, blood markers are easy to measure on a regular basis making them useful nonspecific measures of disease progression. Testing ESR has been invaluable in resource-poor areas where scans may not be as readily available or affordable. The research found that ESR accurately correlated to regression of treatment and when used alongside clinical response can be a useful tool for follow-up.[18] ESR was also found to be an important factor when predicting prognosis in a meta-analysis of 28 NOE patients.[50]

Biopsy

A retrospective study evaluating the importance of tissue sampling argued that biopsies are a useful source of information particularly in cases in which NOE is not responding to antibiotics.[51] The majority of patients are treated with antibiotics targeting *P. aeruginosa*; the most common causative agent. Other possible pathogens include Staphylococcus epidermis, Proteus mirabilis, and Aspergillus fumigatus; the most common fungal cause of NOE.

Clinicians underestimate the growing number of cases caused by fungal infections which have been found to be associated with more invasive infections.[52,53] If biopsies were done at an earlier stage in these scenarios, accurate sensitivities could be established sooner, and thus definitive treatments could be given to patients. This study included 52 cases of which 27 had surgical debridement for refractory treatment.[51] Presence of fungal infection was found to be statistically significantly higher in those who underwent surgical debridement.

Biopsies would direct definitive treatment. For bacterial NOE, oral fluoroquinolones are commonly used given their effectiveness against both gram-negative and positive bacteria and specific cover against *P. aeruginosa*. These are used alongside local bacterial susceptibility patterns of Pseudomonas isolates for 6–8 weeks. If these aren't available, patients would need long-term IV antibiotic treatment; for 6–8 weeks or longer. This can be logistically challenging as it often involves the placement of a peripherally inserted central catheter line for the administration of IV antibiotics at home as well as home nursing services and follow-up. Where fungal NOE is diagnosed, there are fewer clinical guidelines available. Important principles of treatment include aggressive diabetic control and improvement of immunocompetency where possible. Treatment involves a prolonged course of antifungal agents such as amphotericin B and itraconazole. Local guidelines should be consulted to best direct treatment.

CONCLUSION

NOE is a notoriously difficult diagnosis to make, and otolaryngologists should have a high index of suspicion with elderly diabetic patients presenting with severe otalgia and otorrhea that is not responding to topical antibiotics and adequate analgesia. Table 1 summarizes the advantages and limitations of the different diagnostic modalities. Simple blood tests such as ESR are useful markers and can

TABLE 1 Summary of advantages and limitations of diagnostic modalities.

Examinations	Advantages	Limitations
Computerized tomography (CT)	• Quick and easily accessible • Localizes and characterizes the spread of infection to adjacent bone and air spaces • Picks up very small cortical erosion	• Limited ability in following up resolution of infection • Not useful in the early stages of infection or in predicting prognosis
Magnetic resonance imaging (MRI)	• Localizes and characterizes the spread of infection • Specifically visualizes soft tissue intracranial infection • Detects complications	• Limited ability in following up resolution of infection
Radionucleotide scans	• ^{67}Gallium Citrate and ^{111}Indium can assess response to treatment • ^{99m} Technetium MDP can detect early osteomyelitis through osteoblast activity	• Overall poor specificity • 99 m Technetium MDP is not specific to infection and not useful for follow-up • Limited availability
PET 2-deoxy-2-[fluorine-18] fluoro-D-glucose with CT (18F-FDG-PET/CT)	• Specific localization of infection and inflammation • Accurate for diagnosing resolution	• Limited available research • Limited availability • Require experienced interpreters
Laboratory tests	• Quick and easy to measure • Economical • Erythrocyte sedimentation rate (ESR) rises proportionally to disease progression and allows good prognostication	• Lack specificity • Limited usefulness in characterizing the extent of infection
Biopsy	• Useful in cases refractory to treatment	• Invasive • Require skilled surgeons • Limited available research

be employed in measuring response to disease particularly where more advanced tools are not immediately available. Biopsies are useful in distinguishing causative organisms to ensure adequate treatment, especially, in cases of fungal infections which are known to be more severe.

As technology advances imaging modalities are becoming more available and clinically useful. Despite this, CT scans are currently the most common first-line investigations. They can pick up early bony erosion and visualize the degree of infection in the soft tissue to some extent. MRI is superior to CT in imaging soft tissue, but neither is very useful in measuring response to treatment once the diagnosis has been made. MRI scans are useful in accurately demonstrating intracranial involvement, thus allowing clinicians to understand complications and perhaps predict outcomes.

Although radionucleotide scans are not generally recommended in the first-line investigation for NOE, Ga67 tracers are beneficial for their role in differentiating between acute infections, chronic infections, and neoplasms. They are also helpful in measuring response to treatment as Ga67 levels correspond to the severity of infection, unlike ^{99m}Tc tracers. 18F-FDG-PET/CT scans can give very accurate localization of infection and measure the resolution of infection with the disease. For this reason, it is argued in the literature that 18F-FDG-PET/CT scans are the investigation of choice for monitoring response to treatment although their accessibility is somewhat limited.

In conclusion, this review has evaluated the various diagnostic options available to clinicians. The overall available literature, available for review, is limited in its ability to provide accurate, valid conclusions due to generally small sample sizes due to the rare nature of the condition. Furthermore, there are few clear prospective randomized trials comparing imaging modalities to be able to draw accurate conclusions. Despite this, it is fair to conclude that all diagnostic modalities play a complementary role in diagnosing NOE, tracking its progression, its prognosis, and its resolution. Ultimately a combination of modalities will be required in safely treating NOE.

AUTHOR CONTRIBUTIONS

All authors have read and approved the manuscript for submission to this journal; have made a substantial contribution to the writing and intellectual concept of the article; and acknowledge that they have exercised due care in ensuring the integrity of the work.

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CONFLICTS OF INTEREST STATEMENT

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DATA AVAILABILITY STATEMENT

None.

ETHICS STATEMENT

Ethical approval was not required for this review.

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