Richtlijn
Necrotiserende otitis externa – osteomyelitis schedelbasis

Guideline
Necrotizing otitis externa – skull base osteomyelitis

INITIATOR
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Colofon

GUIDELINE NECROTIZING OTITIS EXTERNA – SKULL BASE OSTEOMYELITIS
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Scope and target group
The purpose of the guideline is to provide the best possible care to patients with skull base osteomyelitis, by informing on optimal diagnostic and treatment decisions and reducing unwarranted variation in the delivery of care. It is intended for all healthcare providers in the *secondary and tertiary care setting* who are involved in the care of patients with osteomyelitis of the skull base – necrotizing otitis externa.

However, early recognition of the diagnosis in the *first* line is essential. In the Netherlands, there is a high-quality guideline for common otitis externa, which also includes advice for general practitioners regarding referral to an ENT specialist.
The guideline development group is aware of the low incidence of the disease. By writing the guideline in English the guideline development group aims to make it accessible to a wide audience. Although (local) initiatives are taken aimed at improving various aspects of care related to this condition, this guideline provides a broad, multidisciplinary framework for clinicians treating patients with this condition globally.

Apart from the low incidence of this condition the working group is faced with several challenges:

- There are few available studies, often written in various languages.
- There is no clear consensus about the nomenclature as well as the definition of the disease.
- There is considerable variation in diagnostics, as well as in treatment and treatment monitoring due to major differences in healthcare resources globally and differences in clinical practices.
- When determining the optimal treatment (duration) for such an infection, there is a lack of well-conducted comparative research that takes into account various parameters:
    - Type and virulence of pathogen
    - Extent of the infection at the time of diagnosis
    - Individual patient-dependent parameters that may influence the success of the treatment
    - Significance of residual abnormalities in imaging during the course of treatment.

Finally, the treatment of infectious diseases is also subject to local differences due to varying resistance patterns of the causative pathogens. Where relevant, the guideline will indicate if a specific situation applies to the Dutch healthcare system.

For patients
This guideline is intended for patients with necrotizing otitis externa. It covers the following aspects: recognition of the diagnosis, diagnostics, treatment, and follow-up.

Voor patiënten
Deze richtlijn is bedoeld voor patiënten met osteomyelitis schedelbasis – maligne otitis externa. De richtlijn is geschreven in het Engels. In deze richtlijn komen de volgende onderdelen aan bod: de herkenning van de diagnose, diagnostiek, behandeling en follow-up

Development of the guideline
The initiative for this guideline comes from the Dutch Society for Otorhinolaryngology and Head and Neck Surgery (NVKNO). In 2022, a multidisciplinary guideline development group was formed with representatives from ENT specialists, radiologists, nucleair medicine physicst, infectious disease specialists and medical microbiologists. Hospital pharmacists and a patient representative reviewed the guideline before the commentary phase.

Application
A flowchart was developed to guide clinicians through the appropriate steps of diagnosing and treating the disease.

Status of the guideline
The guideline on osteomyelitis of the skull base – malignant otitis externa is included in the Otology cluster and will be maintained modularly within this cluster. More information about working in clusters and modular maintenance can be found here (in Dutch).

Verantwoording

For more details on the guideline methodology used, we refer you to the Werkwijze. Relevant information for the development of this guideline is presented below.

General information
The revision of this guideline module was supported by the Knowledge Institute of the Federation of Medical Specialists (www.demedischspecialist.nl/kennisinstituut) and was funded by the Quality Funds for Medical Specialists (SKMS).

Composition guideline development group
For the development of the guideline, a multidisciplinary guideline development group was established in 2022, consisting of representatives from all relevant specialties (see Composition of the working group) involved in the care of patients with necrotizing otitis externa.

Declarations of interests
An overview of the conflicts of interests of the guideline development group members and the assessment of how potential conflicts of interest were addressed can be found in the table below. The signed declarations of interest are available upon request from the Secretariat of the Knowledge Institute of the Dutch Federation of Medical Specialists at secretariaat@kennisinstituut.nl.

Werkgroeplid	Functie	Nevenfuncties	Gemelde belangen	Ondernomen actie
Waterval (voorzitter)	KNO-arts MUMC	Accreditatiecommissie Stichting Audiciensregister	Geen	Geen
Glaudemans	Nucleair geneeskundige UMCG	Voorzitter NVNG (onbetaald)	We hebben als ziekenhuis en afdeling een samenwerking met Siemens (UMCG-Siemens PUSH collaboration/Partnership of UMCG-Siemens for building the future of Health). Hieruit vloeit uit voort dat de nieuwste camera's bij ons komen (bv UMCG neemt nieuwe Whole-Body PET/CT-scanner in gebruik) en dat er gezamenlijk onderzoek gedaan wordt. Hierbij heb ik een aantal promovendi die door Siemens betaald worden (niet op het gebied van osteomyelitis schedelbasis)	Geen restricties. Extern gefinancierd onderzoek valt buiten bestek richtlijn

Heusinkveld	Arts-microbioloog in ziekenhuis Gelders Vallei	Richtlijn otitis externa Bestuur SKML sectie infectieserologie (onbetaald)	Geen	Geen
Peters (tot oktober 2022)	Internist-infectioloog-acute geneeskundige, Amsterdam UMC	richtlijnontwikkeling : Covid-19 FMS, diabetische voet NIV, diabetische voet IWGDF, alle onbetaald Organisatie internationaal congres diabetische voet. Onbetaald	afdeling krijgt geld van Roche voor biomarker onderzoek bij diabetische voet osteomyelitis Voorzitter gewrichtsprothese geassocieerde infectie richtlijn. Diabetische voet onderzoek (extern gefinancierd)	Geen restricties. Extern gefinancierd onderzoek valt buiten bestek richtlijn
Pegge	Radioloog (Neuro/Hoofdhals) Radboud UMC Nijmegen	Geen	Geen	Geen
Van Tilburg	KNO-arts ETZ	Geen	Geen	Geen
Sikkens	Internist acute geneeskunde & infectioloog, Amsterdam UMC	post-doc onderzoeker Amsterdam UMC, onbetaald	Ja, via ZonMw (onderzoek naar COVID bij een medewerkerscohort, onderwerp infectiepreventie en vaccin-immunologie)	Geen restricties. Extern gefinancierd onderzoek valt buiten bestek richtlijn
Lowe	Internist-infectioloog. Afdeling Medische Microbiologie, Infectieziekten en Infectiepreventie (MMI), Maastricht UMC+	Geen	Geen	Geen
Mihailescu	Internist-infectioloog OLVG Amsterdam	Geen	Geen	Geen
Jasper Janssen	KNO-arts in opleiding bij het MUMC+ (0,8 FTE), promovendus (0,2 FTE).	Geen	Geen	Geen
Sinkeler	Ziekenhuisapotheker AmsterdamUMC	Geen	Geen	Geen

Jager	Ziekenhuisapotheker	Geen	Geen	Geen

Representation of the patient perspective
Attention was paid to the patient perspective by inviting Stichting Hoormij and Patiëntenfederatie Nederland for the invitational conference, and close contact with Stichting Hoormij during the development of the guideline. The report of this [see related products] was discussed in the guideline development group. The input obtained was taken into account when formulating the key questions, selecting the outcome measures, and drafting the considerations. The draft guideline was also submitted for comments to Stichting Hoormij and Patiëntenfederatie Nederland, and any comments received were reviewed and processed.

Kwalitatieve raming van mogelijke financiële gevolgen in het kader van de Wkkgz
Bij de richtlijnmodule voerde de werkgroep conform de Wet kwaliteit, klachten en geschillen zorg (Wkkgz) een kwalitatieve raming uit om te beoordelen of de aanbevelingen mogelijk leiden tot substantiële financiële gevolgen. Bij het uitvoeren van deze beoordeling is de richtlijnmodule op verschillende domeinen getoetst (zie het stroomschema bij Werkwijze).

Module	Uitkomst raming	Toelichting
Definition and limiting doctor's delay in diagnosing necrotizing otitis externa	geen financiële gevolgen	Uit de toetsing volgt dat de aanbeveling(en) niet breed toepasbaar zijn (<5.000 patiënten) en daarom naar verwachting geen substantiële financiële gevolgen zal hebben voor de collectieve uitgaven.
Diagnostic imaging for primary diagnosis	geen financiële gevolgen	Uit de toetsing volgt dat de aanbeveling(en) niet breed toepasbaar zijn (<5.000 patiënten) en daarom naar verwachting geen substantiële financiële gevolgen zal hebben voor de collectieve uitgaven.
Microbiology and histopathology	geen financiële gevolgen	Uit de toetsing volgt dat de aanbeveling(en) niet breed toepasbaar zijn (<5.000 patiënten) en daarom naar verwachting geen substantiële financiële gevolgen zal hebben voor de collectieve uitgaven.
Antimicrobial treatment	geen financiële gevolgen	Uit de toetsing volgt dat de aanbeveling(en) niet breed toepasbaar zijn (<5.000 patiënten) en daarom naar verwachting geen substantiële financiële gevolgen zal hebben voor de collectieve uitgaven.

Surgical treatment	geen financiële gevolgen	Uit de toetsing volgt dat de aanbeveling(en) niet breed toepasbaar zijn (<5.000 patiënten) en daarom naar verwachting geen substantiële financiële gevolgen zal hebben voor de collectieve uitgaven.
Hyperbaric oxygen therapy	geen financiële gevolgen	Uit de toetsing volgt dat de aanbeveling(en) niet breed toepasbaar zijn (<5.000 patiënten) en daarom naar verwachting geen substantiële financiële gevolgen zal hebben voor de collectieve uitgaven.
Duration of treatment	geen financiële gevolgen	Uit de toetsing volgt dat de aanbeveling(en) niet breed toepasbaar zijn (<5.000 patiënten) en daarom naar verwachting geen substantiële financiële gevolgen zal hebben voor de collectieve uitgaven.
Imaging to monitor treatment response	geen financiële gevolgen	Uit de toetsing volgt dat de aanbeveling(en) niet breed toepasbaar zijn (<5.000 patiënten) en daarom naar verwachting geen substantiële financiële gevolgen zal hebben voor de collectieve uitgaven.
Additional conditions and optimizing care	geen financiële gevolgen	Uit de toetsing volgt dat de aanbeveling(en) niet breed toepasbaar zijn (<5.000 patiënten) en daarom naar verwachting geen substantiële financiële gevolgen zal hebben voor de collectieve uitgaven.

Module 1 – Definition and limiting doctor's delay in diagnosing necrotizing otitis externa

Question
When should one suspect necrotizing otitis externa, to limit doctor's delay?

More specifically, the following subquestions were formulated by the working group:

1. When should (non healing) otitis externa be suspected for necrotizing otitis externa?
2. Which patient factors are important in the recognition of necrotizing otitis externa?
3. Which are alarm symptoms for necrotizing otitis externa?

Introduction
Necrotizing otitis externa (or necrotizing external otitis) is a rare but severe infection associated with high morbidity and potential mortality. It primarily affects elderly individuals and those with comorbidities, such as diabetes or immune deficiencies, making early recognition crucial. The condition arises as a complication of ordinary external otitis, a very common and often self-limiting disorder typically treated with topical therapies. Necrotizing otitis externa develops in only a small minority of cases. Performing diagnostic imaging to rule out necrotizing otitis externa in every patient with otitis externa is unnecessary and would place a significant burden on the healthcare system. Instead, the goal of this module is to help clinicians distinguish patients with necrotizing otitis externa from those with ordinary otitis externa, ensuring awareness, and timely and appropriate intervention.

Search and select
A search question, and consequent systematic literature search, was not performed for this module. The module is descriptive in nature and based on expert opinion.

Considerations – from evidence to recommendation
Balance between desired and undesired effects

Definition of necrotizing otitis externa and skull base osteomyelitis
The definition and staging of the disease have been a longstanding discussion. In earlier days, the disease was firstly called malignant otitis externa (Chandler, 1968). Later, the term necrotizing otitis externa (NOE) was introduced to confirm the severity, but to avoid confusion with a malignancy (Kohut, 1979).

Necrotizing otitis externa (NOENOE) clearly indicates that the condition originates in the ear canal. It is an epithelial infection of the external auditory canal which has spread into the temporal bone affecting soft tissue and bone structures of the skull base.

The term *skull base osteomyelitis* is also used in this context and may be more accurate when the infection extends beyond the temporal bone to involve the skull base. This represents a form of osteomyelitis secondary to otitis externa. However, the term misleadingly implies a purely bony pathology. It does not fully capture the condition, as soft tissue infiltration beneath the skull base is invariably present. This variant is termed *typical skull base osteomyelitis*.

Central skull base osteomyelitis, resulting from sinonasal infections, is also classified as *typical skull base osteomyelitis*. Finally, skull base osteomyelitis may also occur secondary to trauma, iatrogenic causes, or hematogenous spread, though these fall outside the scope of the condition addressed in this guideline.

We consider the term *skull base osteomyelitis* to be correct in this context, but for consistency throughout this guideline, we will invariably use the term *necrotizing otitis externa.*

Clinical application of the definition

The abovementioned discussion concerns the semantics of this type of infection. The clinical implementation and its implications are also not straightforward. For this matter, the guideline committee refers to a recently published, high-quality UK consensus paper in which agreement on key principles was achieved following a systematic literature review. This was performed through a Delphi study involving multidisciplinary specialists (Hodgson, 2023). Primarily, establishing a clear definition, which had varied significantly in earlier literature, serves two important purposes: 1) facilitating the diagnosis as well as the exclusion of NOE (necrotizing otitis externa), and 2) standardizing study populations in future robust research. The criteria required that agreement was reached by at least 70% of respondents and that disagreement on a particular condition or statement was less than 15%.

We also mention the goals that were set in the consensus paper, as they align with the scope of this guideline. While the consensus paper focuses on defining the disease and treatment outcomes, this guideline concentrates on the diagnosis and treatment itself. Given that the target population and type of healthcare system are very similar, the two papers appear to be complementary.

The following aims were defined in terms of the conditions/statements in the consensus paper:

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 (ie, 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.

The results outlined below are proposed with regard to definition and with regard to treatment outcomes:

Definite NOE according to UK consensus paper

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:
    - 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 (eg, bone marrow oedema of the temporal bone with soft tissue inflammation of the external auditory canal).

Possible NOE according to UK consensus paper

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 (eg, 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:
    - Immunodeficiency.
    - Night pain.
    - Raised inflammatory markers (erythrocyte sedimentation rate/C reactive protein) in absence of other plausible cause.
    - Failure to respond to >2 weeks of topical anti-infectives and aural care.

Complex necrotising otitis externa (NOE) according to UK consensus paper

Patients meeting the criteria for 'definite' NOE may be classified as 'complex' (or severe) if the following are present:

- Facial nerve or other lower cranial nerve palsy.
- Cerebral venous thrombosis 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 (eg, 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 (eg, dural thickening, extradural or subdural empyema, cerebral/cerebellar abscess)

<u>Cure</u>

A case of necrotising otitis externa (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.

<u>Relapse</u>

Relapse is recurrence of disease after the patient has been treated and cured, at least 3 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 external auditory canal after 14 days of optimum analgesia, anti-infective therapy, aural care and optimisation of immune state.

Use of definitions

The guideline committee agrees with the definitions and criteria published by Hogdson (2023), with the exception of *possible NOE.* In the opinion of the committee these criteria are more indicative of *severe external otitis.* The boundary between severe otitis externa and necrotizing otitis externanecrotizing otitis externa are sometimes hard to distinguish and might be seen as a fluid spectrum. However, as this guideline focuses on disease defined as necrotizing otitis externanecrotizing otitis externa, it was decided not to use the definition *possible NOE* within the scope of this guideline.

When should (non healing) otitis externa be suspected for necrotizing otitis externa?

Necrotizing otitis externa is a complication of (persisting) external otitis. The presentation of patients with necrotizing otitis externa predominantly starts with symptoms of external otitis. The management of otitis externa should therefore be evaluated at first. In the Netherlands, ways of effective diagnosis and treatment otitis externa are carefully formulated in guidelines, both available for primary and secondary (or tertiary) care.

This actual guideline, however, is made for medical professionals in secondary (or tertiary) care. Therefore, recommendations and considerations are mainly addressed to them. However, considering the topic *limiting doctor's delay,* the recommendations are applicable to both primary and secondary care settings.

Guideline for otitis externa in primary care

Guidelines for primary care are summarized in the NHG standard (Dutch College of General Practicioners) *(*Otitis externa | NHG-Richtlijnen*)*. Recommendations for referring to secondary care setting are the following:

- No remission of symptoms after 5 to 6 weeks of treatment, based on microbial cultures and concordant resistance patterns
- If acceptable treatment results are not met, regarding patients with multiple recurrences of otitis externa.
- Otitis externa, with pain, swelling of the ear, fever or sickness, in (elderly) patients with diabetes or immunodeficiency
- Otitis externa, with fever and sickness, with no improvement of symptoms after administration of 48 hours of oral flucloxacillin

Although this primary care guideline is primarily developed for the diagnosis and treatment (evaluation) of otitis externa, it is the opinion of the guideline committee that this algorithm sufficiently covers precautionary measures to select those patients at risk for development of necrotizing otitis externa. However, it is recommended to specifically mention the disease entity necrotizing otitis externa within the primary care guideline to improve awareness.

Guideline for otitis externa in secondary (and tertiary) care

Guidelines for secondary (and tertiary) care are stated in the Dutch guideline Otitis Externa (Dutch Society of Otolaryngology/Head-Neck Surgery). Treatment includes microscopic debridement of the ear canal (or the placement of an ear wick for a few days in the case of ear canal obstruction), followed by topical treatment with antiseptic (and corticosteroid) drops. If the patient was already treated with this topical treatment, or in case it is ineffective after 48-72 hours, it is recommended to treat with a topical corticosteroid with an antibiotic/antimycotic agent, preferably guided by the results of an ear canal swab. The guideline states in its recommendations that one should re-evaluate the differential diagnosis of external otitis, after 3 weeks of recommended treatment, as most symptoms should resolve within 2 weeks of correct treatment (van Balen, 2003).

When should necrotizing otitis externa be suspected?
Several factors play a role here to secure the accurate and prompt diagnosis.

- *The working group agrees with the aforementioned guidelines and encourages the strict use.* There is no exact cut-off in literature after how many weeks of (correct) treatment necrotizing otitis externa should be considered. The consideration of the diagnosis itself is of utmost importance, as this is often described as an important delaying factor (Jacobson, 2010; Rubin, 1988). *Awareness of the diagnosis* seems to be a key factor in the diagnosis.
- *Partial response of the initial treatment of otitis externa.* Both guidelines provide adequate recommendations in how to treat, or when to refer a patient with external otitis. However, as a panel treating patients with necrotizing otitis externa, it is observed that the diagnosis can be significantly delayed due to the lack of prompt referral. Patients are often seemingly treated according the guidelines, do have partial response and are considered recovered. Then, there is an interval without directed treatment, as pain has decreased, the ear canal skin has improved (or at least not deteriorated) and sometimes even healed. The infection may linger in deeper tissues, whereas the symptoms of the patients are not understood. Subclinically the condition might progress into necrotizing otitis externa.

Which patient factors are important in the recognition of necrotizing otitis externa?
Briefly, the major important factors that raise the suspicion of NOE are patients with *diabetes mellitus, advanced age, or immunocompromised status* who present with severe, refractory otalgia and otorrhea. Early diagnosis and aggressive treatment are essential to prevent complications such as cranial nerve palsies, uncontrollable spread in general, and even death. However, there are more factors, which are associated with NOE. All factors are elaborated below.

1. **Advanced age**: Elderly patients are at higher risk for NOE due to age-related changes in immunity and microvascular circulation (Byun, 2020; Soudry, 2007). Also, the decrease of cerumen production at higher age is thought to contribute to an environment at risk (Kelly, 1996). Cerumen creates an acidic coat containing lysozymes and other substances that are thought to inhibit bacterial and fungal growth. The lipid-rich cerumen is also hydrophobic and prevents water from penetrating througho the skin and causing maceration.
2. **Diabetes mellitus**: In a comprehensive systematic review (Takata et al., 2023), the most reported risk factor was diabetes mellitus, reported in 84% (1400/1668) of patients. This significantly exceeds the general prevalence of diabetes, considered 9.3% (Saeedi 2019). Hyperglycemia impairs immune function and microvascular perfusion, creating an environment prone to infection and tissue necrosis (Kelly, 1996; Darwitz 2024). Some clinicians state that any otitis externa in a patient with

diabetes, presenting with otalgia and otorrhoea, should be presumed to have necrotizing externa until proven otherwise (Lambor, 2013).

3. **Immunocompromised status**: Patients with conditions or treatments that weaken the immune system, such as HIV/AIDS, chemotherapy, long-term corticosteroid use, or organ transplantation, are at increased risk for NOE (Byun, 2020). In the review of Takata (2023), it was stated that six percent (61/994) of patients were immunosuppressed for reasons other than age or diabetes and only 10% (109/1130) had no immunosuppressive risk factor.
4. **Radiation therapy**: Patients who have undergone radiation therapy to the head and neck region may have compromised local tissue integrity and blood supply, increasing the risk of NOE (Treviño González, 2020). This should not be confused with osteoradionecrosis. This is a distinct entity, a chronic condition characterized by radiotherapy-induced avascular necrosis, mainly of the tympanic part of the temporal bone. Patients with osteoradionecrosis are thought to have an increased risk of NOE.
5. **Chronic kidney disease**: While references linking kidney disease directly to NOE are absent, the association can be inferred from the broader literature on infections in immunocompromised patients. Impaired renal function leads to immune dysfunction and metabolic imbalances, contributing to a higher risk of severe infections like NOE (Rubin Grandis, 2004; Sarnak, 2000) . The study of Sarnak highlights the increased risk of severe infections, including those caused by *Pseudomonas aeruginosa*, in patients with end-stage renal disease.
6. **Malnutrition or poor general health**: Poor nutritional status or chronic debilitating conditions can weaken the immune system and delay wound healing, increasing susceptibility to NOE (Carfrae, 2009; Chandra, 1997)
7. **Warm, humid climate** is associated with a higher prevalence of NOE (Nadol, 1980; Yang, 2020).

What are alarm symptoms for necrotizing otitis externa?

As stated in the previously mentioned review (Takata, 2023), the most common presenting symptom was otalgia (96%, 1249/1307) followed by otorrhoea (78%, 972/1255). Fever was infrequently reported. (7%, 28/416). Granulation tissue (69%, 918/1332) and oedema/swelling (76%, 754/987) were the commonest clinical signs. These symptoms can be identical to the presentation other otological conditions, making differentiation virtually impossible without knowing the *course* of the symptoms, without *knowing previous treatment* and without knowing the (clinical) *context* of the patient.

<u>*Severe and increasing otalgia*</u> which is discongruent to the extent of ear canal abnormalities in a patient previously diagnosed with and/or treated for otitis externa should be considered high-risk for (development of) necrotizing otitis externa. Pain is a very important symptom in normal otitis externa as well, but is then accompanied with congruent findings upon physical examination.

<u>*Granulation tissue*</u>. (Bacterial) Otitis externa arises from a skin infection due to discontinuity of the epithelial lining of the ear canal. An epithelial defect can also occur iatrogenically, for example due to the use of hearing aids or ear syringing. The porte d'entrée can usually not be seen in acute otitis externa, due to swelling of the canal skin. This infectious process might also involve (inflammatory) granulation tissue, formationof small abscesses or furuncles. These abnormalities disappear during the healing course upon correct treatment. Although not pathognomonic for necrotizing otitis externa, persisting granulation tissue of

the external auditory canal should raise suspicion, especially if co-existent with other symptoms. This can be a sign of a lingering infection beneath the ear canal skin. Moreover, abnormal tissue in the ear canal after the time window of acute otitis externa can also be caused by cancer of the ear canal.

Another alarm symptom that can occur in necrotizing otitis externa, is *cranial nerve palsy*, in case of progression of the skull base osteomyelitis. In theory, all cranial nerves can be involved, depending on the spreading pattern. However, the nerves that are mostly affected are the facial nerve and other lower cranial nerves (glossopharyngeal, vagus, accessory, hypoglossal). In the study by Takata (2023), 21% (371/1741) of patients had a facial nerve palsy and 5% (73/1447) had two or more affected cranial nerves. Athough cranial nerve palsy can also occur in other otological diseases (e.g., chronic otitis media/cholesteatoma), it generally urges the need for futher diagnostic imaging.

Precautions upon referral

- Patients with untractable acute otitis externa treated according the guidelines and patients suspected for necrotizing otitis externa should be referred as an *urgency*. It is advised *to assess these patients within two weeks*.
- In case of clinical suspicion of NOE and waiting time for a a specialist consultation, it can be wise to discuss the treatment course with the referring doctor. This may lead to meaningful treatment or diagnostic steps upfront the specialist consultation or cessation of treatment on purpose in order to have an unbiased situation at the time of the specialist consultation (also for taking a culture).
- Generally patients are referred to an ENT-specialist. However, if the symptoms are not primarily otologic but neurologic, a patient can end up being referred to a neurologist, geriatric or internal medicine ward. Decreased consciousness, metabolic issues due to infection, dysregulated diabetes and decreased intake can shift the attention off the otologic problem. Again awareness, not only for the general practitioners, but also for medical specialists, is key.

Values and preferences of patients (and family/caretakers)

Patients with necrotizing otitis externa benefit from an early diagnosis, as it can shorten their length of therapy. It also minimalises the chance of complications of the disease, which can be extensive (permanent hearing loss and other neurological damage). This also includes mortality. All cause mortality within one year is estimated a 7%, while disease specific survival within 1 year is estimated at 2%. Furthermore, symptoms such as severe pain and illness often takes a toll on the patients and family/caregivers. Early recognition reduces the length of these symptoms.

Costs

No cost efficiency studies have been performed on this subject. However, the treatment of the disease can take up to several weeks, even months (described in module 4 and 7), which can lead to health care costs such as prolonged admissions to the hospital. The working group promotes further diagnostics in case of suspicion, to rule out the disease or for an early diagnosis. This does not outweigh the potential additional costs of (the complications of) a delayed diagnosis.

Health equity/equitable

Not applicable.

Acceptability and feasibility

It is important that there is adequate access to medical professionals involved. First, medical professionals in primary care for referral to secondary (or tertiary) care: this includes an ENT specialist, radiologist, medical microbiologist and infectious disease specialist. Means for accurate diagnosis and management of disease, such as aforementioned specialists, microbial cultures, imaging facilities and antibiotic treatment should be available in most health care systems.

Recommendations

Consider the diagnosis necrotizing otitis externa, if correct treatment for normal otitis externa fails.

The following patient factors are important in the recognition of necrotizing otitis externa:

- Age
- (Uncontrolled) Diabetes mellitus
- Immunodeficient status

Perform further diagnostic evaluation for necrotizing otitis externa in patients with (a combination of) the following symptoms, especially if a patient complies with the abovementioned criteria:

- Severe and increasing otalgia, which can be discongruent to the extent of ear canal abnormalities in a patient previously diagnosed with and/or treated for otitis externa.
- Persisting (other) symptoms of otitis externa otitis externa after 2 weeks, when given culture specific treatment.
- Cranial nerve palsies
- Persisting granulation tissue of the ear canal, when other characteristics of otitis externa have decreased

Knowledge gaps

No systematic review has been performed for this module. The available literature describes the risk factors of patients with necrotizing otitis externa. However, to adequately assess when necrotizing otitis externa arises, one should preferrably examine cohorts of patients with otitis externa otitis externa for long periods of time. These cohorts should be large considering the low incidence of necrotizing otitis externa and also be prospective in nature.

Verkeerslicht en (de-)implementatietabel

Toelichting
Met het verkeerslicht worden aanbevelingen gecategoriseerd op basis van formulering en bewijskracht. Als eindproduct wordt bij richtlijnmodules met een sterk geformuleerde en voldoende onderbouwde aanbeveling een implementatietabel opgeleverd. Hierin wordt onder andere opgenomen:

- Een beschrijving van het knelpunt om de module uit te werken of herzien;
- De te verwachten belemmerende en bevorderende factoren voor implementatie;
- Welke partijen van belang zijn bij toepassen van de aanbeveling in de praktijk;
- Een inschatting van de implementatietermijn.

Verkeerslichtanalyse

- **ROOD** = sterk geformuleerde aanbeveling om iets niet te doen, met een GRADE high of moderate
- **ORANJE** = zwak geformuleerde aanbeveling; mogelijk kennishiaat
- **GROEN** = sterk geformuleerde aanbeveling om iets wel te doen, met een GRADE high of moderate
- **LICHT ROOD** of **LICHT GROEN** = sterk geformuleerde aanbevelingen met een GRADE low, very low of geen GRADE *(modules waarin geen studies geïncludeerd konden worden in de literatuursamenvatting of waarin geen literatuursamenvatting werd geschreven zoals modules waarin organisatie van zorg wordt beschreven)*

(Sub)aanbeveling	**Sterkte van de aanbeveling**	**Bewijskracht per uitkomstmaat**	**Verkeerslicht per (sub)aanbeveling**
Aanbeveling 1: Consider the diagnosis necrotizing otitis externa, if correct treatment for normal otitis externa fails.	Zwak (overweeg)	**voor de (sub)uitgangsvraag is geen systematische literatuur analyse uitgevoerd**	**LICHT GROEN**
Aanbeveling 2 Perform further diagnostic evaluation for necrotizing otitis externa in patients with (a combination of) the following symptoms, especially if a patient complies with the abovementioned criteria: • Severe and increasing otalgia, which can be discongruent to the extent of ear canal abnormalities in a patient previously	Zwak (overweeg)	**voor de (sub)uitgangsvraag is geen systematische literatuur analyse uitgevoerd**	**LICHT GROEN**

diagnosed with and/or treated for otitis externa. • Persisting (other) symptoms of otitis externa after 2 weeks, when given culture specific treatment. • Cranial nerve palsies • Persisting granulation tissue of the ear canal, when other characteristics of otitis externa have decreased			

Implementatietabel

Tabel A: (De-)Implementatietabel met impuls analyse

Aanbeveling – 1			
1. Wat was het onderliggende probleem om deze uitgangsvraag uit te werken?	x **Ongewenste praktijkvariatie** □ **Nieuwe evidentie** □ **Anders** **Toelichting:** Zie introductie		
2. Maak een inschatting over hoeveel patiënten het ongeveer gaat waar de aanbeveling betrekking op heeft?	x < **1000** □ < **5000** □ **5000-40.000** □ **> 40.000**		
3. Maakt de aanbeveling deel uit van een set van interventies voor hetzelfde probleem?	**x Nee**		
4. Belemmeringen en kansen op verschillende niveaus voor landelijke toepassing van de aanbeveling:	***Voorbeelden***	**Wat zijn mogelijke belemmerende factoren?**	**Wat zijn mogelijke bevorderende factoren?**
a) **Richtlijn/ klinisch traject (innovatie)**	*Voortschrijding/vooruitgang in de praktijk, haalbaarheid, geloofwaardigheid, toegankelijkheid, aantrekkelijkheid*	*Richtlijnen voor eerste en tweede lijn voor otitis externa, hetgeen mogelijk een delay geeft. Dit betreft de richtlijn voor huisartsen (link) en de richtlijn voor de 2e en 3e lijn (link).*	*Richtlijnen voor de 2e en 3e lijn verwijzen de richtlijnen naar elkaar.*

b) **Zorgverleners (artsen en verpleegkundigen)**	*Bewustzijn, kennis, houding, motivatie om te veranderen, gedragsroutines*	*Gedragsroutines, waarin vaak een banale otitis externa te lang wordt doorbehandeld*	*Reeds bestaande richtlijnen voor otitis externa, awareness voor het ziektebeeld NOE*
c) **Patiënt/ cliënt (naasten)**	*Kennis, vaardigheden, houding, compliance*	*geen*	*geen*
d) **Sociale context**	*Mening van collega's, cultuur van het netwerk, samenwerking, leiderschap*	-	-
e) **Organisatorische context**	*Organisatie van zorgprocessen, personeel, capaciteiten, middelen, structuren*	-	*Middelen en organisatie voor herkenning in NOE kunnen overal aanwezig zijn.*
f) **Economische en politieke context**	*Financiële regelingen, regelgeving, beleid (vergoede zorg, betaaltitel)*	-	-

5. Welke personen/partijen zijn van belang bij het toepassen van de aanbeveling in de praktijk?	**x** Patiënt/ cliënt (naaste) **x** Professional
6. Wat zouden deze personen/ partijen moeten veranderen in hun gedrag of organisatie om de aanbeveling toe te passen?	*Belangrijkste is het denken aan het ziektebeeld. Waardoor delay kan worden voorkomen. Hierin is dus een stuk voorlichting belangrijk*
7. Binnen welk tijdsbestek moet de aanbeveling zijn geïmplementeerd?	**x** < 1 jaar
8. Conclusie: is er extra aandacht nodig voor implementatie van de aanbeveling (anders dan publicatie van deze richtlijnmodule)?	**x Ja*** **Toelichting:** Mensen moeten zich bewust zijn van het ziektebeeld. Dit gaat verder dan de KNO-arts, gezien meerdere medisch specialisten betrokken zijn. Derhalve zou verdere bewustworden van het ziektebeeld verder verspreid moeten worden dan alleen deze richtlijn publiceren.

**Deze aanbeveling komt in aanmerking voor plaatsing op de Implementatie Agenda van het programma Zorg Evaluatie & Gepast Gebruik (ZE&GG). In het programma ZE&GG werken patiënten, zorgverleners, zorgaanbieders, zorgverzekeraars en overheid samen aan de bewezen beste zorg voor de patiënt. Daarmee is ZE&GG een programma van alle betrokken partijen in de Medisch Specialistische Zorg. FMS is één van deze betrokken partijen.*

De implementatieagenda van ZE&GG bevat onderwerpen over wat de bewezen beste zorg is en die in de dagelijkse zorgpraktijk geïmplementeerd zouden moeten worden. Zorgverzekeraars Nederland (ZN) en de Nederlandse Vereniging voor Ziekenhuizen (NVZ) hebben landelijke afspraken gemaakt over de implementatie van de onderwerpen van de implementatieagenda. Deze afspraken zijn onderdeel van de zorginkoopafspraken tussen zorgverzekeraars en zorgaanbieders.

Vanuit FMS worden sterke, goed onderbouwde aanbevelingen, getoetst op de behoefte aan een implementatie impuls aangedragen. Voor de beoordeling van onderwerpen uit richtlijnen wordt gekeken naar bovenstaande tabel voor een inschatting van de implementatie impuls. Met de ingevulde implementatietabel kunnen we vanuit FMS de andere HLA-MSZ partijen goed informeren om zo samen te beslissen of de aanbeveling daadwerkelijk op de implementatie agenda zal worden geplaatst.

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Bijlagen bij module 1

Risk of Bias tables
Not applicable.

Literature search strategy
Not applicable.

Module 2 – Diagnostic imaging for primary diagnosis

Question
Which imaging techniques are relevant in the primary diagnosis of necrotizing otitis externa?

Introduction
Currently, the most commonly used imaging modality for the initial diagnosis of necrotizing otitis externa (NOE) is a CT scan. A CT scan can detect bony erosions, which are characteristic of the disease. However, due to the disease's tendency to spread through soft tissue, some clinicians also use MRI scans in addition to CT. In recent years, [18F]-FDG-PET/CT (FDG-PET/CT) has become available and can be used to demonstrate disease activity in the suspected area. The aim of this module is to evaluate the added value of MRI or FDG-PET/CT compared to CT scans in the primary diagnosis of skull base osteomyelitis.

Search and select
A systematic review of the literature was performed to answer the following question:
What is the added value of MRI or FDG-PET/CT to the normally used CT scan in the primary diagnosis of skull base osteomyelitis?

Table 1. PICO

Patients	Patients clinically suspected for NOE
Intervention	MRI and/or FDG-PET/CT
Control	CT scan
Referral	Clinical follow-up and/or histopathology/culture reports
Outcomes	Diagnostic accuracy (sensitivity, specificity, positive predictive value, negative predictive value, area under the ROC curve)
Timing and setting	In cases of suspected NOE, with or without symptoms suggesting involvement of tissues underlying the ear canal, evaluation should be performed in a hospital setting.

Relevant outcome measures
The guideline panel considered diagnostic accuracy; *sensitivity, specificity, positive predictive value* and *negative predictive value* as a **critical** outcome measure for decision making (table 1).

Table 1 Consequences of diagnostic test characteristics

Outcome	Consequences	Relevance
True positives (TP), high sensitivity, high positive prediction value	Patients are justifiably diagnosed with NOE; surgery or giving treatment is justified	Critical
True negatives (TN), high specificity, high negative prediction value	Patients are justifiably not diagnosed with NOE; not giving (surgical) treatment is justified	Critical
False positives (FP), low specificity, low positive prediction value	Patients are unjustifiably diagnosed with NOE; surgery or giving treatment is unjustified	Critical
False negatives (FN), low sensitivity, low negative prediction value	Patients are unjustifiably not diagnosed with NOE; not giving (surgical) treatment is unjustified	Critical

A priori, the working group did not define the outcome measures listed above but used the definitions used in the studies.

The working group defined a difference of 5% in sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) and a difference of 50 per 1000 patients in TP, TN, FP and FN as a minimal clinically (patient) important difference.

Search and select (Methods)
The databases Medline (via OVID) and Embase (via Embase.com) were searched with relevant search terms until May 16, 2023. The detailed search strategy is listed under the tab 'Literature search strategy'. The search resulted in 492 unique hits. Studies were selected based on the following criteria:

- Systematic reviews, randomized controlled trials, and observational studies on diagnostic imaging modalities in the PICO.
- At least one diagnostic accuracy outcome was reported.

Seven studies were initially selected based on title and abstract screening. After reading the full text, 5 studies were excluded (see the exclusion table under the tab 'Evidence tables'), and 2 studies were included. However, both articles (from 2018 and 2020) were derived from the same population, with the same outcome measures. Therefore, only the latter (Kulkarni, 2020), was included.

Summary of literature
Description of studies
One study was included in the analysis of the literature. The assessment of the risk of bias is summarized in the risk of bias tables (under the tab 'Evidence tabellen').

Kulkarni (2020) conducted a retrospective study to evaluate the diagnostic performance of regional fluorine-18 fluorodeoxyglucose ([^{18}F]-FDG) positron emission tomography-computed tomography (PET/CT) in patients with skull base osteomyelitis (SBO). In addition, they evaluated the agreement of the findings between FDG-PET/CT and MRI whenever available.
Patients clinically suspected of SBO were included. Patients with missing data, who were lost to follow-up or with known malignancy were excluded. In total, 77 patients with SBO (male : female = 56:21; mean age 66.4 ± 9.4 years; range 45 – 92 years) who were treated accordingly and with follow up available were included for analyses. All 77 included patients underwent a FDG-PET/CT. In 56 patients (72.7%), MRI scans were also available for agreement analysis for the assessment of disease extent (with a maximum of 10 days interval between FDG-PET/CT and MRI studies). The final diagnosis of the disease was based on the presence of one or more of the following criteria: presence of infective granulation tissue or necrosis on histopathological samples; culture positivity; clinical improvement (reduction in the symptoms or reduction in inflammatory markers) with antimicrobial treatment; response on imaging findings. The prevalence of SBO in the total study population was 61/77.

Results
Diagnostic accuracy [^{18}F]-FDG-PET/CT (critical)
The results for [^{18}F]-FDG-PET/CT are summarized in Table 2 (95% confidence interval not reported).

Table 2. Diagnostic accuracy [^{18}F]-FDG-PET/CT (N=77) (crucial)

FN (% N)	TP (% N)	FP (% N)	TN (% N)	Sensitivity %	Specificity %	PPV %	NPV %
2 (3.3%)	59 (96.7%)	1 (6.2%)	15 (93.7%)	96.7%	93.3%	98.3%	87.5%

The diagnostic performance in establishing the SBO was not reported. However, agreement analysis between FDG-PET/CT and MRI for the assessment of soft tissue disease extent showed a κ value of 0.82. Bony involvement was present in 37 patients (66%). The agreement analysis between these two modalities for assessing bony involvement showed a κ value of 0.81, suggesting good agreement.

Level of evidence of the literature

Diagnostic accuracy (critical)

The level of evidence regarding the outcome diagnostic accuracy originates from diagnostic accuracy studies and therefore initially started high. However, the level of evidence for the outcome measure was downgraded by three levels due to multiple study limitations. These limitations included issues with selection and patient flow (risk of bias, -2), applicability (bias due to indirectness, -1), and the number of included patients (imprecision, -1). As a result, the level of evidence was graded as *very low*.

Conclusions

Diagnostic accuracy FDG PET-CT

Very low GRADE	The evidence is very uncertain about the difference in the number of false positives, true negatives, true positives, specificity and positive prediction value using of FDG-PET/CT in patients with suspected NOE. *Source: Kulkarni (2020)*

Diagnostic accuracy MRI

- GRADE	No evidence was found regarding whether the use of a MRI results in differences in false positive, true negatives, true positives, specificity and positive prediction value when compared to clinical/imaging follow-up in patients with suspected skull base osteomyelitis. *Sources: -*

Considerations – from evidence to recommendation

Balance between desired and undesired effects

Different modalities

A systematic search was performed to determine the diagnostic accuracy in NEO of FDG-PET/CT or MRI, versus CT. Only one study by Kulkarni (2020) was included, which used clinical outcome measures as a referral. It used FDG-PET/CT as index test, with a comparison to MRI. Although the diagnostic accuracy for FDG-PET/CT can be considered high, the evidence shows a high level of uncertainty comparing with MRI. In addition, no comparison with CT was made. The level of evidence was graded as very low.

A large meta-analysis was done by Kim (2023), in which the diagnostic accuracy for diagnosing necrotizing otitis externa of [^{67}Ga]-citrate, [^{99m}Tc}-labelled diphosphonates for bone scintigraphy, MRI and CT was measured. The sensitivities were 0.94 (0.77–0.99), 0.97

(0.88–0.99), 0.94 (0.70–0.99) and 0.96 (0.90–0.98), respectively. Thus, showing comparative results in sensitivity when using only CT or MRI.

Quality of the evidence

The overall quality of evidence is very low. This means we are very uncertain about the estimated effect of the crucial outcomes found.
There is downgrading due to very serious:

- Risk of bias: patient selection; index test
- Imprecision: inaccuracy, due to a very small number of events in a small sample size.

Clinical application and specific characteristics per modality

Based on the literature, there is no available evidence that shows that FDG-PET/CT or MRI leads to significantly higher accuracy compared to CT in diagnosing NOE. Diagnosing NOE can be challenging due to nonspecific symptoms, the potentially prolonged clinical course, and its clinical presentation. The diagnosis is typically made through a combination of clinical symptoms, laboratory findings (microbiology), and imaging results (Chawdhary, 2017). Various imaging modalities can be used not only to diagnose NOE but also to assess the extent of the disease and evaluate potential complications.

The imaging techniques used to diagnose NOE include non-contrast (most used) and contrast-enhanced CT, contrast-enhanced MRI, and nuclear medicine imaging (FDG-PET/CT) (Curtin, 1982; Tsuno, 2022; Shavit, 2018). In patients where limited disease is expected (external ear with surrounding soft tissues), an unenhanced CT is the best option for evaluating bone erosion and demineralization. With CT, opacification of the middle and/or mastoid cells can also be assessed. Adding a soft tissue kernel allows for the evaluation of soft tissue abnormalities. Post-contrast CT helps in evaluating vascular complications (such as venous sinus thrombosis or pseudoaneurysm formation) or abscess formation. CT scan is the initial imaging modality of choice for a suspected case of NOE (Hodgson, 2023).

Contrast-enhanced MRI is useful for evaluating the anatomic location of the NOE and can also be used to assess the extent of the infection in the adjacent soft tissues or bone marrow. Involvement of the skull base foramina and temporomandibular joint can also be visualized. MRI is superior in detecting abscess formation, intracranial extension of the infection (such as dural enhancement or empyema), or ischemic infarcts.

Both CT and MRI provide anatomical information and details on potential complications of NEO; however, they lack functional information. Various nuclear medicine techniques with different radiopharmaceuticals have been used, but fluorine-18 fluorodeoxyglucose ([18F]-FDG) is widely available and is the most commonly used tracer nowadays. This scan provides metabolic information and is taken up in areas of malignancy, infection, and inflammation. As a consequence, this test is highly sensitive but lacks specificity, as it cannot differentiate between infection/inflammation and malignancy. Another limitation is the physiological uptake of FDG in the brain, which makes it difficult to recognize intracranial extension of the infection.

Several neoplastic and inflammatory diseases may mimic the imaging findings of NEO. The most common neoplastic mimickers include nasopharyngeal carcinoma, carcinoma of the external auditory canal, metastases, and lymphoma. The most common inflammatory disease mimickers are IgG4-related disease and granulomatous diseases. Also osteoradionecrosis and medication-related ear canal osteonecrosis (MRECO) may mimic

NEO. The combination of imaging modalities may help in narrowing the differential diagnosis.

Values and preferences of patients (and possibly their relatives/caregivers)
Imaging techniques are used to provide an accurate diagnosis without delaying the diagnostic process. In general, for younger children, an MRI scan can be challenging due to the long acquisition time, noise, or lack of cooperation. However, clinicians should be cautious about using contrast-enhanced CT scans in the diagnostic process due to radiation exposure. This limitation also applies to FDG-PET/CT, as it also involves radiation. For older patients with NEO, an MRI can also be challenging due to motion artifacts, claustrophobia, or contraindications (such as cardiac devices, for example).

Cost considerations
In patients suspected of NEO, an unenhanced CT scan is most frequently used because it is easily available, it has very limited contraindications and results in a first impression of disease extent. There is no evidence that MRI or FDG-PET/CT has higher accuracy than CT for the initial diagnosis of NEO. Replacing CT with MRI or FDG-PET/CT could result in higher costs. However, MRI or FDG-PET/CT may better depict potential complications of NEO, which could influence treatment decisions.

Acceptability, feasibility, and implementation.
Regarding acceptability, feasibility, and implementation, no significant problems are expected because CT, MRI, and FDG-PET/CT are widely available. In cases where there is limited capacity for one or two of the imaging modalities, the remaining third modality serves as a good alternative. If there is a lack of experience in image interpretation, referral to a specialized center is an option.

Recommendation(s)
Rationale of the recommendation: weighing arguments for and against the interventions
NOE clinical symptoms are non-specific and overlap with symptoms of acute external otitis, chronic mastoiditis, and several malignancies. To date, no uniform diagnostic criteria for NOE are available. Imaging has a high sensitivity for NOE and can be suggestive but is sometimes non-specific. The diagnosis of NOE is based on a combination of clinical symptoms, clinical findings, and imaging findings.

Currently, there is no evidence that one imaging modality is superior to another in diagnosing NOE. Depending on the clinical presentation (or clinical suspicion), patient age, comorbidities, possible contraindications, and the patient's own preference, a choice between the different imaging modalities can be made.

In daily practice, an unenhanced CT is the first imaging modality used because it is widely available and does not require intravascular contrast. A CT scan may show bony erosions or demineralization in cases of osteomyelitis. A soft-tissue kernel helps evaluate possible infiltration of fat planes, which can be suggestive of NOE.

When the CT scan is inconclusive or more extensive disease is expected, an additional contrast-enhanced MRI can be performed. MRI is superior in evaluating the extent of soft tissue involvement, skull base foramina, intracranial involvement, and ruling out vascular complications. If an MRI is contraindicated, a contrast-enhanced CT can be considered.

In case of complex (/severe) NEO (see module Definition and limiting doctor's delay in diagnosing necrotizing otitis externa (hyperlink)) FDG-PET/CT(or MRI) imaging provides functional imaging which may be helpful for biopsy guiding and/or in therapy evaluation.

Diagnosing necrotizing otitis externa (NOE) is often a result of a combination of clinical symptoms, laboratory findings and imaging.

Use imaging when suspecting NEO. Several imaging modalities are optional:

- CT scan (most commonly used first modality and widely available). It allows evaluation of cortical bone erosions and trabecular bone destruction. Add soft tissue kernel to evaluate soft tissue abnormalities which aid in the diagnosis.
- Contrast enhanced MRI. It will allow better evaluation of soft tissue abnormalities but also allows evaluation of vascular or intracranial complications.
- In complex cases of NEO, FDG-PET CT (or MRI) could also be used as a baseline scan for treatment monitoring and also for possible biopsy guiding.

Knowledge gaps

During the development of this module, a systematic search for studies addressing the research question was conducted. Through a systematic literature analysis and evidence assessment, it became clear that there are still knowledge gaps within this module. The working group believes that further research is necessary to provide clearer answers to practical questions in the future.

Knowledge question

What is the added value of MRI or FDG-PET/CT to the normally used CT scan in the primary diagnosis of skull base osteomyelitis?

Explanation

This is the original search question. We found no comparative literature regarding all modalities. To fully answer this question, a comparative cohort in which all relevant imaging modalities are performed on patients with NOE should be conducted.

Knowledge question

Is dual energy CT an option for diagnosing NOE?

Explanation

Dual energy CT is used in osteomyelitis of other parts of the body. It shows edema of the bone marrow. It may also be cheaper than MRI and PET/CT. For NOE, no studies have been perfomed with this modality however.

Literature

Chawdhary G, Pankhania M, Douglas S, Bottrill I. Current management of necrotising otitis externa in the UK: survey of 221 UK otolaryngologists. Acta Otolaryngol. 2017 Aug;137(8):818-822. doi: 10.1080/00016489.2017.1295468. Epub 2017 Mar 16. PMID: 28301961.

Curtin HD, Wolfe P, May M. Malignant external otitis: CT evaluation. Radiology. 1982 Nov;145(2):383-8. doi: 10.1148/radiology.145.2.7134442. PMID: 7134442.

Hodgson SH, Khan MM, Patrick-Smith M, Martinez-Devesa P, Stapleton E, Williams OM, Pretorius P, McNally M, Andersson MI; UK NOE Collaborative. UK consensus definitions for necrotising otitis externa: a Delphi study. BMJ Open. 2023 Feb 20;13(2):e061349. doi: 10.1136/bmjopen-2022-061349. PMID: 36806133; PMCID: PMC9945308.

Kulkarni SC, Padma S, Shanmuga Sundaram P. In the evaluation of patients with skull base osteomyelitis, does 18F-FDG PET CT have a role? Nucl Med Commun. 2020 Jun;41(6):550-559. doi: 10.1097/MNM.0000000000001187. PMID: 32282638.

Kim DH, Kim SW, Hwang SH. Predictive value of radiologic studies for malignant otitis externa: a systematic review and meta-analysis. Braz J Otorhinolaryngol. 2023 Jan-Feb;89(1):66-72. doi: 10.1016/j.bjorl.2021.08.011. Epub 2021 Oct 26. PMID: 34799270; PMCID: PMC9874358.

Stern Shavit S, Bernstine H, Sopov V, Nageris B, Hilly O. FDG-PET/CT for diagnosis and follow-up of necrotizing (malignant) external otitis. Laryngoscope. 2019 Apr;129(4):961-966. doi: 10.1002/lary.27526. Epub 2018 Dec 14. PMID: 30549258.

Tsuno NSG, Tsuno MY, Coelho Neto CAF, Noujaim SE, Decnop M, Pacheco FT, Souza SA, Fonseca APA, Garcia MRT. Imaging the External Ear: Practical Approach to Normal and Pathologic Conditions. Radiographics. 2022 Mar-Apr;42(2):522-540. doi: 10.1148/rg.210148. Epub 2022 Feb 4. PMID: 35119966.

Verkeerslicht en (de-)implementatietabel

Toelichting

Met het verkeerslicht worden aanbevelingen gecategoriseerd op basis van formulering en bewijskracht. Als eindproduct wordt bij richtlijnmodules met een sterk geformuleerde en voldoende onderbouwde aanbeveling een implementatietabel opgeleverd. Hierin wordt onder andere opgenomen:

- Een beschrijving van het knelpunt om de module uit te werken of herzien;
- De te verwachten belemmerende en bevorderende factoren voor implementatie;
- Welke partijen van belang zijn bij toepassen van de aanbeveling in de praktijk;
- Een inschatting van de implementatietermijn.

Verkeerslichtanalyse

- **ROOD** = sterk geformuleerde aanbeveling om iets niet te doen, met een GRADE high of moderate
- **ORANJE** = zwak geformuleerde aanbeveling; mogelijk kennishiaat
- **GROEN** = sterk geformuleerde aanbeveling om iets wel te doen, met een GRADE high of moderate
- **LICHT ROOD** of **LICHT GROEN** = sterk geformuleerde aanbevelingen met een GRADE low, very low of geen GRADE *(modules waarin geen studies geïncludeerd konden worden in de literatuursamenvatting of waarin geen literatuursamenvatting werd geschreven zoals modules waarin organisatie van zorg wordt beschreven)*

(Sub)aanbeveling	Sterkte van de aanbeveling	Bewijskracht per uitkomstmaat	Verkeerslicht per (sub)aanbeveling
Aanbeveling 1: Diagnosing NOE often is a result of a combination of clinical symptoms, laboratory findings and imaging. Use imaging when suspecting NOE. Several imaging modalities are optional: • CT scan (most commonly used first modality and widely available). It allows evaluation of cortical bone erosions and trabecular bone destruction. Add soft tissue kernel to evaluate soft tissue abnormalities which aid in the diagnosis. • Contrast enhanced MRI. It will allow better evaluation of soft tissue abnormalities but also allows evaluation of vascular or intracranial complications. FDG-PET CT(or MRI) could also be used as a baseline scan for treatment monitoring and also for possible biopsy guiding.	□ Sterk (doe/ gebruik)	**Overall bewijskracht** □ **VL** **Range bewijskracht van alle uitkomstmaten** □ **VL**	**LICHT GROEN**

Implementatietabel

Tabel A: (De-)Implementatietabel met impuls analyse

Aanbeveling – 1			
1. Wat was het onderliggende probleem om deze uitgangsvraag uit te werken?	**□ Ongewenste praktijkvariatie**		
2. Maak een inschatting over hoeveel patiënten het ongeveer gaat waar de aanbeveling betrekking op heeft?	**□ < 1000**		
3. Maakt de aanbeveling deel uit van een set van interventies voor hetzelfde probleem?	**□ Nee**		
4. Belemmeringen en kansen op verschillende niveaus voor landelijke toepassing van de aanbeveling:	***Voorbeelden***	**Wat zijn mogelijke belemmerende factoren?**	**Wat zijn mogelijke bevorderende factoren?**
a) **Richtlijn/ klinisch traject (innovatie)**	*Voortschrijding/vooruitgang in de praktijk, haalbaarheid, geloofwaardigheid, toegankelijkheid, aantrekkelijkheid*	geen	geen
b) **Zorgverleners (artsen en verpleegkundigen)**	*Bewustzijn, kennis, houding, motivatie om te veranderen, gedragsroutines*	Expertise van radioloog verschilt per modaliteit. Derhalve soms voorkeur voor 1 modaliteit t.o.v. anderen. Dit wisselt ook per kliniek.	Gezien kleine verschillen tussen modaliteiten, lijkt er ruimte te zijn per specialist welke beeldvorming zij willen gebruiken. De richtlijn laat dit ook toe.
c) **Patiënt/ cliënt (naasten)**	*Kennis, vaardigheden, houding, compliance*	Geen	geen

d) **Sociale context**	*Mening van collega's, cultuur van het netwerk, samenwerking, leiderschap*	geen	geen
e) **Organisatorische context**	*Organisatie van zorgprocessen, personeel, capaciteiten, middelen, structuren*	Niet elk ziekenhuis beschikt over een PET-scan, alhoewel dit maar een klein gedeelte is.	Indien zelf geen PET-scanner, hebben klinieken contracten om deze elders (in een andere instelling die wel over een PET beschikt) te laten verrichten. Echter vereist dit wel verplaatsing van de patiënt.
f) **Economische en politieke context**	*Financiële regelingen, regelgeving, beleid (vergoede zorg, betaaltitel)*	geen	geen

5. Welke personen/partijen zijn van belang bij het toepassen van de aanbeveling in de praktijk?	**x** Patiënt/ cliënt (naaste) **x** Professional
6. Wat zouden deze personen/ partijen moeten veranderen in hun gedrag of organisatie om de aanbeveling toe te passen?	Dit kan reeds worden toegepast, geen aanpassingen hoeven te worden gemaakt
7. Binnen welk tijdsbestek moet de aanbeveling zijn geïmplementeerd?	□ < 1 jaar
8. Conclusie: is er extra aandacht nodig voor implementatie van de aanbeveling (anders dan publicatie van deze richtlijnmodule)?	□ **Nee**

**Deze aanbeveling komt in aanmerking voor plaatsing op de Implementatie Agenda van het programma Zorg Evaluatie & Gepast Gebruik (ZE&GG). In het programma ZE&GG werken patiënten, zorgverleners, zorgaanbieders, zorgverzekeraars en overheid samen aan de bewezen beste zorg voor de patiënt. Daarmee is ZE&GG een programma van alle betrokken partijen in de Medisch Specialistische Zorg. FMS is één van deze betrokken partijen.*

De implementatieagenda van ZE&GG bevat onderwerpen over wat de bewezen beste zorg is en die in de dagelijkse zorgpraktijk geïmplementeerd zouden moeten worden. Zorgverzekeraars Nederland (ZN) en de Nederlandse Vereniging voor Ziekenhuizen (NVZ) hebben landelijke afspraken gemaakt over de implementatie van de onderwerpen van de implementatieagenda. Deze afspraken zijn onderdeel van de zorginkoopafspraken tussen zorgverzekeraars en zorgaanbieders.

Vanuit FMS worden sterke, goed onderbouwde aanbevelingen, getoetst op de behoefte aan een implementatie impuls aangedragen. Voor de beoordeling van onderwerpen uit richtlijnen wordt gekeken naar bovenstaande tabel voor een inschatting van de implementatie impuls. Met de ingevulde implementatietabel kunnen we vanuit FMS de andere HLA-MSZ partijen goed informeren om zo samen te beslissen of de aanbeveling daadwerkelijk op de implementatie agenda zal worden geplaatst.

Bijlagen bij Module 2 – Diagnostic imaging

Risk of Bias tables

Risk of bias assessment diagnostic accuracy studies (QUADAS II, 2011)

Study reference (first author, publication year)	**Patient selection**	**Index test**	**Reference standard**	**Flow and timing**	**Comments with respect to applicability**
Kulkarni, 2020	Was a consecutive or random sample of patients enrolled? Yes, due to single-center tertiary centre study a selection bias occured Was a case-control design avoided? yes Did the study avoid inappropriate exclusions? yes	Were the index test results interpreted without knowledge of the results of the reference standard? yes If a threshold was used, was it pre-specified? No threshold was used	Is the reference standard likely to correctly classify the target condition? Probably Were the reference standard results interpreted without knowledge of the results of the index test? no	Was there an appropriate interval between index test(s) and reference standard? yes Did all patients receive a reference standard? Because of the reference standard being multifactorial all patient recieved one or multiple factors Did patients receive the same reference standard? no Were all patients included in the analysis? yes	Are there concerns that the included patients do not match the review question? no Are there concerns that the index test, its conduct, or interpretation differ from the review question? no Are there concerns that the target condition as defined by the reference standard does not match the review question? no

Randomization: generation of allocation sequences have to be unpredictable, for example computer generated random-numbers or drawing lots or envelopes. Examples of inadequate procedures are generation of allocation sequences by alternation, according to case record number, date of birth or date of admission.
Allocation concealment: refers to the protection (blinding) of the randomization process. Concealment of allocation sequences is adequate if patients and enrolling investigators cannot foresee assignment, for example central randomization (performed at a site remote from trial location). Inadequate procedures are all procedures based on inadequate randomization procedures or open allocation schedules..
Blinding: neither the patient nor the care provider (attending physician) knows which patient is getting the special treatment. Blinding is sometimes impossible, for example when comparing surgical with non-surgical treatments, but this should not affect the risk of bias judgement. Blinding of those assessing and collecting outcomes prevents that the knowledge of patient assignment influences the process of outcome assessment or data collection (detection or information bias). If a study has hard (objective) outcome measures, like death, blinding of outcome assessment is usually not necessary. If a study has "soft" (subjective) outcome measures, like the assessment of an X-ray, blinding of outcome assessment is necessary. Finally, data analysts should be blinded to patient assignment to prevents that knowledge of patient assignment influences data analysis.
Lost to follow-up: If the percentage of patients lost to follow-up or the percentage of missing outcome data is large, or differs between treatment groups, or the reasons for loss to follow-up or missing outcome data differ between treatment groups, bias is likely unless the proportion of missing outcomes compared with observed event risk is not enough to have an important impact on the intervention effect estimate or appropriate imputation methods have been used.
Selective outcome reporting: Results of all predefined outcome measures should be reported; if the protocol is available (in publication or trial registry), then outcomes in the protocol and published report can be compared; if not, outcomes listed in the methods section of an article can be compared with those whose results are reported.
Other biases: Problems may include: a potential source of bias related to the specific study design used (e.g., lead-time bias or survivor bias); trial stopped early due to some data-dependent process (including formal stopping rules); relevant baseline imbalance between intervention groups; claims of fraudulent behavior; deviations from intention-to-treat (ITT) analysis; (the role of the) funding body (see also downgrading due to industry funding https://kennisinstituut.viadesk.com/do/document?id=1607796-646f63756d656e74). Note: The principles of an ITT analysis implies that (a) participants are kept in the intervention groups to which they were randomized, regardless of the intervention they actually received, (b) outcome data are measured on all participants, and (c) all randomized participants are included in the analysis.
Overall judgement of risk of bias per study and per outcome measure, including predicted direction of bias (e.g., favors experimental, or favors comparator). Note: the decision to downgrade the certainty of the evidence for a particular outcome measure is taken based on the body of evidence, i.e., considering potential bias and its impact on the certainty of the evidence in all included studies reporting on the outcome.

Table of excluded studies

Reference	Reason for exclusion
Al-Noury K, Lotfy A. Computed tomography and magnetic resonance imaging findings before and after treatment of patients with malignant external otitis. Eur Arch Otorhinolaryngol. 2011 Dec;268(12):1727-34. doi: 10.1007/s00405-011-1552-8. Epub 2011 Mar 15. PMID: 21400256.	No comparison made
van der Meer WL, Waterval JJ, Kunst HPM, Mitea C, Pegge SAH, Postma AA. Diagnosing necrotizing external otitis on CT and MRI: assessment of pattern of extension. Eur Arch Otorhinolaryngol. 2022 Mar;279(3):1323-1328. doi: 10.1007/s00405-021-06809-2. Epub 2021 Apr 25. PMID: 33895893; PMCID: PMC8897339.	Wrong outcomes
Balakrishnan R, Dalakoti P, Nayak DR, Pujary K, Singh R, Kumar R. Efficacy of HRCT Imaging vs SPECT/CT Scans in the Staging of Malignant External Otitis. Otolaryngol Head Neck Surg. 2019 Aug;161(2):336-342. doi: 10.1177/0194599819838834. Epub 2019 Apr 16. PMID: 30987522.	Wrong outcome
Auinger AB, Dahm V, Stanisz I, Schwarz-Nemec U, Arnoldner C. The challenging diagnosis and follow-up of skull base osteomyelitis in clinical practice. Eur Arch Otorhinolaryngol. 2021 Dec;278(12):4681-4688. doi: 10.1007/s00405-020-06576-6. Epub 2021 Jan 28. PMID: 33511482; PMCID: PMC8553694.	Wrong outcome
Chapman PR, Choudhary G, Singhal A. Skull Base Osteomyelitis: A Comprehensive Imaging Review. AJNR Am J Neuroradiol. 2021 Mar;42(3):404-413. doi: 10.3174/ajnr.A7015. Epub 2021 Jan 21. PMID: 33478944; PMCID: PMC7959418.	Review of literature
Maramattom BV, Ram SA, Viswam V, Nair S. Central Skull Base Osteomyelitis: Multimodality Imaging and Clinical Findings from a Large Indian Cohort. Neurol India. 2022 Sep-Oct;70(5):1911-1919. doi: 10.4103/0028-3886.359218. PMID: 36352587.	No comparison made

Literature search strategy

Zoekverantwoording
Algemene informatie

Cluster/richtlijn: Osteomyelitis schedelbasis – Maligne otitis externa	
Uitgangsvraag/modules: Welke beeldvormende diagnostiek is relevant voor het stellen van de diagnose maligne otitis externa (diagnostische vraag)	
Database(s): Ovid/Medline, Embase.com	Datum: 16 mei 2023
Periode: 2000 - heden	Talen: Engels, Nederlands
Literatuurspecialist: Miriam van der Maten	
BMI-zoekblokken: voor verschillende opdrachten wordt (deels) gebruik gemaakt van de zoekblokken van BMI-Online https://blocks.bmi-online.nl/ Bij gebruikmaking van een volledig zoekblok zal naar de betreffende link op de website worden verwezen.	

Toelichting: Voor deze vraag is gezocht op de elementen: • Maligne otitis externa/osteomyelitis schedelbasis • Diagnostische modaliteiten CT of MRI of PET • Diagnostisch filter; termen 'diagnostic imaging' en diagnostics (in titel) toegevoegd. De sleutelartikelen worden gevonden met de zoekopdracht.
Te gebruiken voor richtlijnen tekst: *Nederlands* In de databases Embase.com en Ovid/Medline is op 16 mei 2023 systematisch gezocht naar studies over relevante beeldvormende diagnostiek voor het stellen van de diagnose maligne otitis externa. De literatuurzoekactie leverde 492 unieke treffers op. *Engels* On the 16th of May 2023, we performed a systematic search in the databases Embase.com and Ovid/Medline to find literature about relevant imaging modalities for diagnosing malignant otitis externa. The search resulted in 492 unique hits.

Zoekopbrengst

	EMBASE	**OVID/MEDLINE**	**Ontdubbeld**
Totaal	308	281	**492**

Zoekstrategie

Embase.com

No.	**Query**	**Results**
#6	#1 AND (#2 OR #3 OR #4) AND #5 AND ([english]/lim OR [dutch]/lim) AND [2000-2023]/py NOT (('animal experiment'/exp OR 'animal model'/exp OR 'nonhuman'/exp) NOT 'human'/exp)	308
#5	'diagnostic procedure'/mj OR 'diagnostic imaging'/exp OR 'sensitivity and specificity'/de OR sensitiv*:ab,ti OR specific*:ab,ti OR predict*:ab,ti OR 'roc curve':ab,ti OR 'receiver operator':ab,ti OR 'receiver operators':ab,ti OR likelihood:ab,ti OR 'diagnostic error'/exp OR 'diagnostic accuracy'/exp OR 'diagnostic test accuracy study'/exp OR 'inter observer':ab,ti OR 'intra observer':ab,ti OR interobserver:ab,ti OR intraobserver:ab,ti OR validity:ab,ti OR kappa:ab,ti OR reliability:ab,ti OR reproducibility:ab,ti OR ((test NEAR/2 're-test'):ab,ti) OR ((test NEAR/2 'retest'):ab,ti) OR 'reproducibility'/exp OR accuracy:ab,ti OR 'differential diagnosis'/exp OR 'validation study'/de OR 'measurement precision'/exp OR 'diagnostic value'/exp OR 'reliability'/exp OR 'predictive value'/exp OR ppv:ti,ab,kw OR npv:ti,ab,kw OR diagnos*:ti	10417931
#4	'computer assisted emission tomography'/exp OR 'gated single photon emission computed tomography'/exp OR 'single photon emission computer tomography'/exp OR petscan*:ti,ab,kw OR pet:ti,ab,kw OR ((emission NEAR/3 tomograph*):ti,ab,kw) OR radionuclid*:ti,ab,kw OR 'fluorodeoxyglucose'/exp OR 'fluorodeoxyglucose f 18'/exp OR 'fluorodeoxyglucose':ti,ab,kw OR fdg:ti,ab,kw	439885
#3	'nuclear magnetic resonance imaging'/exp OR 'mri scanner'/exp OR ('magnetic resonance':ab,ti AND (image:ab,ti OR images:ab,ti OR imaging:ab,ti)) OR mri:ab,ti OR mris:ab,ti OR nmr:ab,ti OR mra:ab,ti OR mras:ab,ti OR zeugmatograph*:ab,ti OR 'mr tomography':ab,ti OR 'mr tomographies':ab,ti OR 'mr tomographic':ab,ti OR 'proton spin':ab,ti OR ((magneti*:ab,ti OR 'chemical shift':ab,ti) AND imaging:ab,ti) OR fmri:ab,ti OR fmris:ab,ti OR ((imag* NEAR/3 modalit*):ti,ab,kw)	1554550
#2	'computer assisted tomography'/exp OR 'cat scan':ti,ab,kw OR ((compute* NEAR/3 tomograph*):ti,ab,kw) OR ct:ti,ab,kw	1670461

#1	'malignant otitis externa'/exp/mj OR (((maligna* OR necroti* OR necrosis) NEAR/3 ('otitis externa' OR 'external otitis')):ti,kw) OR ('otitis externa'/mj AND (maligna*:ti,kw OR necroti*:ti,kw OR necrosis:ti,kw)) OR (('osteomyelitis'/exp/mj OR 'osteomyelitis':ti,kw OR osteitis:ti,kw) AND ('skull'/exp/mj OR 'skull disease'/exp/mj OR skull*:ti,ab,kw OR cranial:ti,ab,kw OR cranium:ti,ab,kw))	3383

Ovid/Medline

#	Searches	Results
8	limit 7 to ((english language or dutch) and yr="2000 -Current")	281
7	6 not ((exp animals/ or exp models, animal/) not humans/)	392
6	1 and (2 or 3 or 4) and 5	398
5	exp "Sensitivity and Specificity"/ or (Sensitiv* or Specific*).ti,ab. or (predict* or ROC-curve or receiver-operator*).ti,ab. or (likelihood or LR*).ti,ab. or exp Diagnostic Errors/ or (inter-observer or intra-observer or interobserver or intraobserver or validity or kappa or reliability).ti,ab. or reproducibility.ti,ab. or (test adj2 (re-test or retest)).ti,ab. or "Reproducibility of Results"/ or accuracy.ti,ab. or *Diagnosis, Differential/ or Validation Study/ or exp diagnostic imaging/ or ppv.ti,ab,kf. or npv.ti,ab,kf. or diagnos*.ti.	9937614
4	exp *Tomography, Emission-Computed/ or "petscan*".ti,ab,kf. or "pet".ti,ab,kf. or ("emission" and "tomogra*").ti,ab,kf. or "radionuclid*".ti,ab,kf. or exp Fluorodeoxyglucose F18/ or fluorodeoxyglucose.ti,ab,kf. or FDG.ti,ab,kf.	217767
3	exp *magnetic resonance imaging/ or ("magnetic resonance" and (image or images or imaging)).ti,ab,kf. or mri.ti,ab,kf. or mris.ti,ab,kf. or nmr.ti,ab,kf. or mra.ti,ab,kf. or mras.ti,ab,kf. or zeugmatograph*.ti,ab,kf. or "mr tomography".ti,ab,kf. or "mr tomographies".ti,ab,kf. or "mr tomographic".ti,ab,kf. or "proton spin".ti,ab,kf. or ((magneti* or "chemical shift") and imaging).ti,ab,kf. or fmri.ti,ab,kf. or fmris.ti,ab,kf. or (imag* adj3 modalit*).ti,ab,kf.	825746
2	exp *Tomography, X-Ray Computed/ or computed tomograph*.ti,ab,kf. or ct.ti,ab,kf. or cts.ti,ab,kf. or cat scan*.ti,ab,kf. or computer assisted tomograph*.ti,ab,kf. or computerized tomograph*.ti,ab,kf. or computerised tomograph*.ti,ab,kf. or computed x ray tomograph*.ti,ab,kf. or computed xray tomograph*.ti,ab,kf.	668301
1	((maligna* or necroti* or necrosis) adj3 ('otitis externa' or 'external otitis')).ti,kf. or (exp *Otitis Externa/ and (maligna* or necroti* or necrosis).ti,kf.) or ((exp *Osteomyelitis/ or 'osteomyelitis'.ti,kf. or osteitis.ti,kf.) and (exp Skull/ or skull*.ti,ab,kf. or cranial.ti,ab,kf. or cranium.ti,ab,kf.))	3088

Module 3 – Microbiology and histopathology

Question
What is the added value of microbiological and histopathological tests in patients with proven or suspected NOE?

Background
Necrotizing otitis externa is an infectious process, due to a bacterial or fungal infection. Identifying the correct pathogen is of vital importance for starting the right treatment regimen. Cultures, obtained via ear canal swabs, are standard practice. However, by taking a swab from the canal, skin colonizing bacteria and unharmful microorganisms are likely to get included in the culture. Furthermore, the patient has often been treated with topical antiobiotics. For these reasons the pathogenic microorganism might not be found superficially anymore. The question is therefore whether deeper biopsies have a higher yield of finding pathogens in cultures, or histopathologic examination opposed to ear canal swabs, and whether the current diagnostic workup is sufficient to exclude most other diseases, making histopathological examination redundant. Other added benefits of such a test could be the histopathological findings, in which other diagnoses could be diagnosed, such as neoplasms of the ear canal or inflammatory diseases, clinically mimicking NOE.

Search and select
To answer the primary question, two search questions were formulated. A systematic review of the literature was performed to answer the following questions:

Question 1: biopsy versus swab
What is the added value of deep tissue biopsy versus ear canal swab in order to identify the pathogen and/or making the correct diagnosis?

Table 1. PICO 1

Patients	Patients with proven or suspected NOE
Intervention	Biopsy for microbiological culture
Control	Swab for microbiological culture
Outcomes	Diagnostic accuracy (sensitivity, specificity, positive predictive value, negative predictive value, missed diagnosis/diagnostic error)
Referral	Outcomes after 1 year
Other selection criteria	Systematic reviews, RCT, observational studies

Relevant outcome measures
The guideline development group considered *diagnostic accuracy* as a critical outcome measure for decision making, as displayed in Table 2. The outcome represented comes from any type of culture, either superficial or deep. Missed diagnosis/diagnostic error was considered a critical outcome measure.

Table 2 - consequences of diagnostic test

Properties Outcome	Consequence
True positives (TP)	Patient has NOE; the pathogen is correctly identified by culture of deep tissue the patient will get appropriate treatment.

True negatives (TN)	Patient is correctly identified as not having NOE, no pathogens are found and the patient is managed accordingly.
False positives (FP)	Patients with NOE; there is a positive culture, which is not the causitive agent. Risk of inappropriate / falsely directed treatment.
False negatives (FN)	No microbiological diagnosis. Patient with NOE, but no pathogen is found in culture (deep tissue) ; empirical therapy has to be continued .

Any number of missed diagnoses or diagnostic errors was considered by the working group to be clinically relevant.

Question 2: biopsy vs no biopsy
Is additional histopathological examination relevant in order to exclude other pathology in patients with suspected NOE?

Table 3. PICO 2

Patients	Patients with proven or suspected NOE
Intervention	Histopathological biopsy
Control	No biopsy
Outcomes	Remission, survival, quality of life
Other selection criteria	Missed diagnosis/diagnostic error

Relevant outcome measures
The guideline development group considered missed diagnosis as a critical outcome measure for decision making. Missed diagnosis or diagnostic error is mostly described as a number of patients or a percentage. All numbers of missed diagnosis or diagnostic error were considered clinically important differences.

Search and select (Methods)
The databases Medline (via OVID) and Embase (via Embase.com) were searched using relevant search terms until July 7, 2023. Due to overlap in search terms, both search questions were combined into a single literature search. The detailed search strategy is provided under the "Methods" tab. The systematic literature search yielded 347 unique hits. Studies were selected based on the following criteria: systematic reviews, RCTs, observational studies, and other non-comparative research on the value of surgical treatment for malignant external otitis.

Article selection for both search questions was conducted. Twenty-four studies were initially selected based on title and abstract screening. After full-text review, 23 studies were excluded for question 1, and 1 study was included. For question 2, 24 studies were excluded, and no studies were included. (See the table with reasons for exclusion under the "Methods" tab.)

Summary of literature
Description of studies

Only one studie is included in the analysis of the literature. Important study characteristics and results are summarized in table 2. The assessment of the risk of bias is summarized in the risk of bias tables (under the tab 'Evidence tables').

Table 4. Characteristics of included studies

Study	Participants (number, age, other important characteristics)	Comparison	Follow-up	Outcome measures	Risk of bias (per outcome measure)*
Abu Eta, (2018)	Baseline, 52 patients in total: 27 in the intervention group and 25 in the control group. The cohort consisted of 29 men and 23 women, with a mean age of 70.6 years. All patients were referred from other tertiary hospitals in the region due to the failure of initial conventional treatment for necrotizing otitis externa. Following consultation with an infectious disease specialist, all patients were treated with broad-spectrum antibiotics based on culture results	Twenty-seven patients (51.9%) underwent local treatment and surgical debridement of necrotic bone and soft tissue, with tissue samples obtained for culturing, including fungal cultures. The comparison group of 25 patients received only antibiotic or antifungal medication.	There was no mention of follow-up.	Diagnostic error/missed diagnosis	High

*For further details, see risk of bias table in the appendix

Results

In a study performed by Abu Eta (2018), 52 patients with necrotizing otitis externa were treated with culture-directed antimicrobial therapy. Cultures were obtained by swabs technique. In case of a negative culture, anti-pseudomonal antibiotics were given. 27 of 52 (51.9%) patients with NOE underwent surgery, including 7 patients who underwent mastoidectomy, 6 patients who underwent debridement of the ear canal of soft tissue and bone of external ear canal and 14 (26.9%) who had both debridement and mastoidectomy. The decision to operate was made according to clinical, laboratory and imaging parameters; however, the main decision-making parameter was the clinical examination. Patients, who had shown no clinical improvement on physical examination during the course of conservative treatment, or who had severe edema, granulation tissue or necrosis of the external ear canal skin. This article did not directly compare cultures obtained by swab versus biopsy, and therefore we conclude that no literature was found that answers the PICO question.

Conclusions

Question 1: biopsy versus swab
Diagnostic accuracy

No GRADE	No evidence was found regarding the diagnostic accuracy of biopsies compared to swabs for cultures in patients with suspected skull base osteomyelitis *Source: -*

Missed diagnosis/diagnostic error, biopsy versus swab for cultures

Very low GRADE	The evidence is very uncertain, but a higher rate of microbiological diagnoses might be achieved with deep tissue biopsies compared to swabs for cultures in patients with necrotizing otitis externa. *Source:* Abu Eta (2018)

Question 2: biopsy versus no biopsy
Missed diagnosis/diagnostic error

No GRADE	No evidence was found regarding the difference in diagnostic error/missed diagnosis using histopathological biopsies over no biopsies in patients with suspected skull base osteomyelitis. *Source: -*

Considerations – from evidence to recommendation

Balance between desired and undesired effects

There is very limited literature describing the optimal process for obtaining a microbiological diagnosis for necrotizing otitis externa. Therefore, the guideline committee has arrived at a pragmatic proposal, supported by general principles within microbiology.

Microbiology

The majority of patients (62%) has NOE because of an infection with *Pseudomonas aeruginosa* (Takata, 2023). Other relevant pathogens include *Staphylococcus aureus (6%)*, other bacteria or *Aspergillus* spp (9%). Since these other causative agents are not susceptible to most antipseudomonal antibiotics it is important to continue finding the causative agent in case of negative culture results (from swabs).

Taking a culture with a swab from the external ear is non-invasive, easy to perform, and cost-effective. This is and stays the most favorable primary way of obtaining culture material. The guideline committee considers it useful to take cultures from the ear canal (swab or biopsy) in cases where the clinical presentation is consistent with (necrotizing) otitis externa with pus or debris in the ear canal. If the ear canal does not show signs of infection and previous cultures were negative or inconclusive, and if there is a need for a microbiological diagnosis due to stagnation or deterioration of the clinical condition, a deep or surgical biopsy may be considered.

The patient has usually been treated with topical and systemic antibiotics, which can result in a false-negative culture. Although for NOE there is no specific evidence for the optimal microbiological work-up, it is known from other diseases (such as osteomyelitis in patients with diabetic chronic ulcers) that antibiotic treatment prior to taking a culture might lead to

false-negative results. Therefore, it is recommended to discontinue antibiotics for up to 7 days prior to obtaining cultures (Gramberg, 2023).
When obtaining a swab from the ear canal, skin-colonizing bacteria and non-pathogenic organisms, such as yeast-like fungi, are likely to be included in the culture. These microorganisms can mask the real pathogen.The advantage of taking a tissue biopsy is the higher change of culturing the micro-organism. Especially fungi are not easily grown from a swab but might only be detected in a biopsy (Swab guideline 'Invasieve schimmelinfecties'). In the study conducted by Abu Eta (2018), a higher number of fungal cultures were identified in patients who underwent deep surgical biopsies compared to those with ear canal swab cultures (RR 2.55, 95% CI 0.93–6.97). Furthermore other forms of osteomyelitis it is shown that putting a tissue biopsie in culture is preferable over skin-swabs to identify the right causing agent (Senneville, 2006).

A distinction can be made between two types of biopsies: a biopsy from the ear canal is taken from abnormal-appearing tissue, usually granulation tissue or a granulation polyp. This biopsy is obtained through the ear canal under local anesthesia. Alternatively, a biopsy may be taken from abnormal tissue at another location. This type of biopsy requires a surgical approach, for example, guided by specific abnormalities identified in imaging studies.Tissue biopsies have downsides which should be taken into account. An ear canal biopsy is limited to patient discomfort and minor bleeding after the procedure. A deep surgical biopsy requires surgery under general anesthesia to obtain these samples.

Ultimately, in case of absent or insufficient improvement of the clinical situation after 1-2 weeks of empirical treatment in patients with negative swab cultures microbiological diagnostics should be repeated. For this purpose biopsies for culture and histopathological examination are recommended because of the higher likelihood of finding the actual causative micro-organism, especially fungi. In case of negative culture results from biopsies, collaboration with the medical microbiologist for PCR-techniques might be of help to find the causative agent.

Histolopathology
The added benefit of a tissue biopsy could be to exclude other (severe) diseases. However, this is only scarcely described in the literature. A retrospective study by Sekar (2022) analyzed a cohort of patients in which 68 out of 79 patients with necrotizing otitis externa underwent histopathological biopsies. Biopsies were performed when granulation tissue was observed, and the material taken was the granulation tissue itself. The authors, however, do not mention the results of the biopsies. It can be presumed that the biopsies were negative for malignancies, as only patients with proven NOE were included retrospectively. Nothing was mentioned about biopsies leading to other diagnoses.
Other authors emphasize the importance of biopsies, as histopathology can sometimes reveal diagnoses such as squamous cell carcinoma in patients previously thought to have necrotizing otitis externa based on clinical findings (Saravanam, 2013). Additionally, other diseases can mimic the clinical presentation of necrotizing otitis externa, including granulomatous and inflammatory processes, tumors with different histology, bone disorders, and collagen vascular or autoimmune diseases (Maniu, 2016; Walton, 2014).

Quality of the evidence
The overall quality of evidence is very low. This means that the working group is very uncertain about the estimated effect of the outcomes found.
There is downgrading due to:

- Risk of bias: patient selection; index test

- Imprecision: inaccuracy, due to a very small number of events in a small sample size.
- Indirectness: indirectness due to differences in interventions and outcomes.

Values and preferences of patients (and possibly their caregivers)
Swabs of the external ear canal are non invasive procedures. No problems for the patients should be expected. When taking biopsies of the external ear canal, the procedure can be performed in the outpatient clinic. With local anesthesia, only a small discomfort is expected for the patient. Extended surgery is more demanding, with general anesthesia and hospital admissions. The effects of surgery to obtain patient material in the case of NOE are barely described. However, general ear surgery has in general a low length of admission and a relatively small amount of complications.

Costs (resources)
Microbiological cultures are low in costs. Histopathology is also low in costs. In the very rare case of surgery, costs for this kind of treatment are negligible considering total treatment costs. However, no studies have been performed to show cost-effectiveness of the treatment, let alone for the surgery done in a small percentage of cases.

Equity ((health) equity/equitable)
The guideline panel expects no problems with health equity with regard to medical treatment of necrotizing otitis externa.

Acceptability
The guideline panel expects no problems with ethical acceptability or sustainability with regard to medical treatment of necrotizing otitis externa.

Feasibility
The feasibility depends on the available modalities in the treatment centre. This includes a laboratory with the adequate equipment and personell for microbiology and pathology. It also requires the specialists to execute the recommendations (ENT, microbiologist, pathologist).

Recommendations

Take, at least, a culture swab for bacterial and fungal examination before starting systemic treatment.

Consider taking (surgical, deep tissue) biopsies in case of:
- No clear pathogen is identified in previous microbial swab-cultures
- No clinical improvements are demonstrated after 1-2 weeks of systemic antibiotic therapy
- Send these biopsies for histopathological and microbiological examination (including fungal cultures)

If clinically feasible: cease topical and systemic antibiotics prior to taking the culture swab or biopsy (up to 1 week).

Knowledge gaps
During the development of this module, a systematic search was conducted to find studies that could answer the research question. Through the use of a systematic literature review with an assessment of the strength of evidence, it has become clear that there are still

knowledge gaps within this module. The guideline panel believes that further research is desirable to provide clearer answers to practical questions in the future.

Question
Are polysaccharides of the fungal cell wall (galactomannan) detectabale in patients' serum in case of an untreated NOE by aspergillus fumigatus?

Explanation
Aspergillus species are the fungal pathogens dat can be the cause of necrotizing otitis externa. For invasive fungal infections in other organs like pneumonia it is standard of care to screen for fungal-components in the blood of patients. We question whether this marker might be helpful as a non-invasive marker in our patients with (suspected) NOE.

Verkeerslicht en (de-)implementatietabel

Toelichting
Met het verkeerslicht worden aanbevelingen gecategoriseerd op basis van formulering en bewijskracht. Als eindproduct wordt bij richtlijnmodules met een sterk geformuleerde en voldoende onderbouwde aanbeveling een implementatietabel opgeleverd. Hierin wordt onder andere opgenomen:

- Een beschrijving van het knelpunt om de module uit te werken of herzien;
- De te verwachten belemmerende en bevorderende factoren voor implementatie;
- Welke partijen van belang zijn bij toepassen van de aanbeveling in de praktijk;
- Een inschatting van de implementatietermijn.

Verkeerslichtanalyse

- **ROOD** = sterk geformuleerde aanbeveling om iets niet te doen, met een GRADE high of moderate
- **ORANJE** = zwak geformuleerde aanbeveling; mogelijk kennishiaat
- **GROEN** = sterk geformuleerde aanbeveling om iets wel te doen, met een GRADE high of moderate
- **LICHT ROOD** of **LICHT GROEN** = sterk geformuleerde aanbevelingen met een GRADE low, very low of geen GRADE *(modules waarin geen studies geïncludeerd konden worden in de literatuursamenvatting of waarin geen literatuursamenvatting werd geschreven zoals modules waarin organisatie van zorg wordt beschreven)*

(Sub)aanbeveling	Sterkte van de aanbeveling	Bewijskracht per uitkomstmaat	Verkeerslicht per (sub)aanbeveling
Aanbeveling 1: Take a culture swab for bacterial and fungal examination before starting systemic treatment. Consider taking (surgical, deep tissue) biopsies in case of: • No clear pathogen is identified in previous microbial swab-cultures • No clinical improvements are demonstrated after 1-2 weeks of systemic antibiotic therapy • Send these biopsies for histopathological and microbiological examination (including fungal cultures) If clinically feasible: cease topical and systemic antibiotics prior to taking the culture swab or biopsy (up to 1 week).	□ Sterk (doe/ gebruik) / □	**Overall bewijskracht** □ **VL** **Range bewijskracht van alle uitkomstmaten** **VL**	**LICHT GROEN**

Implementatietabel

Tabel A: (De-)Implementatietabel met impuls analyse

Aanbeveling – 1			
1. Wat was het onderliggende probleem om deze uitgangsvraag uit te werken?	**□ Ongewenste praktijkvariatie**		
2. Maak een inschatting over hoeveel patiënten het ongeveer gaat waar de aanbeveling betrekking op heeft?	**□ < 1000**		
3. Maakt de aanbeveling deel uit van een set van interventies voor hetzelfde probleem?	**□ Nee**		
4. Belemmeringen en kansen op verschillende niveaus voor landelijke toepassing van de aanbeveling:	***Voorbeelden***	**Wat zijn mogelijke belemmerende factoren?**	**Wat zijn mogelijke bevorderende factoren?**
a) **Richtlijn/ klinisch traject (innovatie)**	*Voortschrijding/vooruitgang in de praktijk, haalbaarheid, geloofwaardigheid, toegankelijkheid, aantrekkelijkheid*	-	Swabs worden overal toegpast en zijn haalbaar
b) **Zorgverleners (artsen en verpleegkundigen)**	*Bewustzijn, kennis, houding, motivatie om te veranderen, gedragsroutines*	Vaak lastig om te staken met AB voordat swabs genomen worden.	-

c) **Patiënt/ cliënt (naasten)**	*Kennis, vaardigheden, houding, compliance*	-	-
d) **Sociale context**	*Mening van collega's, cultuur van het netwerk, samenwerking, leiderschap*	-	-
e) **Organisatorische context**	*Organisatie van zorgprocessen, personeel, capaciteiten, middelen, structuren*	-	Eigenlijk alle ziekenhuizen beschikken over deze middelen
f) **Economische en politieke context**	*Financiële regelingen, regelgeving, beleid (vergoede zorg, betaaltitel)*	-	-

5. Welke personen/partijen zijn van belang bij het toepassen van de aanbeveling in de praktijk?	**x** Patiënt/ cliënt (naaste) **x** Professional
6. Wat zouden deze personen/ partijen moeten veranderen in hun gedrag of organisatie om de aanbeveling toe te passen?	*Wordt al veelal toegepast dus geen directe verandering nodig*
7. Binnen welk tijdsbestek moet de aanbeveling zijn geïmplementeerd?	□ < 1 jaar
8. Conclusie: is er extra aandacht nodig voor implementatie van de aanbeveling (anders dan publicatie van deze richtlijnmodule)?	□ **Nee** [

**Deze aanbeveling komt in aanmerking voor plaatsing op de Implementatie Agenda van het programma Zorg Evaluatie & Gepast Gebruik (ZE&GG). In het programma ZE&GG werken patiënten, zorgverleners, zorgaanbieders, zorgverzekeraars en overheid samen aan de bewezen beste zorg voor de patiënt. Daarmee is ZE&GG een programma van alle betrokken partijen in de Medisch Specialistische Zorg. FMS is één van deze betrokken partijen.*

De implementatieagenda van ZE&GG bevat onderwerpen over wat de bewezen beste zorg is en die in de dagelijkse zorgpraktijk geïmplementeerd zouden moeten worden. Zorgverzekeraars Nederland (ZN) en de Nederlandse Vereniging voor Ziekenhuizen (NVZ) hebben landelijke afspraken gemaakt over de implementatie van de onderwerpen van de implementatieagenda. Deze afspraken zijn onderdeel van de zorginkoopafspraken tussen zorgverzekeraars en zorgaanbieders.

Vanuit FMS worden sterke, goed onderbouwde aanbevelingen, getoetst op de behoefte aan een implementatie impuls aangedragen. Voor de beoordeling van onderwerpen uit richtlijnen wordt gekeken naar bovenstaande tabel voor een inschatting van de implementatie impuls. Met de ingevulde implementatietabel kunnen we vanuit FMS de andere HLA-MSZ partijen goed informeren om zo samen te beslissen of de aanbeveling daadwerkelijk op de implementatie agenda zal worden geplaatst.

Literatuur

Abu Eta R, Gavriel H, Stephen K, Eviatar E, Yeheskeli E. The significance of tissue biopsy for fungi in necrotizing otitis externa. Eur Arch Otorhinolaryngol. 2018 Dec;275(12):2941-2945. doi: 10.1007/s00405-018-5151-9. Epub 2018 Oct 5. PMID: 30291437.

Gramberg MCTT, Van Hattem JM, Dijkstra JA, Dros E, Nieuwdorp M, Sabelis LWE, Peters EJG. Effect of Prior Antibiotic Use on Culture Results in People with Diabetes and Foot Osteomyelitis. Antibiotics (Basel). 2023 Mar 31;12(4):684. doi: 10.3390/antibiotics12040684. PMID: 37107046; PMCID: PMC10135220.

Maniu AA, Harabagiu O, Damian LO, Ştefănescu EH, FănuŢă BM, Cătană A, Mogoantă CA. Mastoiditis and facial paralysis as initial manifestations of temporal bone systemic diseases - the significance of the histopathological examination. Rom J Morphol Embryol. 2016;57(1):243-8. PMID: 27151715.

Saravanam, Prasanna & Ravikumar, Arunachalam & Somu, Lakshmanan & Ismail, Nazrin. (2013). Malignant otitis externa: An emerging scourge. Journal of Clinical Gerontology and Geriatrics. 4. 128–131. 10.1016/j.jcgg.2013.02.003.

Senneville E, Melliez H, Beltrand E, Legout L, Valette M, Cazaubiel M, Cordonnier M, Caillaux M, Yazdanpanah Y, Mouton Y. Culture of percutaneous bone biopsy specimens for diagnosis of diabetic foot osteomyelitis: concordance with ulcer swab cultures. Clin Infect Dis. 2006 Jan 1;42(1):57-62. doi: 10.1086/498112. Epub 2005 Nov 21. PMID: 16323092.

Sekar R, Raja K, Ganesan S, Alexander A, Saxena SK. Clinical and Current Microbiological Profile with Changing Antibiotic Sensitivity in Malignant Otitis Externa. Indian J Otolaryngol Head Neck Surg. 2022 Dec;74(Suppl 3):4422-4427. doi: 10.1007/s12070-021-03068-9. Epub 2022 Jan 22. PMID: 36742648; PMCID: PMC9895493.

Takata J, Hopkins M, Alexander V, Bannister O, Dalton L, Harrison L, Groves E, Kanona H, Jones GL, Mohammed H, Andersson MI, Hodgson SH. Systematic review of the diagnosis and management of necrotising otitis externa: Highlighting the need for high-quality research. Clin Otolaryngol. 2023 May;48(3):381-394. doi: 10.1111/coa.14041. Epub 2023 Feb 22. PMID: 36759416.

Walton J, Coulson C. Fungal malignant otitis externa with facial nerve palsy: tissue biopsy AIDS diagnosis. Case Rep Otolaryngol. 2014;2014:192318. doi: 10.1155/2014/192318. Epub 2014 Feb 5. PMID: 24649388; PMCID: PMC3933303.

Bijlagen

Table of excluded studies

Reference	Reason for exclusion PICO 1	Reason for exclusion PICO 2
Bernheim J, Sade J. Histopathology of the soft parts in 50 patients with malignant external otitis. J Laryngol Otol. 1989 Apr;103(4):366-8. doi: 10.1017/s0022215100108977. PMID: 2715689.	No outcomes reported	No outcomes reported
Johnson AK, Batra PS. Central skull base osteomyelitis: an emerging clinical entity. Laryngoscope. 2014 May;124(5):1083-7. doi: 10.1002/lary.24440. Epub 2013 Nov 7. PMID: 24115113.	Non comparitive research	No outcomes reported
Sekar R, Raja K, Ganesan S, Alexander A, Saxena SK. Clinical and Current Microbiological Profile with Changing Antibiotic Sensitivity in Malignant Otitis Externa. Indian J Otolaryngol Head Neck Surg. 2022 Dec;74(Suppl 3):4422-4427. doi: 10.1007/s12070-021-03068-9. Epub 2022 Jan 22. PMID: 36742648; PMCID: PMC9895493.	No deep tissue biopsies were send for cultures	No outcomes reported
S. Prasanna Kumar, A. Ravikumar, L. Somu, Nazrin Mohd Ismail, Malignant otitis externa: An emerging scourge, Journal of Clinical Gerontology and Geriatrics, Volume 4, Issue 4, 2013, Pages 128-131, ISSN 2210-8335, https://doi.org/10.1016/j.jcgg.2013.02.003. (https://www.sciencedirect.com/science/article/pii/S2210833513000282)	Non comparive research	No outcomes reported
Bertrand K, Lamy B, De Boutray M, Yachouh J, Galmiche S, Leprêtre P, de Champfleur NM, Reynes J, Le Moing V, Morquin D. Osteomyelitis of the jaw: time to rethink the bone sampling strategy? Eur J Clin Microbiol Infect Dis. 2018 Jun;37(6):1071-1080. doi: 10.1007/s10096-018-3219-5. Epub 2018 Mar 7. PMID: 29516234.	Wrong population	Wrong population
Maniu AA, Harabagiu O, Damian LO, Ştefănescu EH, FănuŢă BM, Cătană A, Mogoantă CA. Mastoiditis and facial paralysis as initial manifestations of temporal bone systemic diseases - the significance of the histopathological examination. Rom J Morphol Embryol. 2016;57(1):243-8. PMID: 27151715.	Non comparative research	Non comparative research

Risk of bias table for intervention studies (observational: non-randomized clinical trials, cohort and case-control studies)

Study reference (first author, year of publication)	**Bias due to a non-representative or ill-defined sample of patients?**[1] (unlikely/likely/unclear)	**Bias due to insufficiently long, or incomplete follow-up, or differences in follow-up between treatment groups?**[2] (unlikely/likely/unclear)	**Bias due to ill-defined or inadequately measured outcome ?**[3] (unlikely/likely/unclear)	**Bias due to inadequate adjustment for all important prognostic factors?**[4] (unlikely/likely/unclear)
Abu-Eta, 2018	Likely	Unlikely	Likely	unclear

Literature search strategy

Zoekverantwoording
Algemene informatie

Richtlijn: NVKNO Osteomyelitis Schedelbase -maligne otitis externa	
Uitgangsvraag: 1. Wat is de meerwaarde van het biopt t.o.v. van een swab voor vinden een pathogeen, danwel stellen van diagnose? 2. Is aanvullend histopathologisch onderzoek zinvol om andere pathologie uit te sluiten?	
Database(s): Ovid/Medline, Embase	Datum: 17-7-2023
Periode: nvt	Talen: nvt
Literatuurspecialist: Ingeborg van Dusseldorp	
BMI zoekblokken: voor verschillende opdrachten wordt (deels) gebruik gemaakt van de zoekblokken van BMI-Online https://blocks.bmi-online.nl/ Bij gebruikmaking van een volledig zoekblok zal naar de betreffende link op de website worden verwezen.	
Toelichting: Omdat voor beide vragen wordt gezocht naar maligne otitis externa en biopsie en er weinig literatuur wordt gevonden, is in overleg met de adviseur afgesproken dat er 1 vraag wordt geformuleerd met de volgende concepten: Maligne otitis externe EN biopsie Vanwege het beperkte aantal referenties worden alle artikelen exclusief dierstudies in Rayyan aangeboden.	
Te gebruiken voor richtlijnen tekst: In de databases Embase en Ovid/Medline is op 17-7-2023 met relevante zoektermen gezocht naar studies over de waarde van een biopt bij maligne otitis externa. De literatuurzoekactie leverde unieke treffers op.	

Zoekopbrengst

	EMBASE	**OVID/MEDLINE**	**Ontdubbeld**
SRs	7	1	8
RCTs	4	3	5
Observationele studies	35	32	56
Overig	221	109	278
Totaal			347

Zoekstrategie

Embase

No.	Query	Results
#12	#8 NOT #9 NOT #10 NOT #11 Overige	221
#11	(#6 OR #7) AND #8 NOT #9 NOT #10 Overige observationeel	35
#10	#5 AND #8 NOT #9 Clinical trials, RCTs	4
#9	#4 AND #8 SR	7
#8	#3 NOT ('conference abstract'/it OR 'editorial'/it OR 'letter'/it OR 'note'/it) NOT (('animal'/exp OR 'animal experiment'/exp OR 'animal model'/exp OR 'nonhuman'/exp) NOT 'human'/exp)	267
#7	'case control study'/de OR 'comparative study'/exp OR 'control group'/de OR 'controlled study'/de OR 'controlled clinical trial'/de OR 'crossover procedure'/de OR 'double blind procedure'/de OR 'phase 2 clinical trial'/de OR 'phase 3 clinical trial'/de OR 'phase 4 clinical trial'/de OR 'pretest posttest design'/de OR 'pretest posttest control group design'/de OR 'quasi experimental study'/de OR 'single blind procedure'/de OR 'triple blind procedure'/de OR (((control OR controlled) NEAR/6 trial):ti,ab,kw) OR (((control OR controlled) NEAR/6 (study OR studies)):ti,ab,kw) OR (((control OR controlled) NEAR/1 active):ti,ab,kw) OR 'open label*':ti,ab,kw OR (((double OR two OR three OR multi OR trial) NEAR/1 (arm OR arms)):ti,ab,kw) OR ((allocat* NEAR/10 (arm OR arms)):ti,ab,kw) OR placebo*:ti,ab,kw OR 'sham-control*':ti,ab,kw OR (((single OR double OR triple OR assessor) NEAR/1 (blind* OR masked)):ti,ab,kw) OR nonrandom*:ti,ab,kw OR 'non-random*':ti,ab,kw OR 'quasi-experiment*':ti,ab,kw OR crossover:ti,ab,kw OR 'cross over':ti,ab,kw OR 'parallel group*':ti,ab,kw OR 'factorial trial':ti,ab,kw OR ((phase NEAR/5 (study OR trial)):ti,ab,kw) OR ((case* NEAR/6 (matched OR control*)):ti,ab,kw) OR ((match* NEAR/6 (pair OR pairs OR cohort* OR control* OR group* OR healthy OR age OR sex OR gender OR patient* OR subject* OR participant*)):ti,ab,kw) OR ((propensity NEAR/6 (scor* OR match*)):ti,ab,kw) OR versus:ti OR vs:ti OR compar*:ti OR ((compar* NEAR/1 study):ti,ab,kw) OR (('major clinical study'/de OR 'clinical study'/de OR 'cohort analysis'/de OR 'observational study'/de OR 'cross-sectional study'/de OR 'multicenter study'/de OR 'correlational study'/de OR 'follow up'/de OR cohort*:ti,ab,kw OR 'follow up':ti,ab,kw OR followup:ti,ab,kw OR longitudinal*:ti,ab,kw OR prospective*:ti,ab,kw OR retrospective*:ti,ab,kw OR observational*:ti,ab,kw OR 'cross sectional*':ti,ab,kw OR	14246308

	cross?ectional*:ti,ab,kw OR multicent*:ti,ab,kw OR 'multi-cent*':ti,ab,kw OR consecutive*:ti,ab,kw) AND (group:ti,ab,kw OR groups:ti,ab,kw OR subgroup*:ti,ab,kw OR versus:ti,ab,kw OR vs:ti,ab,kw OR compar*:ti,ab,kw OR 'odds ratio*':ab OR 'relative odds':ab OR 'risk ratio*':ab OR 'relative risk*':ab OR 'rate ratio':ab OR aor:ab OR arr:ab OR rrr:ab OR ((('or' OR 'rr') NEAR/6 ci):ab)))	
#6	'major clinical study'/de OR 'clinical study'/de OR 'case control study'/de OR 'family study'/de OR 'longitudinal study'/de OR 'retrospective study'/de OR 'prospective study'/de OR 'comparative study'/de OR 'cohort analysis'/de OR ((cohort NEAR/1 (study OR studies)):ab,ti) OR (('case control' NEAR/1 (study OR studies)):ab,ti) OR (('follow up' NEAR/1 (study OR studies)):ab,ti) OR (observational NEAR/1 (study OR studies)) OR ((epidemiologic NEAR/1 (study OR studies)):ab,ti) OR (('cross sectional' NEAR/1 (study OR studies)):ab,ti)	6767914
#5	'clinical trial'/exp OR 'randomization'/exp OR 'single blind procedure'/exp OR 'double blind procedure'/exp OR 'crossover procedure'/exp OR 'placebo'/exp OR 'prospective study'/exp OR rct:ab,ti OR random*:ab,ti OR 'single blind':ab,ti OR 'randomised controlled trial':ab,ti OR 'randomized controlled trial'/exp OR placebo*:ab,ti	3302394
#4	'meta analysis'/exp OR 'meta analysis (topic)'/exp OR metaanaly*:ti,ab OR 'meta analy*':ti,ab OR metanaly*:ti,ab OR 'systematic review'/de OR 'cochrane database of systematic reviews'/jt OR prisma:ti,ab OR prospero:ti,ab OR (((systemati* OR scoping OR umbrella OR 'structured literature') NEAR/3 (review* OR overview*)):ti,ab) OR ((systemic* NEAR/1 review*):ti,ab) OR (((systemati* OR literature OR database* OR 'data base*') NEAR/10 search*):ti,ab) OR (((structured OR comprehensive* OR systemic*) NEAR/3 search*):ti,ab) OR (((literature NEAR/3 review*):ti,ab) AND (search*:ti,ab OR database*:ti,ab OR 'data base*':ti,ab)) OR (('data extraction':ti,ab OR 'data source*':ti,ab) AND 'study selection':ti,ab) OR ('search strategy':ti,ab AND 'selection criteria':ti,ab) OR ('data source*':ti,ab AND 'data synthesis':ti,ab) OR medline:ab OR pubmed:ab OR embase:ab OR cochrane:ab OR (((critical OR rapid) NEAR/2 (review* OR overview* OR synthes*)):ti) OR ((((critical* OR rapid*) NEAR/3 (review* OR overview* OR synthes*)):ab) AND (search*:ab OR database*:ab OR 'data base*':ab)) OR metasynthes*:ti,ab OR 'meta synthes*':ti,ab	733409
#3	#1 AND #2	367
#2	'biopsy'/exp OR 'biopsy':ti,ab,kw OR biopt*:ti,ab,kw OR rebiops*:ti,ab,kw OR rebiopt*:ti,ab,kw	1088201
#1	'malignant otitis externa'/exp OR (((maligna* OR necroti* OR necrosis) NEAR/3 ('otitis externa' OR 'external otitis')):ti,ab,kw) OR ('otitis externa'/mj AND (maligna*:ti,kw OR necroti*:ti,kw OR necrosis:ti,kw)) OR (('osteomyelitis'/exp/mj OR 'osteomyelitis':ti,kw OR osteitis:ti,kw) AND ('skull'/exp/mj OR 'skull disease'/exp/mj OR skull*:ti,ab,kw OR cranial:ti,ab,kw OR cranium:ti,ab,kw))	3634

Ovid/Medline

#	Searches	Results

12	8 or 9 or 10 or 11	145
11	3 not 8 not 9 not 10 Overige	109
10	(3 and (6 or 7)) not 8 not 9 Overige OBS	32
9	(3 and 5) not 8 Clinical trials, RCTs	1
8	3 and 4 SR	3
7	Case-control Studies/ or clinical trial, phase ii/ or clinical trial, phase iii/ or clinical trial, phase iv/ or comparative study/ or control groups/ or controlled before-after studies/ or controlled clinical trial/ or double-blind method/ or historically controlled study/ or matched-pair analysis/ or single-blind method/ or (((control or controlled) adj6 (study or studies or trial)) or (compar* adj (study or studies)) or ((control or controlled) adj1 active) or "open label*" or ((double or two or three or multi or trial) adj (arm or arms)) or (allocat* adj10 (arm or arms)) or placebo* or "sham-control*" or ((single or double or triple or assessor) adj1 (blind* or masked)) or nonrandom* or "non-random*" or "quasi-experiment*" or "parallel group*" or "factorial trial" or "pretest posttest" or (phase adj5 (study or trial)) or (case* adj6 (matched or control*)) or (match* adj6 (pair or pairs or cohort* or control* or group* or healthy or age or sex or gender or patient* or subject* or participant*)) or (propensity adj6 (scor* or match*))).ti,ab,kf. or (confounding adj6 adjust*).ti,ab. or (versus or vs or compar*).ti. or ((exp cohort studies/ or epidemiologic studies/ or multicenter study/ or observational study/ or seroepidemiologic studies/ or (cohort* or 'follow up' or followup or longitudinal* or prospective* or retrospective* or observational* or multicent* or 'multi-cent*' or consecutive*).ti,ab,kf.) and ((group or groups or subgroup* or versus or vs or compar*).ti,ab,kf. or ('odds ratio*' or 'relative odds' or 'risk ratio*' or 'relative risk*' or aor or arr or rrr).ab. or (("OR" or "RR") adj6 CI).ab.))	5466913
6	Epidemiologic studies/ or case control studies/ or exp cohort studies/ or Controlled Before-After Studies/ or Case control.tw. or cohort.tw. or Cohort analy$.tw. or (Follow up adj (study or studies)).tw. or (observational adj (study or studies)).tw. or Longitudinal.tw. or Retrospective*.tw. or prospective*.tw. or consecutive*.tw. or Cross sectional.tw. or Cross-sectional studies/ or historically controlled study/ or interrupted time series analysis/ [Onder exp cohort studies vallen ook longitudinale, prospectieve en retrospectieve studies]	4484618
5	exp clinical trial/ or randomized controlled trial/ or exp clinical trials as topic/ or randomized controlled trials as topic/ or Random Allocation/ or Double-Blind Method/ or Single-Blind Method/ or (clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or controlled clinical trial or randomized controlled trial or multicenter study or clinical trial).pt. or random*.ti,ab. or (clinic* adj trial*).tw. or ((singl* or doubl* or treb* or tripl*) adj (blind$3 or mask$3)).tw. or Placebos/ or placebo*.tw.	2610273
4	meta-analysis/ or meta-analysis as topic/ or (metaanaly* or meta-analy* or metanaly*).ti,ab,kf. or systematic review/ or cochrane.jw. or (prisma or prospero).ti,ab,kf. or ((systemati* or scoping or umbrella or "structured literature") adj3 (review* or overview*)).ti,ab,kf. or (systemic* adj1 review*).ti,ab,kf. or ((systemati* or literature or database* or data-base*) adj10 search*).ti,ab,kf. or ((structured or comprehensive* or systemic*) adj3 search*).ti,ab,kf. or ((literature adj3 review*) and (search* or	680557

	database* or data-base*)).ti,ab,kf. or (("data extraction" or "data source*") and "study selection").ti,ab,kf. or ("search strategy" and "selection criteria").ti,ab,kf. or ("data source*" and "data synthesis").ti,ab,kf. or (medline or pubmed or embase or cochrane).ab. or ((critical or rapid) adj2 (review* or overview* or synthes*)).ti. or (((critical* or rapid*) adj3 (review* or overview* or synthes*)) and (search* or database* or data-base*)).ab. or (metasynthes* or meta-synthes*).ti,ab,kf.	
3	1 and 2	145
2	exp Biopsy/ or biopsy.ti,ab,kf. or biopt*.ti,ab,kf. or rebiops*.ti,ab,kf. or rebiopt*.ti,ab,kf.	535397
1	((maligna* or necroti* or necrosis) adj3 ('otitis externa' or 'external otitis')).ti,kf. or (exp *Otitis Externa/ and (maligna* or necroti* or necrosis).ti,ab,kf.) or ((exp *Osteomyelitis/ or 'osteomyelitis'.ti,kf.) and (exp Skull/ or skull*.ti,ab,kf. or cranial.ti,ab,kf. or cranium.ti,ab,kf.))	2710

Module 4 – Antimicrobial treatment

Question
What is the optimal medical therapy for necrotizing otitis externa / skull base osteomyelitis?

More specifically, the following subquestions were included:

1. What is the optimal empirical antimicrobial treatment regimen?
2. In case of failure of the initial empirical treatment, what should be changed in the empirical treatment regimen?
3. What is the optimal directed antimicrobial treatment regimen?
4. What is the optimal treatment modality? Intravenous or (partial) oral administration? Is there an added role for topical therapy?

Introduction
The most common pathogens in necrotizing otitis externa are bacteria, most often *Pseudomonas aeruginosa.* Fungal causes are also possible, most often *Aspergillus* spp. Treatment regimens are either empirical, when the responsible pathogen is not yet identified, or directed, in cases where the pathogen is known. The treatment preferably consists of antimicrobial drugs with: proven effectiveness in infections of the bone, likely (in case of empiric therapy) or proven (in case of directed therapy) effectiveness against the (presumed) responsible pathogen(s), reaching the site of infection, availability of oral administration, the narrowest spectrum, acceptable side effects profile and low costs. The length of treatment is as short as possible, without sacrificing effectiveness. Historically, Pseudomonas aeruginosa infections, including necrotizing otitis externa, have been preferably treated with combination therapy, even when the susceptibility of the cultured Pseudomonas was known (i.e., in directed therapy). However, evidence for this preference is lacking and clinical practice in other *Pseudomonas aeruginosa* infections has moved away from combination therapy as the first choice directed therapy. Currently, there are no guidelines providing advice on the optimal empirical treatment regimen in necrotizing otitis externa, including the benefits of combination over monotherapy. Moreover, no guideline advice is available on how to amend the empirical treatment regimen in case of treatment failure.

In the experience of the committee, the severity of the clinical presentation of skull base osteomyelitis varies greatly. The severity variety is such that some patients with less severe disease can be treated as outpatients with oral antimicrobials, whereas others warrant admission and parenteral antimicrobial therapy. However, there is currently no accepted method in literature to assess and categorize severity of infection so in this guideline this is left to the clinicians' discretion.

Search and select
A systematic review of the literature was performed to answer the following question(s):
Is empiric combination antimicrobial therapy more effective than monotherapy in improving outcomes of necrotizing otitis externa treatment?

Table 1. PICO

Patients	Patients with proven necrotizing otitis externa
Intervention	Combination therapy (combination of two or more of the following:

	cephalosporin or broad spectrum penicillin, or carbapenem or fluoroquinolone or aminoglycoside)
Control	Monotherapy (cephalosporin or broadspectrum penicillin, or carbapenem or fluoroquinolone)
Outcomes	Remission, survival, quality of life
Other selection criteria	Study design: systematic reviews, randomized controlled trials, observational studies

Relevant outcome measures

The guideline panel considered remission and survival as **critical** outcome measures for decision making; and quality of life as an **important** outcome measure for decision making.

A priori, the guideline panel did not define the outcome measures listed above but used the definitions used in the studies.

The guideline panel defined the following differences as a minimal clinically (patient) important difference.

- Remission: 25% difference in relative risk (GRADE standard limits)*
- Survival: 25% difference in relative risk (GRADE standard limits)*
- Quality of life: 25% difference in relative risk or 0.5 standard deviations difference (GRADE standard limits)*

* Default thresholds proposed by the international GRADE working group were used: a 25% difference in relative risk (RR) for dichotomous outcomes (RR <0.80 or RR >1.25), or 0.5 standard deviations (SD) for continuous outcomes

Search and select (Methods)

The databases Medline (via OVID) and Embase (via Embase.com) were searched with relevant search terms until 7 February 2023. The detailed search strategy is listed under the tab 'Literature search strategy'. The systematic literature search resulted in 215 hits. Studies were selected based on the following criteria: systematic reviews, RCT, observational studies, and other non-comparative research about the value of surgical treatment for necrotizing otitis externa. Fifty-eight studies were initially selected based on title and abstract screening. After reading the full text, 57 studies were excluded (see the exclusion table under the tab 'Evidence tabellen'), and one study was included.

Summary of literature

Description of studies

One observational study was included in the analysis of the literature. Important study characteristics and results are summarized in table 2. The assessment of the risk of bias is summarized in the risk of bias tables (under the tab 'Evidence tables').

Table 2. Characteristics of included studies

Study	Participants (number, age, other important characteristics)	Comparison	Follow-up	Outcome measures	Comments	Risk of bias (per outcome measure)*
Meyers (1987)	N at baseline Total: 20 Intervention: 11 Control: 12	Intervention: conventional antipseudomonal	5 to 57 months	Remission	There was an overlap in groups. One failure	Bias due to insufficiently long, or incomplete

	Age (mean) Intervention: *69 years* Control: *74 years* Sex (F/M) Intervention: 0/11 Control: 2/10 *Cranial nerve palsy:* Intervention: *7/11 (64%)* *Control: 4/12 (33.3%)* Diabetes mellitus (%) Intervention: 100% Control: 100% Underlying vascular disease Intervention: 8/11 (72.7%) Control: 4/12 (33.3%)	combination therapy: an antipseudomonal (broad spectrum) penicillin plus aminoglycoside in ten patients and an antipseudomonal penicillin alone (piperacillin sodium) followed by aminoglycoside alone in one patient Control: intravenous cefsulodin (cefalosporine monotherapy)			overlapped groups. Also note that all patients included were given treatment after a positive culture of Pseudomonas. Regarding side effects of therapy: the study reported the frequency and type of side effects of monotherapy (cefsulodin) and combination therapy (piperacillin sodium with or followed by an aminoglycoside) and found similar rates of therapy complications (4/12; 33% and 4/11; 36% respectively).	follow-up, or differences in follow-up between treatment groups

*For further details, see risk of bias table in the appendix

Results
The results section is divided into empirical therapy and directed therapy.

Empirical therapy
Remission (critical)
No studies meeting the criteria and reporting the outcome remission were identified.

Survival (critical)
No studies meeting the criteria and reporting the outcome survival were identified.

Quality of life (important)
No studies meeting the criteria and reporting quality of life were identified.

Directed therapy
Remission (critical)
The single included study by Meyers (1987) reported the outcome remission, defined as occurrence of incomplete responses or relapse. Clinical response was defined as follows: (1) Remission: resolution of pain, drainage, erythema, swelling, and granulation tissue;

(2) Failure: an incomplete response (an improvement with persistence of clinical findings or relapse), recurrence of pain, granulation tissue, or development of new cranial-nerve palsies or active infection found at autopsy following an initial response to therapy.
They reported one incomplete response and two relapses, resulting in remission of disease of 70% (7/10) in the intervention (combination therapy) group. This is compared to three incomplete responses and one relapse, resulting in remission of disease of 64% (7/11) in the control (monotherapy) group (risk ratio [RR] 1.1, 95% CI 0.60 to 2.01), in favor of the control (monotherapy) group.

Survival (critical)
No studies meeting the criteria and reporting the outcome survival were identified.

Quality of life (important)
No studies meeting the criteria and reporting quality of life were identified.

Summary of Findings

Summary of Findings table: Combination therapy compared to monotherapy for necrotizing otitis externa

Population: Patients with necrotizing otitis externa

Intervention: Combination therapy

Comparator: Monotherapy

Outcome	Study results and measurements	Absolute effect estimates		Certainty of the Evidence (Quality of evidence)	Conclusions
		Monotherapy	Combination therapy		
Empirical therapy					
Remission (critical)	-	-		**No GRADE** (no evidence was found)	No evidence was found regarding the effect of combination therapy when compared with monotherapy in patients with necrotizing otitis externa
Survival (critical)	-	-		**No GRADE** (no evidence was found)	No evidence was found regarding the effect of combination therapy when compared with monotherapy in patients with necrotizing otitis externa
Quality of life (important)	-	-		**No GRADE** (no evidence was found)	No evidence was found regarding the effect of combination therapy when compared with monotherapy in patients with necrotizing otitis externa
Directed therapy					
Remission (critical)	Relative risk: 1.10 (CI 95% 0.60 - 2.01) Based on data from 21 participants in 1 study	-		**Very low** Due to serious risk of bias, due to serious imprecision[1]	The evidence is very uncertain about the effect of combination therapy on remission when compared with monotherapy in patients with necrotizing otitis externa. *(Meyers, 1987)*
Survival (critical)	-	-		**No GRADE** (no evidence was found)	No evidence was found regarding the effect of combination therapy when compared with monotherapy in patients with necrotizing otitis externa
Quality of life (important)	-	-		**No GRADE** (no evidence was found)	No evidence was found regarding the effect of combination therapy when compared with monotherapy in patients with necrotizing otitis externa

1. **Risk of Bias: serious.** Due to lack of blinding
   Imprecision: serious. Due to overlap of the upper limit of the 95% confidence interval with the minimal clinically important difference.

Considerations – from evidence to recommendation

Balance between desired and undesired effects

The most common pathogen in skull base osteomyelitis is *Pseudomonas aeruginosa.* Less frequent pathogens are fungi such as *Aspergillus* spp and *Staphylococcus aureus* (Takata, 2023) but a substantial portion of cases remain without identified pathogen.

Empirical therapy

Current practice is highly variable, as illustrated by the guidelines of Dutch hospitals, which can be found in a nationally summarized from here). It shows 5 different treatment strategies, ranging from oral monotherapy to combination therapy with two intravenous antibiotics. Most medical centers make use of an combination of a cephalosporin (e.g., ceftazidime) or broad-spectrum penicillin (piperacillin [with tazobactam]) in combination with an aminoglycoside (e.g., tobramycin). However, monotherapy comprising the aforementioned betalactam antibiotics without the addition of the aminoglycoside is also used.

Based on the current systematic literature search for empirical therapy, the effect of combination antimicrobial therapy compared to monotherapy on the remission outcome or any other outcomes of necrotizing otitis externa is highly uncertain as the search did not identify any studies on the subject.

Directed therapy

Directed therapy, based on susceptibility tested in the laboratory, consists preferably of an oral fluoroquinolone in the case of *Pseudomonas aeruginosa*, or a different directed therapy against the cultured pathogen(s). Fluoroquinolones, like ciprofloxacin or levofloxacin are the only oral medicines available against *Pseudomonas aeruginosa.* The other treatment regimens are only available intravenously, which makes *outpatient parenteral antibiotic therapy* (OPAT) a necessity for treating patients at home. A (full) intravenous treatment is not necessary in bone infections in general. Oral treatment with antimicrobials with high bioavailability, such as quinolones, has proven to be non-inferior to intravenous therapy in bone infections in general (Li, 2019) The susceptibility profile of the pathogen should drive the choice of treatment, not the fact that it can be administered intravenous or orally. A recent review showed no clear differences in effectiveness of monotherapy for these agents against severe *Pseudomonas* spp. infections overall(Tekes-Manuva, 2024). When a different pathogen than *Pseudomonas aeruginosa* is found, treatment should be adapted according to susceptibility testing and advice from the local infectious diseases expert.

Based on the current systematic literature search, the effect of combination antimicrobial therapy compared to monotherapy on the remission outcome of necrotizing otitis externa is highly uncertain. The confidence interval around the estimated effect in the single included study on directed therapy is wide and allows for the possibility of both clinically relevant benefits and clinically relevant harm. It is also highly uncertain based on the literature what the difference is in adverse effects (e.g., medication side effects) between the two strategies in the treatment of necrotizing otitis externa. It should be noted that side effects are often specific to the particular medication, so the choice of antimicrobial agents within the strategy plays an important role.

General consideration on combination therapy versus monotherapy

Given the aforementioned paucity of evidence, the committee is of the opinion that the choice between combination therapy or monotherapy for both empirical and directed therapy should be based on expert opinion based on theoretical considerations and literature from other but similar infections. These will be dicussed here.

The theoretical basis for the potentially superior effectiveness of combination therapy over monotherapy rests on two different arguments. First, it is based on the idea that therapy with two antimicrobial agents to which the micro-organism is susceptible leads to better outcomes in severe infections, such as with *Pseudomonas aeruginosa*, due to a synergistic effect, compared to treatment with just one active agent. Secondly, it increases the likelihood that an empirical regimen includes at least one active agent against the microorganism. However, literature from other serious infections shows no convincing evidence for the first hypothesis, for instance in the case of mortality and other important outcomes in sepsis (Sjövall, 2017; Paul, 2014) and *Pseudomonas aeruginosa* bacteremia or pneumonia (Onorata, 2022). This is also reflected in the recommendations for empirical and directed treatment of sepsis, where combination therapy is not advised in sepsis or septic shock unless there is a high suspicion of multidrug-resistant microorganisms (Evans, 2021). Similarly, in patients with diabetic foot infections, where bone involvement, *Pseudomonas aeruginosa*, and diabetes mellitus also play a significant role, combination therapy is not recommended (Lipsky, 2020).

Lessons can also be learned from the literature on other infections regarding the adverse effects of combination therapy. From this it is clear that more antibiotic use leads to more antibiotic resistance (Bell, 2014), *Clostridioides difficile* infections (Slimings, 2021), and other side effects (Paul, 2014; Arulkumaran, 2020).

Treatment modality

Parenteral versus oral administration

The current systematic review was not specifically focused on the optimal treatment modality (parenteral versus oral) but it did not identify any comparisons based on treatment modality. Importantly, the commonly presumed superiority of parenteral over oral therapy has no convincing pathophysiological basis and studies on bloodstream, endocarditis and bone-infections have shown similar or superior efficacy of partial or fully oral regimens versus fully intravenous regimens (Wald-Dickler, 2022; Li, 2019; Iversen 2019). The committee is therefore of the opinion that oral treatment should be the preferred administration method whenever possible, as this is associated with lower cost and fewer side effects (Wald-Dickler, 2022). Additionally, the committee has formulated the following prerequisite conditions for oral treatment based on expert opinion:

- Availability of an antimicrobial agent with good oral bioavailability* for which the pathogen is:
    - Proven to be susceptible,
    - In case of empiric treatment, the presumed pathogen is likely susceptible
- Absence of sepsis or shock
- Absence of factors prohibiting absorption of the antimicrobial agent, such as severe diarrhea or vomiting, short-bowel syndrome, concomitant administration of oral iron or magnesium suppletion etc.
- No or only limited interactions with other medication, e.g., those causing prolongation of QT time.

*oral bioavailability refers to the extent to which an orally ingested drug is absorbed into the systemic circulation

Local treatment

According to the guideline committee, the role of local treatment in necrotizing otitis externa is limited and is not considered primary therapy. Necrotizing otitis externa is an infection which affects deeper tissues and often the bone of the skull base, requiring

systemic antibiotics. However, topical treatment can be administered as an adjunctive in certain situations (Rosenfeld, 2014).
Local treatment can be administered in adjunct to systemic therapy in the following situations:

1. To physically clean the external auditory canal and remove pus or debris.
2. To reduce local symptoms (such as otorrhea and inflammation).

Topical agents that can be used are antibacterial ear drops (with or without corticosteroids) or antiseptic solutions.

Conclusion

Empirical therapy

In the opinion of the committee, there is no compelling argument to prefer combination therapy over monotherapy, as long as there is low risk for resistance of the main expected pathogen (i.e., *Pseudomonas aeruginosa)* against the empirical regimen. This is based on evidence from infections other than necrotizing otitis externa and considering antimicrobial stewardship principles to minimize antibiotic selection pressure and adverse events. The probability of resistance of the expected pathogen will generally depend on the context: previous cultures in a patient play an important role, as well as local or national degree of resistance. In many countries, this will come down to a choice for one of the commonly used anti-pseudomonal antibiotics such as ciprofloxacin, ceftazidime or piperacillin-tazobactam; or a carbapenem (e.g., meropenem) for countries with higher resistance levels.

Directed therapy

In the opinion of the committee, given the evidence from infections other than necrotizing otitis externa and considering antimicrobial stewardship principles to minimize antibiotic selection pressure and adverse events, there is no compelling argument to prefer combination therapy over monotherapy.

Treatment modality

Oral treatment is preferred wherever possible for patients with mild disease as judged by the clinician. For most cases the only suitable oral agent will be an anti-Pseudomonal quinolone like ciprofloxacin. Topical treatment cannot replace systemic antimicrobial treatment but may have an adjunctive role for specific goals (i.e., external ear canal decontamination, reduction of local symptoms and to promote local healing).

<u>Empirical therapy in case of failure of previous regimen</u>

In cases where initial empiric antimicrobial treatment has failed, the empiric regimen should be amended based on the most likely reasons for failure. Possible reasons for treatment failure include:

1. No or insufficient antimicrobial coverage of the causative pathogen, due to resistance (e.g., resistant *Pseudomonas aeruginosa)* or intrinsic non-susceptibility (e.g., a non-bacterial cause like *Aspergillus* spp., or ceftazidime-treatment for necrotizing otitis externa caused by *Staphylococcus aureus)*.
2. Insufficient intestinal absorption in case of oral therapy, for instance due to diarrhea or other gastro-intestinal disease, farmacokinetic interactions or non-adherence.
3. Incorrect diagnosis, for instance in case of malignancy as cause of the symptoms.

In the absence of a clear explanation for treatment failure, the committee suggests to consider performing diagnostic investigations such as (repeat) biopsy to get more information on the diagnosis in these cases. If no additional information about the etiology

is obtained (yet) the committee is of the opinion that changing or extending the antimicrobial regimen to include coverage of fungal pathogens like *Aspergillus* spp. should be considered. Choice of antifungal regimen will depend on the most actual information on resistance and advice from a local infectious disease expert, preferably as part of a multidisciplinary team.

Specific recommendations for empirical therapy for the Dutch situation
For the current (2025) Dutch situation, *Pseudomonas aeruginosa* data for hospital outpatients show resistance percentages of 11, 3 and 5% for ciprofloxacin, ceftazidime and piperacillin-tazobactam respectively (de Greeff, 2024). Levofloxacin, which is an orally available quinolone like ciprofloxacin, is another option for oral therapy but seen as second choice behind ciprofloxacin due its lower in vitro activity and higher minimum inhibitory concentration s (MICs) against *Pseudmononas* (MacGowan, 1999). Ciprofloxacin also has a higher mutant prevention concentration in *Pseudomonas* (Hansen, 2006). Ciprofloxacin can therefore be assumed to have superior potency and a lower risk of developing of resistance during treatment of *Pseudomonas* infections. The opposite is the case for *S. aureus*; In a multicenter trial to uncomplicated skin and skin structure infections, levofloxacin achieved 100% eradication of *S. aureus* versus 87% for ciprofloxacin (Nichols, 1997). Although we have to be cautious not to extrapolate these studies directly to efficacy in NOE, there does seem to be a generally different efficacy of levofloxacin and ciprofloxacin on *P. aeruginosa* and *S. aureus* and we consider ciprofloxacin the first-choice quinolone for *Pseudomonas* infections. Quinolones like ciprofloxaxin are the only agents where oral administration is possible. This option is not recommended for patients already treated with ciprofloxacin (or another quinolone) during the current course of disease as the probability of resistance will be increased.

For all other cases the choice is either empirical ceftazidime or piperacillin-tazobactam monotherapy. In situations where the expected resistance percentage is similar, the choice between ceftazidime and piperacillin-tazobactam can also be guided by the advantage of methicillin-susceptible *Staphylococcus aureus* coverage by piperacillin-tazobactam, which can be a cause of the infection in a minority of cases. Methicillin-resistant *Staphylococcus aureus* (MRSA) is rare in the Netherlands. On the other hand, the additional anaerobic coverage supplied by piperacillin-tazobactam may have (thusfar mainly theoretical) disadvantages due to its impact on the patient's enteric microbiota with potential harmful clinical consequences (Kullberg, 2024).
Based on the above, the committee is of the opinion that for the current Dutch situation empirical therapy with piperacillin-tazobactam is the first choice therapy in all severe cases and all other cases where oral ciprofloxacin treatment is not possible. Ceftazidime therapy is a good alternative choice, offering slightly lower *Pseudomonas* spp. resistance, but is not effective against *Staphylococcus aureus* which is a reported as a cause in around 6% of cases (Takata, 2023). Because of the uncertainty of the potential downside of the anaerobic coverage of piperacillin-tazobactam, the committee prefers the advantage of the additional *Staphylococcus aureus* in this case.

<u>Quality of the evidence</u>
For empirical therapy, no studies meeting our criteria could be identified. For directed therapy, the overall quality of evidence is very low. This means that we are very uncertain about the estimated effect found for the critical outcome measures. The evidence was downgraded due to:

- Risk of Bias: methodological limitations in study design

- Imprecision: the confidence interval exceeds both limits of clinical relevance; not achieving the optimal sample size.

Moreover, the antibiotic agent, cefsulodin that was used in the only study that was included, is not often used in currently clinical practices and not available in the Netherlands.

Values and preferences of patients (and possibly their caregivers)
The primary preferred outcome of patients will be effective treatment of the infection. Given that, the possible options for therapy mainly differ with regard to the possibility for oral administration (generally only possible for ciprofloxacin) as this precludes the need for intravenous cathethers with their added discomfort (e.g., pain) and complications (e.g., infection, bleeding). Also, intravenous therapy generally necessitates hospital admission for at least a part of the therapy duration and/or outpatient parenteral therapy. The committee therefore assumes that oral therapy will be preferable for patients provided that the chance of treatment success is high.

Costs (resources)
No studies on cost or cost-effectiveness were identified. Medical costs will generally be lower for cases where all or a part of treatment can be delivered orally.

Equity ((health) equity/equitable)
The guideline panel expects no problems with health equity with regard to medical treatment of necrotizing otitis externa.

Acceptability
The guideline panel expects no problems with ethical acceptability or sustainability with regard to medical treatment of necrotizing otitis externa.

Feasibility
The intervention seems feasible. The intervention is generally already standard care in practice. For cases where no oral treatment is possible, outpatient parenteral antibiotic therapy (OPAT) would be preferable, but this is not universally available, which may lead to prolonged hospital admissions.

Further explanation about OPAT is described in module 9: additional conditions optimizing care.

Recommendation(s)

Rationale of the recommendation: weighing arguments for and against the interventions
The literature on the desired and undesired effects of combination versus monotherapy in necrotizing otitis externa provides insufficient certainty, but literature and guidelines on relevant other infections provides evidence that there is no added value of combination empirical or directed therapy, but increased risks of adverse effects, including side effects and antibiotic resistance, may be expected. Therefore, the committee is of the opinion that the optimal empirical treatment regimen consists of monotherapy with ciprofloxacin or a beta-lactam antibiotic for which *Pseudomonas aeruginosa* is likely susceptible, which will depend on the local resistance situation and previous cultures. In some clinical contexts this may mean that treatment with multiple antimicrobials is needed to form a regimen with likely activity against *Pseudomonas aeruginosa*; however, this is different from combination therapy which entails giving therapy with two or more presumed active antimicrobials. Preferred directed therapy is also monotherapy with an antimicrobial agent for which the pathogen is proven susceptible. If possible, upfront oral therapy or early intravenous-to oral

switch is preferable to minimize cost and side effects without reducing efficacy, given specific conditions for oral therapy (see above).

Final judgment:
Weak recommendation for empirical monotherapy. Weak recommendation for directed monotherapy.

Empirical therapy (no known pathogen)
Mild disease *
Treat previously untreated patients with mild necrotizing otitis externa preferably with an oral regimen if conditions listed under treatment modality are met.

In the current Dutch situation: treat patients meeting the above criteria with ciprofloxacin 750mg twice daily (or lower dose if necessary due to renal insufficiency), or see https://adult.nl.antibiotica.app/nl/node/1240 (use the highest dose/frequency listed)

Severe disease * or no oral therapy recommended
Treat all other patients with necrotizing otitis externa with empirical intravenous monotherapy for which *Pseudomonas aeruginosa* is likely susceptible using local antimicrobial resistance information

**No system for classification of disease severity is available in literature so this is left to the individual treating clinician's discretion. For suggested guidance, classify patients with cranial nerve involvement or systemic symptoms (e.g., fever, hypotension, systemic illness) as having severe disease*

In the current Dutch situation, treat these patients with
1. *piperacillin-tazobactam 4000/500mg four times daily (or lower if necessary due to renal insufficiency), or continuous infusion, see for actual dosing guidelines https://adult.nl.antibiotica.app/nl/node/1696; or*
2. *ceftazidime 2000mg thrice daily (or lower if necessary due to renal insufficiency), or see https://adult.nl.antibiotica.app/nl/node/1176 (use the highest dose/frequency listed)*

Directed therapy (known pathogen & susceptibility)
Treat patients with a proven causative pathogen with monotherapy based on susceptibility results.

Treatment modality
Consider treating patients with oral regimens wherever possible, when the following conditions are met:
- Absence of sepsis or shock
- Availability of an antimicrobial agent with good oral bioavailability for which the presumed pathogen is likely susceptible. The antimicrobial agent has shown favorable efficacy as an oral treatment of necrotizing otitis externa or other bone-infections (e.g., ciprofloxacin)
- Absence of factors prohibiting absorption of the antimicrobial agent, such as severe diarrhea, vomiting or short-bowel syndrome.

For most cases the only suitable oral agent will be ciprofloxacin. Based on the good biological availability of ciprofloxacin, oral therapy should also be possible for patients with severe disease.

Do not use topical treatment as a substitute for systemic therapy.

Use adjunctive topical treatment for patients in cases where there is a need for external ear canal decontamination, reduction of local symptoms or promotion of local healing.

Empirical therapy in case of failure of previous regimen
Do the following in case of failure of the previous empiric regimen and without known pathogen:

- Consult an infectious diseases specialist
- Perform additional diagnostic steps (see module microbiology and histopathology (hyperlink)
- Consider surgical intervention (module Surgical treatment (hyperlink))
- Change antimicrobial therapy:
  - In case of previous oral therapy, change to an intravenous antimicrobial regimen, i.e., for the current Dutch situation change from ciprofloxacin to piperacillin-tazobactam to decrease *Pseudomonas* spp. resistance risk and improve *Staphylococcus aureus* coverage
  - In case of a previous intravenous regimen:
    a. Make sure the antibiotic therapy covers S. aureus (for example switch ceftazidime to piperacillin-tazobactam)
    b. Consider switching to or adding antifungal therapy to the empiric regimen based on local epidemiology and resistance and based on advice of multidisciplinary team including an infectious disease expert.

Knowledge gaps
During the development of this module, a systematic search was conducted to find studies that could answer the research question. Through the use of a systematic literature review with an assessment of the strength of evidence, it has become clear that there are still knowledge gaps within this module. The guideline panel believes that further research is desirable to provide clearer answers to practical questions in the future.

Knowledge question
What is the optimal medical therapy for necrotizing otitis externa?

Explanation
There is a paucity of evidence on the optimal empirical or directed medical treatment of necrotizing otitis externa. Although anecdotal evidence and evidence from other fields aids in giving guidance for treatment policy, more certainty is needed around the optimal make-up of the treatment regime and the optimal administration route / moment for IV-to-oral switch. A randomized controlled trial comparing several strategies (e.g., empirical ciprofloxacin oral therapy vs ceftazidime iv therapy) would be beneficial to yield more evidence to guide policy and improve outcomes.

Verkeerslicht en (de-)implementatietabel

Toelichting
Met het verkeerslicht worden aanbevelingen gecategoriseerd op basis van formulering en bewijskracht. Als eindproduct wordt bij richtlijnmodules met een sterk geformuleerde en voldoende onderbouwde aanbeveling een implementatietabel opgeleverd. Hierin wordt onder andere opgenomen:

- Een beschrijving van het knelpunt om de module uit te werken of herzien;
- De te verwachten belemmerende en bevorderende factoren voor implementatie;
- Welke partijen van belang zijn bij toepassen van de aanbeveling in de praktijk;
- Een inschatting van de implementatietermijn.

Verkeerslichtanalyse

- **ROOD** = sterk geformuleerde aanbeveling om iets niet te doen, met een GRADE high of moderate
- **ORANJE** = zwak geformuleerde aanbeveling; mogelijk kennishiaat
- **GROEN** = sterk geformuleerde aanbeveling om iets wel te doen, met een GRADE high of moderate
- **LICHT ROOD** of **LICHT GROEN** = sterk geformuleerde aanbevelingen met een GRADE low, very low of geen GRADE *(modules waarin geen studies geïncludeerd konden worden in de literatuursamenvatting of waarin geen literatuursamenvatting werd geschreven zoals modules waarin organisatie van zorg wordt beschreven)*

(Sub)aanbeveling	Sterkte van de aanbeveling	Bewijskracht per uitkomstmaat	Verkeerslicht per (sub)aanbeveling
Aanbeveling 1: **Empirical therapy (no known pathogen)** <u>Mild disease</u> Treat previously untreated patients with mild necrotizing otitis externa preferably with an oral regimen if conditions listed under treatment modality are met. <u>Severe disease or no oral therapy recommended</u> Treat all other patients with necrotizing otitis externa with empirical intravenous monotherapy	□ Sterk (doe/ gebruik)	**Overall bewijskracht** □ **NG**	**LICHT GROEN**
Aanbevelling 2: **Directed therapy (known pathogen & susceptibility)** Treat patients with a proven causative pathogen with monotherapy based	□ Sterk (doe/ gebruik)	**Overall bewijskracht** □ **VL** **Range bewijskracht van alle uitkomstmaten** □ **VL**	**LICHT GROEN**

on susceptibility results			
Aanbeveling 3: **Empirical therapy in case of failure of previous regimen** Do the following in case of failure of the previous empiric regimen and without known pathogen: • Consult an infectious diseases specialist • Perform additional diagnostic steps • Consider surgical intervention • Change antimicrobial therapy:	□ Sterk (doe/ gebruik)	□ **voor de (sub)uitgangsvraag is geen systematische literatuur analyse uitgevoerd**	**LICHT GROEN**

Implementatietabel

Tabel A: (De-)Implementatietabel met impuls analyse

Aanbeveling – 1 t/m 3			
1. Wat was het onderliggende probleem om deze uitgangsvraag uit te werken?	□ **Ongewenste praktijkvariatie**		
2. Maak een inschatting over hoeveel patiënten het ongeveer gaat waar de aanbeveling betrekking op heeft?	□ **< 1000 in NL**		
3. Maakt de aanbeveling deel uit van een set van interventies voor hetzelfde probleem?	□ **Ja**: gedeelte van antibiotische therapie		
4. Belemmeringen en kansen op verschillende niveaus voor landelijke toepassing van de aanbeveling:	***Voorbeelden***	**Wat zijn mogelijke belemmerende factoren?**	**Wat zijn mogelijke bevorderende factoren?**
a) **Richtlijn/ klinisch traject (innovatie)**	*Voortschrijding/vooruitgang in de praktijk, haalbaarheid, geloofwaardigheid, toegankelijkheid, aantrekkelijkheid*	geen	Wijde beschikbaarheid van antibiotica in het hele land
b) **Zorgverleners (artsen en verpleegkundigen)**	*Bewustzijn, kennis, houding, motivatie om te veranderen, gedragsroutines*	Geen	geen
c) **Patiënt/ cliënt (naasten)**	*Kennis, vaardigheden, houding, compliance*	Compliance bij orale therapie.	geen
d) **Sociale context**	*Mening van collega's, cultuur van het netwerk, samenwerking, leiderschap*	geen	geen
e) **Organisatorische context**	*Organisatie van zorgprocessen, personeel, capaciteiten, middelen, structuren*	geen	Gebruik van een OPAT team voor behandeling in thuissituatie
f) **Economische en politieke context**	*Financiële regelingen, regelgeving, beleid (vergoede zorg, betaaltitel)*	geen	Vergoede zorg

5. Welke personen/partijen zijn van belang bij het toepassen van de aanbeveling in de praktijk?	**x** Patiënt/ cliënt (naaste) **x** Professional
6. Wat zouden deze personen/ partijen moeten veranderen in hun gedrag of organisatie om de aanbeveling toe te passen?	Het is al mogelijk, dus er zullen weinig tot geen aanpassingen nodig zijn.
7. Binnen welk tijdsbestek moet de aanbeveling zijn geïmplementeerd?	□ < 1 jaar
8. Conclusie: is er extra aandacht nodig voor implementatie van de aanbeveling (anders dan publicatie van deze richtlijnmodule)?	□ **Nee**

**Deze aanbeveling komt in aanmerking voor plaatsing op de Implementatie Agenda van het programma Zorg Evaluatie & Gepast Gebruik (ZE&GG). In het programma ZE&GG werken patiënten, zorgverleners, zorgaanbieders, zorgverzekeraars en overheid samen aan de bewezen beste zorg voor de patiënt. Daarmee is ZE&GG een programma van alle betrokken partijen in de Medisch Specialistische Zorg. FMS is één van deze betrokken partijen.*

De implementatieagenda van ZE&GG bevat onderwerpen over wat de bewezen beste zorg is en die in de dagelijkse zorgpraktijk geïmplementeerd zouden moeten worden. Zorgverzekeraars Nederland (ZN) en de Nederlandse Vereniging voor Ziekenhuizen (NVZ) hebben landelijke afspraken gemaakt over de implementatie van de onderwerpen van de implementatieagenda. Deze afspraken zijn onderdeel van de zorginkoopafspraken tussen zorgverzekeraars en zorgaanbieders.

Vanuit FMS worden sterke, goed onderbouwde aanbevelingen, getoetst op de behoefte aan een implementatie impuls aangedragen. Voor de beoordeling van onderwerpen uit richtlijnen wordt gekeken naar bovenstaande tabel voor een inschatting van de implementatie impuls. Met de ingevulde implementatietabel kunnen we vanuit FMS de andere HLA-MSZ partijen goed informeren om zo samen te beslissen of de aanbeveling daadwerkelijk op de implementatie agenda zal worden geplaatst.

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Bijlagen bij module 4 – Antibiotic treatment

Risk of Bias tables

Risk of bias table for intervention studies (observational: non-randomized clinical trials, cohort and case-control studies)

Study reference	Bias due to a non-representative or ill-defined sample of patients?[1]	Bias due to insufficiently long, or incomplete follow-up, or differences in follow-up between treatment groups?[2]	Bias due to ill-defined or inadequately measured outcome ?[3]	Bias due to inadequate adjustment for all important prognostic factors?[4]
(first author, year of publication)	(unlikely/likely/unclear)	(unlikely/likely/unclear)	(unlikely/likely/unclear)	(unlikely/likely/unclear)
Meyers, 1987	Unlikely	Likely	Likely	Unlikely

Table of excluded studies

Reference	Reason for exclusion
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Stapleton E, Watson G. Emerging themes in necrotising otitis externa: a scoping review of the literature 2011-2020 and recommendations for future research. J Laryngol Otol. 2021 Nov 26:1-30. doi: 10.1017/S0022215121003789. Epub ahead of print. PMID: 34823614.	No comparison made
Danjou W, Chabert P, Perpoint T, Pradat P, Miailhes P, Boibieux A, Becker A, Fuchsmann C, Laurent F, Tringali S, Roux S, Triffault-Fillit C, Valour F, Ferry T; Lyon Bone and Joint Infection Study Group. Necrotizing external otitis: analysis of relapse risk factors in 66 patients managed during a 12 year period. J Antimicrob Chemother. 2022 Aug 25;77(9):2532-2535. doi: 10.1093/jac/dkac193. PMID: 35696322.	No comparison made
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Hasibi M, Ashtiani MK, Motassadi Zarandi M, Yazdani N, Borghei P, Kuhi A, Dabiri S, Hosseini R, Sardashti S. A Treatment Protocol for Management of Bacterial and Fungal Malignant External Otitis: A Large Cohort in Tehran, Iran. Ann Otol Rhinol Laryngol. 2017	No comparison made

Jul;126(7):561-567. doi: 10.1177/0003489417710473. Epub 2017 May 21. PMID: 28528568.	
Haverkos HW, Caparosa R, Yu VL, Kamerer D. Moxalactam therapy. Its use in chronic suppurative otitis media and malignant external otitis. Arch Otolaryngol. 1982 Jun;108(6):329-33. doi: 10.1001/archotol.1982.00790540001001. PMID: 6212042.	Wrong intervention

Literature search strategy

Zoekverantwoording
Algemene informatie

Cluster/richtlijn: Osteomyelitis schedelbasis – maligne otitis externa	
Uitgangsvraag/modules: Wat zijn de optimale empirische en gerichte medicamenteuze behandeling van osteomyelitis van de schedelbasis?	
Database(s): Ovid/Medline, Embase.com	Datum: 7 februari 2023
Periode: Geen restrictie	Talen: Geen restrictie
Literatuurspecialist: Miriam van der Maten	
BMI-zoekblokken: voor verschillende opdrachten wordt (deels) gebruik gemaakt van de zoekblokken van BMI-Online https://blocks.bmi-online.nl/ Bij gebruikmaking van een volledig zoekblok zal naar de betreffende link op de website worden verwezen.	
Toelichting: Voor deze vraag is gezocht op de elementen: • Maligne otitis externa of osteomyelitis schedel Er is gezocht met major/focus Emtree/MeSH en in titel/keyword i.p.v. titel/abstract/keyword om ruis eruit te filteren. • Verschillende antibiotica Er gezocht op antibiotische/antifungale therapie in het algemeen, combinatie/dual therapie en de specifiek genoemde middelen. Het opgegeven SR van Mion wordt niet gevonden omdat hier niet direct wordt gesproken over behandeling met antibiotica. Er wordt gesproken over 'conservative treatment' in het abstract van dit artikel, maar verder is het ook niet duidelijk geïndexeerd. Het zal bij UV5 over chirurgie wel gevonden worden.	
Te gebruiken voor richtlijnen tekst: *Nederlands* In de databases Embase.com en Ovid/Medline is op 7 februari 2023 systematisch gezocht naar systematische reviews, RCT en observationele studies over medicamenteuze behandeling met antibiotica van osteomyelitis van de schedelbasis. De literatuurzoekactie leverde [215/964] unieke treffers op. *Engels* On the 7th of February 2023, we performed a systematic search in the databases Embase.com and Ovid/Medline to find systematic reviews, RCT and observational studies about antibiotic treatment of osteomyelitis of the skull. The search resulted in [215/964] unique hits.	

Zoekopbrengst

	EMBASE	**OVID/MEDLINE**	**Ontdubbeld**
SRs	18	7	20
RCT en vergelijkend observationeel onderzoek	149	115	195

Overige studies (e.g., case reports)	586	370	749
Totaal	753	492	**964**

Zoekstrategie

Embase.com

No.	Query	Results
#11	#7 OR #8 OR #9 OR #10	753
#10	#3 NOT (#7 OR #8 OR #9)	586
#9	#3 AND #6 NOT (#7 OR #8)	146
#8	#3 AND #5 NOT #7	3
#7	#3 AND #4	18
#6	'clinical trial'/exp OR 'randomization'/exp OR 'single blind procedure'/exp OR 'double blind procedure'/exp OR 'crossover procedure'/exp OR 'placebo'/exp OR 'prospective study'/exp OR rct:ab,ti OR random*:ab,ti OR 'single blind':ab,ti OR 'randomised controlled trial':ab,ti OR 'randomized controlled trial'/exp OR placebo*:ab,ti OR 'comparative study'/exp OR 'control group'/de OR 'controlled study'/de OR 'controlled clinical trial'/de OR 'crossover procedure'/de OR 'double blind procedure'/de OR 'phase 2 clinical trial'/de OR 'phase 3 clinical trial'/de OR 'phase 4 clinical trial'/de OR 'pretest posttest design'/de OR 'pretest posttest control group design'/de OR 'quasi experimental study'/de OR 'single blind procedure'/de OR 'triple blind procedure'/de OR (((control OR controlled) NEAR/6 trial):ti,ab,kw) OR (((control OR controlled) NEAR/6 (study OR studies)):ti,ab,kw) OR (((control OR controlled) NEAR/1 active):ti,ab,kw) OR 'open label*':ti,ab,kw OR (((double OR two OR three OR multi OR trial) NEAR/1 (arm OR arms)):ti,ab,kw) OR ((allocat* NEAR/10 (arm OR arms)):ti,ab,kw) OR placebo*:ti,ab,kw OR 'sham-control*':ti,ab,kw OR (((single OR double OR triple OR assessor) NEAR/1 (blind* OR masked)):ti,ab,kw) OR nonrandom*:ti,ab,kw OR 'non-random*':ti,ab,kw OR 'quasi-experiment*':ti,ab,kw OR crossover:ti,ab,kw OR 'cross over':ti,ab,kw OR 'parallel group*':ti,ab,kw OR 'factorial trial':ti,ab,kw OR ((phase NEAR/5 (study OR trial)):ti,ab,kw) OR ((case* NEAR/6 (matched OR control*)):ti,ab,kw) OR ((match* NEAR/6 (pair OR pairs OR cohort* OR control* OR group* OR healthy OR age OR sex OR gender OR patient* OR subject* OR participant*)):ti,ab,kw) OR ((propensity NEAR/6 (scor* OR match*)):ti,ab,kw) OR versus:ti OR vs:ti OR compar*:ti OR ((compar* NEAR/1 study):ti,ab,kw) OR (('major clinical study'/de OR 'clinical study'/de OR 'cohort analysis'/de OR 'observational study'/de OR 'cross-sectional study'/de OR 'multicenter study'/de OR 'correlational study'/de OR 'follow up'/de OR cohort*:ti,ab,kw OR 'follow up':ti,ab,kw OR followup:ti,ab,kw OR longitudinal*:ti,ab,kw OR prospective*:ti,ab,kw OR retrospective*:ti,ab,kw OR observational*:ti,ab,kw OR 'cross sectional*':ti,ab,kw OR cross?ectional*:ti,ab,kw OR multicent*:ti,ab,kw OR 'multi-cent*':ti,ab,kw OR consecutive*:ti,ab,kw) AND (group:ti,ab,kw OR groups:ti,ab,kw OR subgroup*:ti,ab,kw OR versus:ti,ab,kw OR vs:ti,ab,kw OR compar*:ti,ab,kw OR 'odds ratio*':ab OR 'relative odds':ab OR 'risk ratio*':ab OR 'relative risk*':ab OR 'rate ratio':ab OR aor:ab OR arr:ab OR rrr:ab OR ((('or' OR 'rr') NEAR/6 ci):ab))) OR 'major clinical study'/de OR 'clinical study'/de OR 'case control study'/de OR 'family study'/de OR 'longitudinal study'/de OR 'retrospective study'/de OR 'prospective study'/de OR 'comparative study'/de OR 'cohort analysis'/de OR ((cohort NEAR/1 (study OR studies)):ab,ti) OR (('case control' NEAR/1 (study OR studies)):ab,ti) OR (('follow up' NEAR/1 (study OR studies)):ab,ti) OR (observational NEAR/1 (study OR studies)) OR ((epidemiologic NEAR/1 (study OR studies)):ab,ti) OR (('cross sectional' NEAR/1 (study OR studies)):ab,ti)	16360334

#5	'randomized controlled trial'/exp OR random*:ti,ab OR (((pragmatic OR practical) NEAR/1 'clinical trial*'):ti,ab) OR ((('non inferiority' OR noninferiority OR superiority OR equivalence) NEAR/3 trial*):ti,ab) OR rct:ti,ab,kw	1839814
#4	'meta analysis'/exp OR 'meta analysis (topic)'/exp OR metaanaly*:ti,ab OR 'meta analy*':ti,ab OR metanaly*:ti,ab OR 'systematic review'/de OR 'cochrane database of systematic reviews'/jt OR prisma:ti,ab OR prospero:ti,ab OR (((systemati* OR scoping OR umbrella OR 'structured literature') NEAR/3 (review* OR overview*)):ti,ab) OR ((systemic* NEAR/1 review*):ti,ab) OR (((systemati* OR literature OR database* OR 'data base*') NEAR/10 search*):ti,ab) OR (((structured OR comprehensive* OR systemic*) NEAR/3 search*):ti,ab) OR (((literature NEAR/3 review*):ti,ab) AND (search*:ti,ab OR database*:ti,ab OR 'data base*':ti,ab)) OR (('data extraction':ti,ab OR 'data source*':ti,ab) AND 'study selection':ti,ab) OR ('search strategy':ti,ab AND 'selection criteria':ti,ab) OR ('data source*':ti,ab AND 'data synthesis':ti,ab) OR medline:ab OR pubmed:ab OR embase:ab OR cochrane:ab OR (((critical OR rapid) NEAR/2 (review* OR overview* OR synthes*)):ti) OR ((((critical* OR rapid*) NEAR/3 (review* OR overview* OR synthes*)):ab) AND (search*:ab OR database*:ab OR 'data base*':ab)) OR metasynthes*:ti,ab OR 'meta synthes*':ti,ab	733409
#3	#1 AND #2 NOT ('conference abstract'/it OR 'editorial'/it OR 'letter'/it OR 'note'/it) NOT (('animal experiment'/exp OR 'animal model'/exp OR 'nonhuman'/exp) NOT 'human'/exp)	753
#2	'antibiotic therapy'/exp/mj OR 'antibiotic agent'/exp/mj OR 'antifungal agent'/exp/mj OR 'antifungal therapy'/exp/mj OR antibiotic*:ti,kw OR antifung*:ti,ab,kw OR 'anti-biotic*':ti,ab,kw OR 'anti-fung*':ti,ab,kw OR 'cephalosporin'/exp OR 'cefalosporin*':ti,ab,kw OR 'cephalosporin*':ti,ab,kw OR 'penicillin derivative'/exp OR 'penicillin*':ti,ab,kw OR 'carbapenem'/exp OR 'carbapenem':ti,ab,kw OR 'quinoline derived antiinfective agent'/exp OR 'quinolone derivative'/exp OR fluoroquinolon*:ti,ab,kw OR quinolon*:ti,ab,kw OR 'aminoglycoside antibiotic agent'/exp OR 'aminoglycoside'/exp OR aminoglycoside*:ti,ab,kw OR 'aminoglucoside*':ti,ab,kw OR 'meropenem'/exp OR 'meropenem':ti,ab,kw OR merrem:ti,ab,kw OR 'ceftazidime'/exp OR 'ceftazidime':ti,ab,kw OR fortum:ti,ab,kw OR 'tobramycin'/exp OR 'tobramycin*':ti,ab,kw OR 'piperacillin'/exp OR 'piperacillin*':ti,ab,kw OR pipracil:ti,ab,kw OR 'tazobactam'/exp OR 'tazobactam':ti,ab,kw OR 'combination drug therapy'/exp OR (((dual OR mono OR combination* OR combined OR double OR multimodality) NEAR/3 (therap* OR treat*)):ti,ab,kw)	1841381
#1	'malignant otitis externa'/exp/mj OR (((maligna* OR necroti* OR necrosis) NEAR/3 ('otitis externa' OR 'external otitis')):ti,kw) OR ('otitis externa'/mj AND (maligna*:ti,kw OR necroti*:ti,kw OR necrosis:ti,kw)) OR (('osteomyelitis'/exp/mj OR 'osteomyelitis':ti,kw) AND ('skull'/exp/mj OR 'skull disease'/exp/mj OR skull*:ti,ab,kw OR cranial:ti,ab,kw OR cranium:ti,ab,kw))	3086

Ovid/Medline

#	Searches	Results
12	8 or 9 or 10 or 11	492
11	4 not (8 or 9 or 10)	370
10	(4 and 7) not (8 or 9)	111
9	(4 and 6) not 8	4
8	4 and 5	7
7	exp clinical trial/ or randomized controlled trial/ or exp clinical trials as topic/ or randomized controlled trials as topic/ or Random Allocation/ or Double-Blind Method/ or Single-Blind Method/ or (clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or controlled clinical trial or randomized controlled trial or multicenter study or clinical trial).pt. or random*.ti,ab. or (clinic* adj trial*).tw. or ((singl* or doubl* or treb* or tripl*) adj	8139491

	(blind$3 or mask$3)).tw. or Placebos/ or placebo*.tw. or Epidemiologic studies/ or case control studies/ or exp cohort studies/ or Controlled Before-After Studies/ or Case control.tw. or cohort.tw. or Cohort analy$.tw. or (Follow up adj (study or studies)).tw. or (observational adj (study or studies)).tw. or Longitudinal.tw. or Retrospective*.tw. or prospective*.tw. or consecutive*.tw. or Cross sectional.tw. or Cross-sectional studies/ or historically controlled study/ or interrupted time series analysis/ or Case-control Studies/ or clinical trial, phase ii/ or clinical trial, phase iii/ or clinical trial, phase iv/ or comparative study/ or control groups/ or controlled before-after studies/ or controlled clinical trial/ or double-blind method/ or historically controlled study/ or matched-pair analysis/ or single-blind method/ or (((control or controlled) adj6 (study or studies or trial)) or (compar* adj (study or studies)) or ((control or controlled) adj1 active) or "open label*" or ((double or two or three or multi or trial) adj (arm or arms)) or (allocat* adj10 (arm or arms)) or placebo* or "sham-control*" or ((single or double or triple or assessor) adj1 (blind* or masked)) or nonrandom* or "non-random*" or "quasi-experiment*" or "parallel group*" or "factorial trial" or "pretest posttest" or (phase adj5 (study or trial)) or (case* adj6 (matched or control*)) or (match* adj6 (pair or pairs or cohort* or control* or group* or healthy or age or sex or gender or patient* or subject* or participant*)) or (propensity adj6 (scor* or match*))).ti,ab,kf. or (confounding adj6 adjust*).ti,ab. or (versus or vs or compar*).ti. or ((exp cohort studies/ or epidemiologic studies/ or multicenter study/ or observational study/ or seroepidemiologic studies/ or (cohort* or 'follow up' or followup or longitudinal* or prospective* or retrospective* or observational* or multicent* or 'multi-cent*' or consecutive*).ti,ab,kf.) and ((group or groups or subgroup* or versus or vs or compar*).ti,ab,kf. or ('odds ratio*' or 'relative odds' or 'risk ratio*' or 'relative risk*' or aor or arr or rrr).ab. or (("OR" or "RR") adj6 CI).ab.))	
6	exp randomized controlled trial/ or randomized controlled trials as topic/ or random*.ti,ab. or rct?.ti,ab. or ((pragmatic or practical) adj "clinical trial*").ti,ab,kf. or ((non-inferiority or noninferiority or superiority or equivalence) adj3 trial*).ti,ab,kf.	1590441
5	meta-analysis/ or meta-analysis as topic/ or (metaanaly* or meta-analy* or metanaly*).ti,ab,kf. or systematic review/ or cochrane.jw. or (prisma or prospero).ti,ab,kf. or ((systemati* or scoping or umbrella or "structured literature") adj3 (review* or overview*)).ti,ab,kf. or (systemic* adj1 review*).ti,ab,kf. or ((systemati* or literature or database* or data-base*) adj10 search*).ti,ab,kf. or ((structured or comprehensive* or systemic*) adj3 search*).ti,ab,kf. or ((literature adj3 review*) and (search* or database* or data-base*)).ti,ab,kf. or (("data extraction" or "data source*") and "study selection").ti,ab,kf. or ("search strategy" and "selection criteria").ti,ab,kf. or ("data source*" and "data synthesis").ti,ab,kf. or (medline or pubmed or embase or cochrane).ab. or ((critical or rapid) adj2 (review* or overview* or synthes*)).ti. or (((critical* or rapid*) adj3 (review* or overview* or synthes*)) and (search* or database* or data-base*)).ab. or (metasynthes* or meta-synthes*).ti,ab,kf.	651703
4	3 not (comment/ or editorial/ or letter/ or ((exp animals/ or exp models, animal/) not humans/))	492
3	1 and 2	517
2	exp *Anti-Bacterial Agents/ or exp Antifungal Agents/ or antibiotic*.ti,kf. or antifung*.ti,ab,kf. or 'anti-biotic*'.ti,ab,kf. or 'anti-fung*'.ti,ab,kf. or exp Cephalosporins/ or exp Penicillins/ or exp Carbapenems/ or exp Fluoroquinolones/ or exp Aminoglycosides/ or exp Meropenem/ or exp Ceftazidime/ or exp Tobramycin/ or exp Piperacillin/ or exp Tazobactam/ or 'cefalosporin*'.ti,ab,kf. or 'cephalosporin*'.ti,ab,kf. or 'penicillin*'.ti,ab,kf. or 'carbapenem'.ti,ab,kf. or fluoroquinolon*.ti,ab,kf. or quinolon*.ti,ab,kf. or aminoglycoside*.ti,ab,kf. or 'aminoglucoside*'.ti,ab,kf. or 'meropenem'.ti,ab,kf. or merrem.ti,ab,kf. or 'ceftazidime'.ti,ab,kf. or fortum.ti,ab,kf. or 'tobramycin*'.ti,ab,kf. or	1371853

	'piperacillin*'.ti,ab,kf. or Pipracil.ti,ab,kf. or 'tazobactam'.ti,ab,kf. or exp Drug Therapy, Combination/ or ((dual or mono or combination* or combined or double or multimodality) adj3 (therap* or treat*)).ti,ab,kf.	
1	((maligna* or necroti* or necrosis) adj3 ('otitis externa' or 'external otitis')).ti,kf. or (exp *Otitis Externa/ and (maligna* or necroti* or necrosis).ti,kf.) or ((exp *Osteomyelitis/ or 'osteomyelitis'.ti,kf.) and (exp Skull/ or skull*.ti,ab,kf. or cranial.ti,ab,kf. or cranium.ti,ab,kf.))	2627

Module 5 – Surgical treatment

Question
What is the added value of surgical treatment, compared to medical treatment only, for necrotizing otitis externa?

Introduction
It is generally accepted that the treatment of necrotizing otitis externa (NOE) involves long-term administration of antibiotics (or antimycotics in the case of fungal infections). In specific scenarios, surgical treatment may be considered:

- If no pathogen can be identified, surgery may be performed to obtain deep tissue samples. This is considered a diagnostic procedure rather than a curative treatment.
- If there is no or insufficient response to medical treatment; this is also referred to as salvage surgery.
- Surgery aimed at curing or preventing (further) damage to vital structures, such as the facial nerve or the inner ear.

Surgery in the infected area can be complex and carries risks, particularly in frail patients, which NOE patients often are.

Search and Selection
A systematic review of the literature was conducted to address the following question: What are the benefits and disadvantages of surgical treatment for necrotizing otitis externa compared to medical treatment?

Table 1. PICO

Patients	Patients with proven necrotizing otitis externa
Intervention	Surgical treatment (with or without medical treatment)
Control	Medical treatment
Outcomes	(Disease specific) survival, remission, quality of life
Other selection criteria	Study design: systematic reviews and randomized controlled trials

<u>Relevant outcome measures</u>
The guideline panel considered remission, (disease-free) survival and disease control as **critical** outcome measures for decision-making; and quality of life as an **important** outcome measure for decision making.

The guideline panel defined the outcome measures as follows:

- Survival:
    - Overall survival: Time to death from any cause.
    - Disease free survival: Time to death, caused by the effects of necrotizing otitis externa/skull base osteomyelitis.
- Remission: Rate of curation of disease, defined after prolonged disappearance of the signs and symptoms of a disease.
- Health-related Quality of Life (HR-QoL): Preferably measured with EQ-5D-5L

The guideline panel defined the following as a minimal clinically (patient) important difference.

The guideline panel defined the following differences as a minimal clinically (patient) important difference.

- Remission: 25% difference in relative risk (GRADE standard limits)*
- Survival: 25% difference in relative risk (GRADE standard limits)*
- Quality of life: 25% difference in relative risk or 0.5 standard deviations difference (GRADE standard limits)*

* Default thresholds proposed by the international GRADE working group were used: a 25% difference in relative risk (RR) for dichotomous outcomes (RR <0.80 or RR >1.25), or 0.5 standard deviations (SD) for continuous outcomes

Search and select (Methods)
The databases Medline (via OVID) and Embase (via Embase.com) were searched using relevant search terms from 2000 until February 6th, 2023. The detailed search strategy is provided under the tab 'Literature Search Strategy'. The systematic literature search yielded 456 unique hits. Studies were selected based on the following criteria: systematic reviews, RCTs, observational studies, and other non-comparative research on the value of surgical treatment for necrotizing otitis externa. Forty-six studies were initially selected based on title and abstract screening. After full-text review, 43 studies were excluded (see the table with reasons for exclusion under the tab 'Evidence Tables'), and 3 studies were included.

Results
Three studies, consisting of 1 RCT and 2 observational studies, were included in the literature analysis. Key study characteristics and results are summarized in the evidence tables. The risk of bias assessment is summarized in the risk of bias tables.

Summary of literature
Description of studies
A total of 3 studies were included in the literature analysis. Key study characteristics and results are summarized in Table 2. The risk of bias assessment is summarized in the risk of bias tables (under the tab 'Evidence tables'). One RCT (Singh, 2018) and two observational studies (Omran, 2012; Freeman, 2023) were included. For details, See also Table 2 below.

Table 2. Characteristics of included studies

Study	Participants (number, age, other important characteristics)	Comparison	Follow-up	Outcome measures	Comments	Risk of bias (per outcome measure)*
Individual studies						
Singh, 2018	N at baseline Intervention: 10 Control: 10 Age Means not reported. 30% were in age group 40–60 years. 70% were in age group 60–80 years. Sex 14 males, 6 females Relevant characteristic: Patients with refractory malignant necrotizing otitis externa; (no disease response after 6 weeks of oral ciprofloxacin).	Patients were randomized into two groups. **Group A**: Patients received intravenous ceftazidime along with oral ciprofloxacin 750 mg twice daily and acetic acid washes three times a day. **Group B**: Patients were started on oral ciprofloxacin 750 mg twice daily, combined with surgical intervention and regular postoperative care. The aim of the surgical treatment was: 1. Local debridement of necrotic tissue. 2. Abscess drainage and creation of a drainage route. 3. Control of complications.	Short follow-up (mean follow-up not described)	Remission	Type of study: RCT	Remission: High
Lambor, 2013	N at baseline Intervention: 12 Control: 15	Intervention: Surgical intervention in addition to antibiotic treatment (see control)	4-6 months after discharge.	No statistical analysis was	Type of study: Retrospective cohort study	Remission: High

	Age between 50 and 80 years (no mean) *Sex* 22 males, 5 female	Control: 3–4 weeks of parenteral antibiotics (depending on the antibiotic sensitivity report) and the daily insertion of medicated (polymyxin B and neomycin sulphates ointment) wicks.		performed in this study.		
Freeman, 2023	N at baseline Intervention: 12 Control: 15 Patients were treated with medical therapy with or without surgical intervention: - 5 with mastoidectomy + facial nerve decompression, - 5 with mastoidectomy alone, - 4 with medical management alone.	Intervention was surgery, further divided into two groups: - Mastoidectomy with debridement of the affected ear. - Transmastoid facial nerve decompression alongside surgical debridement of the affected ear. All patients received systemic antibiotics. Control: Systemic antibiotics only.	The median length of follow-up after the onset of facial palsy was 280 days.	Survival,	Type of study: Retrospective cohort study	Survival: High

*For further details, see risk of bias table in the appendix

Results

Survival (critical)

Freeman (2023) reported no deaths in both surgical and medical groups.

Remission (critical)

One study reported remission as an outcome measure (Singh, 2018). However, the authors did not report remission as a dichotomous result. Instead, to compare the treatment responses, the number of resolutions per criterion per group was assessed:

1. Complete resolution of edema and granulation.
2. Resolution of pain (nocturnal pain).
3. Hearing loss resolution.
4. No disease on post treatment gallium scan.
5. Resolution of ear discharge.
6. TM joint pain resolution.

Group A was the antibiotic group, and group B was the surgical group. To determine the preferred treatment for the overall best resolution of aforementioned criteria, a Mann–Whitney U test was applied, which found surgical treatment to be more effective. However, the exact methods are not specifically mentioned and are, therefore, not reproducible.
The number of patients with resolved disease on the post-treatment gallium scan were 6 out of 10 in group B versus 2 out of 10 in group A. The risk ratio (RR) was 3.0 (95% CI: 0.79 to 11.4), favoring the surgery group.

Lambor (2013) found a remission rate of 11 out of 12 in the surgery group and 12 out of 15 in the control group (Risk Ratio 1.12, 95% CI 0.85–1.55).

Quality of life (important)

None of the included studies reported quality of life as an outcome measure.

Summary of Findings

PICO (1.1)

Population: Patients with proven necrotizing otitis externa
Intervention: Surgical treatment
Comparison: Medical treatment

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates**		**Certainty of the Evidence** (Quality of evidence)	**Summary**
		Medical treatment	Surgical treatment		
Survival	1 study reported no mortality	-		**Very low** By very serious imprecision[2]	The evidence is very uncertain about the effect of surgical management to improve survival in patients with skull base osteomyelitis. (*Freeman 2023)*

Remission	The risk ratio (RR) is 1.15 (95% CI: 0.84 to 1.55), based on 27 participant from one study.	-	**Very low** By very serious imprecision[3]	The evidence is very uncertain about the effect of surgical management to improve disease control in patients with skull base osteomyelitis. *(Lambor, 2013*)
Quality of life	-	-	-	No evidence was found about the effect of surgical management to improve the quality of life in patients with skull base osteomyelitis.

2. **Imprecision: very serious.** Low population (<100)
3. **Imprecision: very serious.** Low population (<100)
4. **Imprecision: very serious.** Low population (<100)

Considerations – from evidence to recommendation

Balance between desired and undesired effects

The systematic literature search yielded conflicting results in the few selected articles. Only one RCT was identified, which favored surgery for treatment response in patients with refractory necrotizing otitis externa who were unsuccessfully treated with antibiotics for 6 weeks. However, the methodological and statistical approaches were questionable (Singh, 2018). An observational study on the primary treatment of necrotizing otitis externa found no clinically relevant improvement in remission rates favoring surgical treatment over antibiotics alone (RR 1.15, 95% CI: 0.84 to 1.55) (Lambor, 2013).

Current literature cannot provide a clear answer regarding the role of surgery in necrotizing otitis externa. This is partly due to the rarity of the condition and partly because the cornerstone of treatment is medical. Recent trends also show a sharp decline in the use of extensive surgical therapy for the disease (which included mastoidectomy, facial nerve decompression, and/or middle ear exploration), with 13.3% of patients undergoing extensive surgery before 2009 compared to 3.7% after 2009 (Byun, 2020).

A variety of surgical options are described in the literature, ranging from nettoyage of the ear canal to lateral temporal bone resection. Based on the literature search, it is evident that no clear surgical indication exists. However, specific procedures could be considered for different indications. This list is explicitly not a hierarchical ste-by-step enumeration of treatment options; it is a list of treatment options that is opted for in literature in specific conditions.

- Nettoyage of the ear canal: This can be performed in combination with obtaining culture material or tissue biopsy for diagnostic purposes. Cleaning the ear canal of debris might not be considered a surgical intervention, but it is mentioned because it is reported in literature as (part of) a treatment.
- Other studies describe more extensive surgical interventions of the ear canal, including sequestrectomy and smoothing of bony irregularities / canalplasty. In our opinion, it is important not to confuse NOE with osteitis of the temporal bone for this indication. Osteitis due to a localized infection and/or inflammation can be a major cause of sequestra and epithelial defects in the ear canal, leading to granulation tissue and loss of the canal's migratory capacity. Moreover, prior radiotherapy of the parotid

gland or nasopharynx can cause avascular necrosis or osteoradionecrosis of the temporal bone, leading to tissue defects as mentioned earlier, which can mimic NOE. Again, this should not be confused with NOE, especially because the nature of this problem is not primarily infectious.

- Mastoidectomy: The guideline panel believes that the main incentive for this procedure would be diagnostic, as local treatment of the ear canal might not reveal pathogens. Local epithelialization in the ear canal may be restored due to local treatment, whereas the infectious process can progress in deeper tissues. Mastoidectomy solely to reduce infectious load has been described but is considered obsolete.
- (Sub)total petrosectomy/lateral temporal bone resection: The most invasive type of surgery consists of (sub)total petrosectomy or lateral temporal bone resection. No evidence supports the indication for these procedures. These types of surgery could be considered as salvage surgery if all other treatments fail, potentially aiding in reducing disease burden. However, morbidity and mortality rates are high, making these procedures generally discouraged (Peleg, 2007; Omran, 2012).
- Facial nerve decompression: Facial nerve decompression in cases of facial nerve palsy is described as an indication for surgical intervention, with one study reporting its positive effects (Freeman, 2023). Facial nerve decompression is automatically performed in combination with mastoidectomy due to the surgical approach.

The extent of surgical intervention, if any, depends on multiple factors. Moreover, a combination of procedures can be chosen if indicated. The most obvious surgical indication is the search for a causative pathogen, especially in cases of failed initial medical treatment. Imaging can guide the determination of the anatomical area to approach for tissue sampling. The ear canal, mastoid, and skull base can be areas of interest, and occasionally the nasopharynx, if affected, is easily accessible.

Given the sparse literature available, it is difficult to provide clear recommendations. If no pathogen is identified, antibiotic treatment cannot be optimized, surgical intervention should be considered. The type of surgery will be determined on an individual basis and depends on multiple factors. Imaging reveals which areas are affected, guiding the choice of surgery. The clinical state of the patient, as well as cranial nerve involvement, is weighed in the decision to perform surgery. If there is a suspicion of malignancy tissue samples need to be obtained, and more invasive surgery might be necessary to collect relevant tissue samples. Unequivocally, antibiotic treatment will remain the primary treatment modality in case of NOE. Studies to determine the benefit of surgical interventions will continue to be challenging, as necrotizing otitis externa is rare and indications are unclear. However, a large multicenter study with clear indications might provide more insight into the role of surgery in the treatment of necrotizing otitis externa.

Quality of the evidence

The overall quality of evidence is very low. This means that the estimated effect of the critical outcomes that were found are very uncertain. There was a downgrade due to the following:

- Risk of Bias: methodological limitations.
- Inconsistency: inconsistency of the results.
- Indirectness: indirectness of the evidence, due to differences in the use of surrogate outcomes.
- Imprecision: inaccuracy, due to a very small number of events in a small sample size.

Moreover, the inconsistent terminology used in surgical approaches and the doubtful use of correct diagnoses might give a distorted image of literature, with a high risk of publication bias.

Values and preferences of patients (and possibly their caregivers)
Since studies describing surgery for necrotizing otitis externa are rare, it can be difficult to decide when to opt for surgery. Moreover, available reports are unclear and inconsistent regarding the type and extent of surgery. Patients should be informed about the goal of the procedure and the associated risks. The uncertainty of the outcome should also be addressed. The alternative to surgical intervention depends on the indication for the procedure. If the causative pathogen is unknown, surgery to obtain tissue samples is a reasonable indication. In cases of cranial nerve palsy, the indication and outcome are more uncertain, and both physicians and patients should be aware of this. If (optimal) conservative treatment does not result in clinical improvement, similar considerations must be made, and specialized (tertiary) centers should be consulted regarding further treatment.

Costs (resources)
Since surgery for NOE is rare, costs for this kind of treatment are negligible considering total treatment costs. However, no studies have been performed to show cost-effectiveness of the treatment, let alone for the surgery done in a small percentage of cases.

Equity ((health) equity/equitable)
The guideline panel expects no problems with health equity with regard to medical treatment of necrotizing otitis externa.

Acceptability
The guideline panel expects no problems with ethical acceptability or sustainability with regard to medical treatment of necrotizing otitis externa.

Feasibility
Regardless of the eventual recommendation, surgical intervention is feasible. The intervention is a treatment option for some clinicians. Even though the surgical procedure is feasible, the indication is complex, if existent, as mentioned before. Given this complexity the advice is to consult a specialist in NOE when surgery is considered in patients that do not seem to respond to conservative treatment. No specialized equipment is needed for surgical procedures.

Recommendation(s)
Rationale of the recommendation: weighing arguments for and against the interventions
The literature on outcome or effect of surgical intervention as a standard treatment is of insufficient certainty and different studies all use different outcome measures. Therefore, the recommendations are expert opinions.
The available literature for surgical treatment in NOE suggests that surgery has a very limited role. The main indication for surgical exploration is in case of failing conservative treatment in case of an unknown causative pathogen.
There is insufficient available evidence on the effect of facial nerve decompression in case of facial nerve palsy in NOE.

Final judgment:
Weak recommendation against surgical intervention in patients with necrotizing otitis externa.

Treat patients with necrotizing otitis externa medically. There is no role for surgery as the primary treatment for patients with necrotizing otitis externa.

In the following scenarios a surgical approach can be chosen, apart from medical treatment:

- In case of failing treatment. A surgical approach for diagnostic purposes can be undertaken to improve the chance of a positive culture, or to exclude a different diagnosis. Ablative surgery as salvage treatment is not advised.
- No advise is given on the role for surgery in case of facial nerve palsy, due to the limited evidence.

Take into account that most patients with necrotizing otitis externa are frail. The risk of general anesthesia should also be considered and weighed in the (shared) decision making.

Knowledge gaps

During the development of this module, a systematic search was conducted to find studies that could answer the research question. Through the use of a systematic literature review with an assessment of the strength of evidence, it has become clear that there are still knowledge gaps within this module. The working group believes that further research is desirable to provide clearer answers to practical questions in the future.

Question

What are the benefits and disadvantages of surgical treatment for necrotizing otitis externa compared to medical treatment?

Explanation

Because of the sparse availability of literature regarding the subject, a RCT should be performed with sufficient numbers, to ultimately answer the question beyond reasonable doubt. The same question as the original search question can be used.

Verkeerslicht en (de-)implementatietabel

Toelichting

Met het verkeerslicht worden aanbevelingen gecategoriseerd op basis van formulering en bewijskracht. Als eindproduct wordt bij richtlijnmodules met een sterk geformuleerde en voldoende onderbouwde aanbeveling een implementatietabel opgeleverd. Hierin wordt onder andere opgenomen:

- Een beschrijving van het knelpunt om de module uit te werken of herzien;
- De te verwachten belemmerende en bevorderende factoren voor implementatie;
- Welke partijen van belang zijn bij toepassen van de aanbeveling in de praktijk;
- Een inschatting van de implementatietermijn.

Verkeerslichtanalyse

- **ROOD** = sterk geformuleerde aanbeveling om iets niet te doen, met een GRADE high of moderate
- **ORANJE** = zwak geformuleerde aanbeveling; mogelijk kennishiaat
- **GROEN** = sterk geformuleerde aanbeveling om iets wel te doen, met een GRADE high of moderate
- **LICHT ROOD** of **LICHT GROEN** = sterk geformuleerde aanbevelingen met een GRADE low, very low of geen GRADE *(modules waarin geen studies geïncludeerd konden worden in*

de literatuursamenvatting of waarin geen literatuursamenvatting werd geschreven zoals modules waarin organisatie van zorg wordt beschreven)

(Sub)aanbeveling	Sterkte van de aanbeveling	Bewijskracht per uitkomstmaat	Verkeerslicht per (sub)aanbeveling
Aanbeveling: Treat patients with necrotizing otitis externa medically. There is no role for surgery as the primary treatment for patients with NOE.	□ Sterk (doe/ gebruik) /	**Overall bewijskracht** □ **VL** **Range bewijskracht van alle uitkomstmaten** □ **VL**	**LICHT GROEN**

Implementatietabel

Tabel A: (De-)Implementatietabel met impuls analyse

Aanbeveling – 1			
1. Wat was het onderliggende probleem om deze uitgangsvraag uit te werken?	**□ Ongewenste praktijkvariatie**		
2. Maak een inschatting over hoeveel patiënten het ongeveer gaat waar de aanbeveling betrekking op heeft?	**□ < 1000**		
3. Maakt de aanbeveling deel uit van een set van interventies voor hetzelfde probleem?	**□ Nee**		
4. Belemmeringen en kansen op verschillende niveaus voor landelijke toepassing van de aanbeveling:	***Voorbeelden***	**Wat zijn mogelijke belemmerende factoren?**	**Wat zijn mogelijke bevorderende factoren?**
g) **Richtlijn/ klinisch traject (innovatie)**	*Voortschrijding/vooruitgang in de praktijk, haalbaarheid, geloofwaardigheid, toegankelijkheid, aantrekkelijkheid*	Weinig aangezien we aanbeveling tegen doen. Echter gezien er nog wel onduidelijkheid is, kan er praktijkvariatie nog steeds onstaan	Goede resultaten die worden gehaald met medische therapie
h) **Zorgverleners (artsen en verpleegkundigen)**	*Bewustzijn, kennis, houding, motivatie om te veranderen, gedragsroutines*	Weinig expertise per centum in chirurgie voor dit specifieke probleem. Vaak alleen tertiair en zelfs specifief	-
i) **Patiënt/ cliënt (naasten)**	*Kennis, vaardigheden, houding, compliance*	-	-

j) **Sociale context**	*Mening van collega's, cultuur van het netwerk, samenwerking, leiderschap*	-	-
k) **Organisatorische context**	*Organisatie van zorgprocessen, personeel, capaciteiten, middelen, structuren*	Indien chirurgie dit alleen mogelijk in specifieke centra.	Indien geen interventie, waar deze richtlijn in adviseert, is het intravenous, hetgeen overall goed mogelijk is.
l) **Economische en politieke context**	*Financiële regelingen, regelgeving, beleid (vergoede zorg, betaaltitel)*	-	-

5. Welke personen/partijen zijn van belang bij het toepassen van de aanbeveling in de praktijk?	**x** Patiënt/ cliënt (naaste) **x** Professional
6. Wat zouden deze personen/ partijen moeten veranderen in hun gedrag of organisatie om de aanbeveling toe te passen?	Gezien er in NL nauwelijk tot geen chirurgie wordt toegpast voor dit probleem zullen er maar weinig aanpassingen moeten worden gemaakt.
7. Binnen welk tijdsbestek moet de aanbeveling zijn geïmplementeerd?	□ < 1 jaar
8. Conclusie: is er extra aandacht nodig voor implementatie van de aanbeveling (anders dan publicatie van deze richtlijnmodule)?	□ **Nee**

**Deze aanbeveling komt in aanmerking voor plaatsing op de Implementatie Agenda van het programma Zorg Evaluatie & Gepast Gebruik (ZE&GG). In het programma ZE&GG werken patiënten, zorgverleners, zorgaanbieders, zorgverzekeraars en overheid samen aan de bewezen beste zorg voor de patiënt. Daarmee is ZE&GG een programma van alle betrokken partijen in de Medisch Specialistische Zorg. FMS is één van deze betrokken partijen.*

De implementatieagenda van ZE&GG bevat onderwerpen over wat de bewezen beste zorg is en die in de dagelijkse zorgpraktijk geïmplementeerd zouden moeten worden. Zorgverzekeraars Nederland (ZN) en de Nederlandse Vereniging voor Ziekenhuizen (NVZ) hebben landelijke afspraken gemaakt over de implementatie van de onderwerpen van de implementatieagenda. Deze afspraken zijn onderdeel van de zorginkoopafspraken tussen zorgverzekeraars en zorgaanbieders.

Vanuit FMS worden sterke, goed onderbouwde aanbevelingen, getoetst op de behoefte aan een implementatie impuls aangedragen. Voor de beoordeling van onderwerpen uit richtlijnen wordt gekeken naar bovenstaande tabel voor een inschatting van de implementatie impuls. Met de ingevulde implementatietabel kunnen we vanuit FMS de andere HLA-MSZ partijen goed informeren om zo samen te beslissen of de aanbeveling daadwerkelijk op de implementatie agenda zal worden geplaatst.

Literatuur

Byun YJ, Patel J, Nguyen SA, Lambert PR. Necrotizing Otitis Externa: A Systematic Review and Analysis of Changing Trends. Otol Neurotol. 2020 Sep;41(8):1004-1011. doi: 10.1097/MAO.0000000000002723. PMID: 32569149.

Freeman MH, Perkins EL, Tawfik KO, O'Malley MR, Labadie RF, Haynes DS, Bennett ML. Facial Paralysis in Skull Base Osteomyelitis - Comparison of Surgical and Nonsurgical Management. Laryngoscope. 2023 Jan;133(1):179-183. doi: 10.1002/lary.30161. Epub 2022 May 12. PMID: 35546515.

Lambor DV, Das CP, Goel HC, Tiwari M, Lambor SD, Fegade MV. Necrotising otitis externa: clinical profile and management protocol. J Laryngol Otol. 2013 Nov;127(11):1071-7. doi: 10.1017/S0022215113002259. Epub 2013 Oct 29. PMID: 24169084.

Omran AA, El Garem HF, Al Alem RK. Recurrent malignant otitis externa: management and outcome. Eur Arch Otorhinolaryngol. 2012 Mar;269(3):807-11. doi: 10.1007/s00405-011-1736-2. Epub 2011 Aug 11. PMID: 21833561.

Peleg U, Perez R, Raveh D, Berelowitz D, Cohen D. Stratification for malignant external otitis. Otolaryngol Head Neck Surg. 2007 Aug;137(2):301-5. doi: 10.1016/j.otohns.2007.02.029. PMID: 17666260.

Singh J, Bhardwaj B. The Role of Surgical Debridement in Cases of Refractory Malignant Otitis Externa. Indian J Otolaryngol Head Neck Surg. 2018 Dec;70(4):549-554. doi: 10.1007/s12070-018-1426-0. Epub 2018 Jun 18. PMID: 30464914; PMCID: PMC6224839.

Bijlagen bij module 5 - Surgical treatment

Risk of Bias tables

Risk of bias table for intervention studies (observational: non-randomized clinical trials, cohort and case-control studies

Study reference (first author, year of publication)	**Bias due to a non-representative or ill-defined sample of patients?**[1] (unlikely/likely/unclear)	**Bias due to insufficiently long, or incomplete follow-up, or differences in follow-up between treatment groups?**[2] (unlikely/likely/unclear)	**Bias due to ill-defined or inadequately measured outcome ?**[3] (unlikely/likely/unclear)	**Bias due to inadequate adjustment for all important prognostic factors?**[4] (unlikely/likely/unclear)
Lambor, 2013	Unlikely	Unlikely	likely	Unclear
Freeman, 2023	likely	unlikely	Likely	Unclear

Risk of bias table for intervention studies (randomized controlled trials; based on Cochrane risk of bias tool and suggestions by the CLARITY Group at McMaster University)

Study reference (first author, publication year)	**Was the allocation sequence adequately generated?**	**Was the allocation adequately concealed?**	**Blinding:**	**Was loss to follow-up (missing outcome data) infrequent ?**	**Are reports of the study free of selective outcome reporting ?**	**Was the study apparently free of other problems that could put it at a risk of bias?**	**Overall risk of bias** **If applicable/necessary, per outcome measure**
Singh, 2018	Definitely yes; Reason: Central randomization with computer generated random numbers	Probably no Reason: concealment of allocation was not reported in the article	Definitely no Reason: Open-label trial (patients and health care providers not blinded), outcome assessors blinded (blinding of data collectors and analysts not reported)	Definitely yes. Reason: no patients were lost to follow up.	definitely no; Reason: only some symptoms reported, on which was decided that one therapy was better than the other.	Definitely yes; Reason: No other problems noted	**HIGH (Disease control)**

Table of excluded studies

Reference	Reason for exclusion
Das S, Iyadurai R, Gunasekaran K, Karuppusamy R, Mathew Z, Rajadurai E, John AO, Mani S, George T. Clinical characteristics and complications of skull base osteomyelitis: A 12-year study in a teaching hospital in South India. J Family Med Prim Care. 2019 Mar;8(3):834-839. doi: 10.4103/jfmpc.jfmpc_62_19. PMID: 31041210; PMCID: PMC6482749.	Wrong population (also including non otogenic)
Chawdhary G, Pankhania M, Douglas S, Bottrill I. Current management of necrotising otitis externa in the UK: survey of 221 UK otolaryngologists. Acta Otolaryngol. 2017 Aug;137(8):818-822. doi: 10.1080/00016489.2017.1295468. Epub 2017 Mar 16. PMID: 28301961.	No comparison made
Chawdhary G, Pankhania M, Douglas S, Bottrill I. Current management of necrotising otitis externa in the UK: survey of 221 UK otolaryngologists. Acta Otolaryngol. 2017 Aug;137(8):818-822. doi: 10.1080/00016489.2017.1295468. Epub 2017 Mar 16. PMID: 28301961.	Wrong study design
Peled C, Parra A, El-Saied S, Kraus M, Kaplan DM. Surgery for necrotizing otitis externa-indications and surgical findings. Eur Arch Otorhinolaryngol. 2020 May;277(5):1327-1334. doi: 10.1007/s00405-020-05842-x. Epub 2020 Feb 12. PMID: 32052142.	No comparison made

Literature search strategy

Zoekverantwoording
Algemene informatie

Cluster/richtlijn: Osteomyelitis schedelbasis – maligne otitis externa	
Uitgangsvraag/modules: Wat is de waarde van chirurgische behandeling bij maligne otitis externa, ten opzichte van alleen medicamenteuze behandeling?	
Database(s): Ovid/Medline, Embase.com	Datum: 6 februari 2023
Periode: 2000* - heden	Talen: Engels, Nederlands
Literatuurspecialist: Miriam van der Maten	
BMI-zoekblokken: voor verschillende opdrachten wordt (deels) gebruik gemaakt van de zoekblokken van BMI-Online https://blocks.bmi-online.nl/ Bij gebruikmaking van een volledig zoekblok zal naar de betreffende link op de website worden verwezen.	
Toelichting: Voor deze vraag is gezocht op de elementen: • Maligne otitis externa of osteomyelitis schedel • Chirurgische behandeling → De opgegeven sleutelartikelen worden gevonden met de zoekopdracht → Er is gezocht met major/focus Emtree/MeSH en in titel/keyword i.p.v. titel/abstract/keyword om ruis eruit te filteren. *Er is gezocht vanaf het jaar 2000. Terugkomend op de opmerking van het zoekformulier, verder terugzoeken zal minimaal 250 hits extra betekenen.	

Te gebruiken voor richtlijnen tekst:
Nederlands
In de databases Embase.com en Ovid/Medline is op 6 februari 2023 systematisch gezocht naar systematische reviews, RCT, observationele studies, niet-vergelijkend onderzoek over de waarde van chirurgische behandeling bij maligne otitis externa. De literatuurzoekactie leverde 456 unieke treffers op.

Engels
On the 6th of February 2023, we performed a systematic search in the databases Embase.com and Ovid/Medline to find systematic reviews, RCT, observational studies, and other non-comparative research about the value of surgical treatment for malignant external otitis. The search resulted in 456 unique hits.

Zoekopbrengst

	EMBASE	**OVID/MEDLINE**	**Ontdubbeld**
SRs	14	14	21
Overige designs	234	325	435
Totaal	248	339	**456**

Zoekstrategie

Embase.com

No.	**Query**	**Results**
#10	#8 OR #9	248
#9	#6 NOT #8 **= overige designs**	234
#8	#6 AND #7 **= SR**	14
#7	'meta analysis'/exp OR 'meta analysis (topic)'/exp OR metaanaly*:ti,ab OR 'meta analy*':ti,ab OR metanaly*:ti,ab OR 'systematic review'/de OR 'cochrane database of systematic reviews'/jt OR prisma:ti,ab OR prospero:ti,ab OR (((systemati* OR scoping OR umbrella OR 'structured literature') NEAR/3 (review* OR overview*)):ti,ab) OR ((systemic* NEAR/1 review*):ti,ab) OR (((systemati* OR literature OR database* OR 'data base*') NEAR/10 search*):ti,ab) OR (((structured OR comprehensive* OR systemic*) NEAR/3 search*):ti,ab) OR (((literature NEAR/3 review*):ti,ab) AND (search*:ti,ab OR database*:ti,ab OR 'data base*':ti,ab)) OR (('data extraction':ti,ab OR 'data source*':ti,ab) AND 'study selection':ti,ab) OR ('search strategy':ti,ab AND 'selection criteria':ti,ab) OR ('data source*':ti,ab AND 'data synthesis':ti,ab) OR medline:ab OR pubmed:ab OR embase:ab OR cochrane:ab OR (((critical OR rapid) NEAR/2 (review* OR overview* OR synthes*)):ti) OR ((((critical* OR rapid*) NEAR/3 (review* OR overview* OR synthes*)):ab) AND (search*:ab OR database*:ab OR 'data base*':ab)) OR metasynthes*:ti,ab OR 'meta synthes*':ti,ab	898726
#6	#4 AND #5 AND [2000-2023]/py NOT ('conference abstract'/it OR 'editorial'/it OR 'letter'/it OR 'note'/it) NOT (('animal experiment'/exp OR 'animal model'/exp OR 'nonhuman'/exp) NOT 'human'/exp)	248
#5	'surgery'/exp/mj OR 'surgical patient'/exp/mj OR 'surgical risk'/exp/mj OR 'perioperative period'/exp/mj OR surgic*:ti,kw OR surger*:ti,kw OR operation*:ti,kw OR operative:ti,kw OR presurg*:ti,kw OR preoperati*:ti,kw OR 'pre-surg*':ti,kw OR 'pre-operati*':ti,kw OR perisurg*:ti,kw OR perioperati*:ti,kw OR 'peri-surg*':ti,kw OR 'peri-operati*':ti,kw OR postsurg*:ti,kw OR postoperati*:ti,kw OR 'post-surg*':ti,kw OR 'post-operati*':ti,kw OR 'debridement'/exp OR 'debridement':ti,ab,kw OR resect*:ti,ab,kw OR mastoidectom*:ti,ab,kw	3894874

#4	'malignant otitis externa'/exp/mj OR (((maligna* OR necroti* OR necrosis) NEAR/3 ('otitis externa' OR 'external otitis')):ti,kw) OR ('otitis externa'/mj AND (maligna*:ti,kw OR necroti*:ti,kw OR necrosis:ti,kw)) OR (('osteomyelitis'/exp/mj OR 'osteomyelitis':ti,kw) AND ('skull'/exp/mj OR 'skull disease'/exp/mj OR skull*:ti,ab,kw OR cranial:ti,ab,kw OR cranium:ti,ab,kw))	3086

Ovid/Medline

#	Searches	Results
9	7 or 8	339
8	5 not 7**= overige designs**	325
7	5 and 6 **= SR**	14
6	meta-analysis/ or meta-analysis as topic/ or (metaanaly* or meta-analy* or metanaly*).ti,ab,kf. or systematic review/ or cochrane.jw. or (prisma or prospero).ti,ab,kf. or ((systemati* or scoping or umbrella or "structured literature") adj3 (review* or overview*)).ti,ab,kf. or (systemic* adj1 review*).ti,ab,kf. or ((systemati* or literature or database* or data-base*) adj10 search*).ti,ab,kf. or ((structured or comprehensive* or systemic*) adj3 search*).ti,ab,kf. or ((literature adj3 review*) and (search* or database* or data-base*)).ti,ab,kf. or (("data extraction" or "data source*") and "study selection").ti,ab,kf. or ("search strategy" and "selection criteria").ti,ab,kf. or ("data source*" and "data synthesis").ti,ab,kf. or (medline or pubmed or embase or cochrane).ab. or ((critical or rapid) adj2 (review* or overview* or synthes*)).ti. or (((critical* or rapid*) adj3 (review* or overview* or synthes*)) and (search* or database* or data-base*)).ab. or (metasynthes* or meta-synthes*).ti,ab,kf.	650866
5	limit 4 to yr="2000 -Current"	339
4	3 not (comment/ or editorial/ or letter/ or ((exp animals/ or exp models, animal/) not humans/))	580
3	1 and 2	606
2	exp *Surgical Procedures, Operative/ or exp *Specialties, Surgical/ or exp *Perioperative Period/ or surgic*.ti,kf. or surger*.ti,kf. or operation*.ti,kf. or operative.ti,kf. or presurg*.ti,kf. or preoperati*.ti,kf. or pre-surg*.ti,kf. or pre-operati*.ti,kf. or perisurg*.ti,kf. or perioperati*.ti,kf. or peri-surg*.ti,kf. or peri-operati*.ti,kf. or postsurg*.ti,kf. or postoperati*.ti,kf. or post-surg*.ti,kf. or post-operati*.ti,kf. or exp Debridement/ or 'debridement'.ti,ab,kf. or resect*.ti,ab,kf. or mastoidectom*.ti,ab,kf.	3205775
1	((maligna* or necroti* or necrosis) adj3 ('otitis externa' or 'external otitis')).ti,kf. or (exp *Otitis Externa/ and (maligna* or necroti* or necrosis).ti,kf.) or ((exp *Osteomyelitis/ or 'osteomyelitis'.ti,kf.) and (exp Skull/ or skull*.ti,ab,kf. or cranial.ti,ab,kf. or cranium.ti,ab,kf.))	2625

Module 6 – Hyperbaric oxygen therapy

Question
What is the added value of hyperbaric oxygen therapy, as opposed to medical treatment alone?

Introduction
Hyperbaric oxygen therapy (HBOT) is a treatment modality used for enhanced recovery of tissues. It consists of exposure to more than 99% oxygen at a pressure higher than the atmospheric pressure. A patient is placed in a pressure vessel during a predetermined treatment schedule. HBOT has proven efficacy for several medical conditions (Moon, 2019). The main principle is to increase the availability of oxygen throughout the body (Gordon, 2023), which is thought to result in fibroblast activation, upregulation of growth factors, downregulation of inflammatory cytokines and reduction of leukocyte chemotaxis (Sethuraman, 2022). Several diagnoses have been widely approved as an indication for HBOT and can be divided into two main categories: disorders primary related to gas exchange (carbon monoxide poisoning, decompression sickness) and disorders related to tissue perfusion, amongst others: wound problems, necrotizing soft tissue infections, refractory osteomyelitis (Moon, 2019). Necrotizing otitis externa, or skull base osteomyelitis is not explicitly mentioned as such, but can be interpreted as a necrotizing soft tissue infection as well as refractory osteomyelitis.

Search and select
A systematic review of the literature was performed to answer the following question(s): What are the benefits of hyperbaric oxygen therapy, as opposed to standard medical treatment.

Table 1. PICO

Patients	Patients with proven necrotizing otitis externa
Intervention	Hyperbaric oxygen therapy, with or without added standard medical therapy
Control	Standard medical therapy
Outcomes	Remission, length of treatment
Other selection criteria	Study design: systematic reviews and randomized controlled trials, observational studies [Minimal follow-up: not defined]

<u>Relevant outcome measures</u>
The guideline panel considered remission, recurrence and length of treatment as a **critical** outcome measure for decision making;

The guideline panel defined the outcome measures as follows:

- Remission: cure rate of disease after treatment, sometimes defined in the numbers of failure of treatment
- Length of treatment: the time of treatment until successful curation of disease

The guideline panel defined the following as a minimal clinically (patient) important difference.

- Remission: GRADE standard limits*
- Length of treatment: GRADE standard Limits*

* Default thresholds proposed by the international GRADE working group were used: a 25% difference in relative risk (RR) for dichotomous outcomes (RR <0.80 or RR >1.25), or 0.5 standard deviations (SD) for continuous outcomes

Search and select (Methods)
The databases [Medline (via OVID) and Embase (via Embase.com)] were searched with relevant search terms until 11-07-2023 The detailed search strategy is listed under the tab 'Literature search strategy'. The systematic literature search resulted in 143 hits. Studies were initially selected based on title and abstract screening. After reading the full text, 35 studies were excluded (see the exclusion table under the tab 'Evidence tabellen'), and 1 non-randomized comparative study was included.

Summary of literature
Description of studies
A total of 1 study was included in the analysis of the literature. Important study characteristics and results are summarized in table 2. The assessment of the risk of bias is summarized in the risk of bias tables (under the tab 'Evidence tables').

Table 2. Characteristics of included study

Study	Participants (number, age, other important characteristics)	Comparison	Follow-up	Outcome measures	Comments	Risk of bias (per outcome measure)*
Individual study, non-randomized comparative study						
Mardassi, 2016	*N at baseline* Intervention: 19 Control: 23 *Age* 67 (50 to 84) Sex: male to female ratio was 0.82 All patients had diabetes.	Intervention: 19 patients underwent standard medical care (see control) with added HBOT (daily 90 minute sessions with a mean of 20 sessions per patient) Control: Standard medical therapy: Antibiotics intravenously and then orally for a mean period of 8 weeks (5 to 15 weeks).	The period of inclusion was 9 years. No length of follow up was specified.	Remission and recurrence		High for recurrence and remission

*For further details, see risk of bias table in the appendix

Results

Remission

The study of Mardassi (2016) included 42 patients, in which 19 underwent HBOT, in addition to standard antibiotic treatment (i.v. 3rd generation cephalosporin for 3 to 4 weeks, followed by oral fluoroquinolones for a total mean period of 8 weeks (5 to 15 weeks). In the group with HBOT, there was total remission in 19 of 19 patients (100%). The group with only antibiotic treatment had a remission in 17 out of 23 (74%)

Length of treatment

No studies regarding length of treatment as an outcome measure were found

Summary of Findings

Population: Patients with proven necrotizing otitis externa
Intervention: Hyperbaric oxygen therapy, with or without additional standard therapy
Comparator: Standard therapy

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Standard therapy	Hyperbaric oxygen therapy, with or without additional standard	**Certainty of the evidence** (Quality of evidence)	**Summary**
		Difference: **63 fewer per 1000** (CI 95% 68 fewer - 37 more)			
Remission[3] 1 year	Relative risk: 1.35 (CI 95% 1.06 - 1.72) Based on data from 42 participants in 1 studies[5] Follow up unknown	**776** per 1000	**1048** per 1000	**Very low** By serious risk of bias and indirectness. Extremely serious imprecision[5]	We are unsure if hyperbaric oxygen therapy, will improve the remission of disease in patients with proven necrotizing otitis externa (Mardassi, 2016)
		Difference: **272 more per 1000** (CI 95% 47 more - 559 more)			
Length of treatment[6] 1 year				**No GRADE** (no evidence was found)	No evidence was found regarding the length of treatment with hyperbaric oxygen therapy.

1. Primary study [2] **Baseline/comparator** Systematic review [1] .
2. **Risk of Bias: serious.** loss to follow up; **Indirectness: very serious. Imprecision: extremely serious.**
3. Remission of disease afther therapy. Also known as curation rate
4. Primary study [2] **Baseline/comparator** Systematic review [1] .
5. **Risk of Bias: serious. Indirectness: very serious. Imprecision: extremely serious.**
6. Total duration of treatment

Considerations – from evidence to recommendation

Balance between desired and undesired effects

Evidence

Reviewing the results found in literature, we found only one study comparing the remission of patients treated with additional hyperbaric oxygen therapy, versus standard therapy consisting primarily of antibiotics (Mardassi, 2016). They found a rate of remission of 100% in the HBOT group, versus 74% in the group without HBOT (Relative risk: 1.35 (CI 95% 1.06 - 1.72)).. However, in the light of the overall quality of evidence, the effect of HBOT is uncertain. Analogous to the methodology of this literature search, the same conclusion was drawn in the Cochrane review (Philips, 2013): no identified articles described randomized controlled trials of hyperbaric oxygen therapy in the treatment of malignant otitis externa.

Expert opinion

As there is only one comparative study on this topic, this caption summarizes the available literature with lower evidence level, including case series and retrospective observational studies opinion, along with the panel's expert opinion.

According to the European Committee for Hyperbaric Medicine (ECHM) (Mathieu, 2017), during the 10th European Consensus Conference on Hyperbaric Medicine, recommendations were given for accepted and non-accepted clinical indications. The recommendations were given on three components: 1) level of evidence 2) the interpretation of the evidence 3) the type or strength of the recommended practice. In this paper the Committee acknowledges that there are several conditions of interest that are so complex or where there are so many variables that it would be impossible to design a study sufficiently powerful to assess any single procedure. For malignant otitis externa, no specific recommendations on the use of HBOT were given, owing to the very low levels of evidence (level D): the disease is placed in the category "non-accepted indications". This should not be confused with evidence against the use of HBOT (this category of indications is mentioned separately). The ECHM ultimately advises, in case of treatment of patients with conditions in which HBOT (such as NOE) is considered not to be indicated, to discuss a benefit/risk balance for each specific patient before using HBOT.

A systematic review by Byun (2020) describes results of 58 pooled patients from 16 studies. The reported studies are studies in which additional HBOT was given, either concomitantly or in case of failing medical or surgical treatment. In most cases the HBOT regimen was well reported. An overall cure rate of 91.4% was found. The most extensive systematic review on NOE (Takata, 2023) reports on 70 papers on a total of over 2000 patients. 10 papers report on the use of HBOT, also either concomitant or as salvage treatment. There seems a regional preference for this treatment modality, as most papers are from the US, Turkey or Israel. The article states that there is no clear evidence to support HBOT use in NOE.

Unless this clear statement of the ECHM, research papers are published on case series describing the use of HBOT and case series in which a fraction of patients is treated with HBOT. This might be a reflection of the therapeutic dilemmas of clinicians in severe cases looking for additional treatment options, or the lack of opportunity to create a higher level of evidence due to the low incidence.

Studies on HBOT in patients with NOE / skull base osteomyelitis

Well-structured reports on HBOT for NOE are very limited. One study reports on the results of a single hyperbaric center in Portugal, summarizing the results of 16 patients over 9 years from 8 tertiary referral centers (Amaro, 2019). Patients were at least treated 3 months prior to HBOT (average 5 months). The majority of the patients had extensive disease with cranial

nerve palsies and had had surgery prior HBOT. The overall disease-specific survival was 100%. The authors share these results along with the limitations and state that HBOT can be considered in in patients who failed conventional therapy and in severe cases. Although all cases are well documented, the most important limitation is that no proof about objective monitoring of disease control is given. Moreover, the study population is thought to be highly biased towards the extraordinarily severe case load.

A recent study reports on 15 patients treated with HBOT over the course of 15 years, all referred by tertiary care centers after failed medical, and in some cases, surgical treatment (Gomes, 2024). Although a detailed description of the prior treatment lacks, 100% remission is reported after combined medical and hyperbaric therapy.

Quality of the evidence

The overall quality of evidence is very low. This means that we are very uncertain about the estimated effect of the critical outcomes found. There was a downgrade due to:

- Risk of Bias: methodological limitations
- Indirectness: indirectness of the evidence, due to differences in population.
- Imprecision: inaccuracy, due to a very small number of events in a small sample size.

Values and preferences of patients (and possibly their caregivers)

Due to the unknown effects of HBOT. Any possible complications for the patient are very significant. Although often self-limiting after treatment, some complications such a pneumothorax can occur and should be taken into consideration for a treatment with unknown therapeutic effects for necrotizing otitis externa.

Costs (resources)

HBOT is not unreasonably expensive as a treatment option. However, if the added value is debatable, the cost aspect should definitely be weighed.

Equity ((health) equity/equitable)

The guideline panel expects no problems with health equity with regard to medical treatment of necrotizing otitis externa. HBOT treatment facilities however, are not widespread. Especially because patients are often frail and elderly, it is not obvious to offer HBOT as a (daily) treatment regimen if the nearest facility requires daily transport.

Acceptability

The guideline panel expects no problems with ethical acceptability with regard to HBOT treatment of necrotizing external otitis. A practical problem can be the limited availability of HBOT facilities. HBOT cannot be considered sustainable for a debatable indication in terms of resource use and costs. It requires extensive training and expensive infrastructure (the tanks) and has high energy consumption.

Feasibility

The implementation of HBOT as standard treatment modality for NOE is not feasible, due to the lack of evidence as well as the sparse availability of HBOT facilities.

Recommendation(s)

Rationale of the recommendation: weighing arguments for and against the interventions

Literature on the efficacy of HBOT on NOE / skull base osteomyelitis is limited to case series, case reports and a single comparative study with its limitations and high risk of publication bias. Parallels are drawn with HBOT as a treatment modality for different conditions with similarities, such as complicated wound healing and refractory osteomyelitis, and are used to

justify HBOT for this disorder. Although there are some reports that incline towards a positive effect of HBOT on NOE / skull base osteomyelitis, the quality of the evidence is low.
The guideline panel therefore confirms the opinion / position of the European Committee on Hyperbaric Medicine and does not recommend HBOT as a standard intervention for NOE / skull base osteomyelitis.

Apart from the uncertain beneficial effects of HBOT, possible side effects should also be taken into account: barotrauma, dental problems, sinus compression, claustrophobia, seizures and pulmonary oxygen toxicity. These are rare, but can occur even when the procedure is performed correctly. Costs and availability also play a role when the quality of evidence is considered too low.

Final judgment:
Weak recommendation against the standard treatment of NOE / skull base osteomyelitis with HBOT.

Do not use hyperbaric oxygen therapy as a treatment regimen for patients with necrotizing external otitis.

Knowledge gaps
During the development of this module, a systematic search was conducted to find studies that could answer the research question. Through the use of a systematic literature review with an assessment of the strength of evidence, it has become clear that there is a lack of literature regarding HBOT in this specific disease. There is, however, literature about HBOT in other diseases, added with expert opinion. The guideline panel considers this to be sufficient.

Verkeerslicht en (de-)implementatietabel

Toelichting
Met het verkeerslicht worden aanbevelingen gecategoriseerd op basis van formulering en bewijskracht. Als eindproduct wordt bij richtlijnmodules met een sterk geformuleerde en voldoende onderbouwde aanbeveling een implementatietabel opgeleverd. Hierin wordt onder andere opgenomen:

- Een beschrijving van het knelpunt om de module uit te werken of herzien;
- De te verwachten belemmerende en bevorderende factoren voor implementatie;
- Welke partijen van belang zijn bij toepassen van de aanbeveling in de praktijk;
- Een inschatting van de implementatietermijn.

Verkeerslichtanalyse

- **ROOD** = sterk geformuleerde aanbeveling om iets niet te doen, met een GRADE high of moderate
- **ORANJE** = zwak geformuleerde aanbeveling; mogelijk kennishiaat
- **GROEN** = sterk geformuleerde aanbeveling om iets wel te doen, met een GRADE high of moderate
- **LICHT ROOD** of **LICHT GROEN** = sterk geformuleerde aanbevelingen met een GRADE low, very low of geen GRADE *(modules waarin geen studies geïncludeerd konden worden in de literatuursamenvatting of waarin geen literatuursamenvatting werd geschreven zoals modules waarin organisatie van zorg wordt beschreven)*

(Sub)aanbeveling	Sterkte van de aanbeveling	Bewijskracht per uitkomstmaat	Verkeerslicht per (sub)aanbeveling
Aanbeveling 1: Do not use hyperbaric oxygen therapy as a standard treatment regimen for patients with NOE / skull base osteomyelitis.	□ Sterk (doe/ gebruik) /	**Overall bewijskracht** □ **VL** **Range bewijskracht van alle uitkomstmaten** □ **VL**	**LICHT GROEN**

Implementatietabel

Tabel A: (De-)Implementatietabel met impuls analyse

Aanbeveling – 1			
1. Wat was het onderliggende probleem om deze uitgangsvraag uit te werken?	□ **Ongewenste praktijkvariatie**		
2. Maak een inschatting over hoeveel patiënten het ongeveer gaat waar de aanbeveling betrekking op heeft?	□ **< 1000**		
3. Maakt de aanbeveling deel uit van een set van interventies voor hetzelfde probleem?	□ **Nee**		
4. Belemmeringen en kansen op verschillende niveaus voor landelijke toepassing van de aanbeveling:	***Voorbeelden***	**Wat zijn mogelijke belemmerende factoren?**	**Wat zijn mogelijke bevorderende factoren?**
a) **Richtlijn/ klinisch traject (innovatie)**	*Voortschrijding/vooruitgang in de praktijk, haalbaarheid, geloofwaardigheid, toegankelijkheid, aantrekkelijkheid*	Beperkte toepassing van HBOT in NL, met hierdoor beperkte geloofwaardigheid ervan.	-
b) **Zorgverleners (artsen en verpleegkundigen)**	*Bewustzijn, kennis, houding, motivatie om te veranderen, gedragsroutines*	Beperkte mogelijke centra voor HBOT. Is niet geïmplementeerd in de dagelijkse praktijk, mede wegens gebrek aan kennis erover.	Gezien aanbeveling tegen HBOT ook niet van toepassing.
c) **Patiënt/ cliënt (naasten)**	*Kennis, vaardigheden, houding, compliance*	-	-

d) **Sociale context**	*Mening van collega's, cultuur van het netwerk, samenwerking, leiderschap*	Beperkte mogelijke centra voor HBOT.	Gezien aanbeveling tegen HBOT ook niet van toepassing.
e) **Organisatorische context**	*Organisatie van zorgprocessen, personeel, capaciteiten, middelen, structuren*	Wegens beperkte toepasbaarheid vaak ook niet in de organisatie van zorgproces	Gezien aanbeveling tegen HBOT ook niet van toepassing.
f) **Economische en politieke context**	*Financiële regelingen, regelgeving, beleid (vergoede zorg, betaaltitel)*	-	Wordt meestal wel vergoed.

5. Welke personen/partijen zijn van belang bij het toepassen van de aanbeveling in de praktijk?	**x** Patiënt/ cliënt (naaste) **x** Professional
6. Wat zouden deze personen/ partijen moeten veranderen in hun gedrag of organisatie om de aanbeveling toe te passen?	Niets.
7. Binnen welk tijdsbestek moet de aanbeveling zijn geïmplementeerd?	□ < 1 jaar
8. Conclusie: is er extra aandacht nodig voor implementatie van de aanbeveling (anders dan publicatie van deze richtlijnmodule)?	□ **Nee**

**Deze aanbeveling komt in aanmerking voor plaatsing op de Implementatie Agenda van het programma Zorg Evaluatie & Gepast Gebruik (ZE&GG). In het programma ZE&GG werken patiënten, zorgverleners, zorgaanbieders, zorgverzekeraars en overheid samen aan de bewezen beste zorg voor de patiënt. Daarmee is ZE&GG een programma van alle betrokken partijen in de Medisch Specialistische Zorg. FMS is één van deze betrokken partijen.*

De implementatieagenda van ZE&GG bevat onderwerpen over wat de bewezen beste zorg is en die in de dagelijkse zorgpraktijk geïmplementeerd zouden moeten worden. Zorgverzekeraars Nederland (ZN) en de Nederlandse Vereniging voor Ziekenhuizen (NVZ) hebben landelijke afspraken gemaakt over de implementatie van de onderwerpen van de implementatieagenda. Deze afspraken zijn onderdeel van de zorginkoopafspraken tussen zorgverzekeraars en zorgaanbieders.

Vanuit FMS worden sterke, goed onderbouwde aanbevelingen, getoetst op de behoefte aan een implementatie impuls aangedragen. Voor de beoordeling van onderwerpen uit richtlijnen wordt gekeken naar bovenstaande tabel voor een inschatting van de implementatie impuls. Met de ingevulde implementatietabel kunnen we vanuit FMS de andere HLA-MSZ partijen goed informeren om zo samen te beslissen of de aanbeveling daadwerkelijk op de implementatie agenda zal worden geplaatst.

Literatuur

Amaro C, Espiney R, Radu L, Guerreiro F. Malignant (necrotizing) externa otitis: the experience of a single hyperbaric centre. Eur Arch Otorhinolaryngol. 2019 Jul;276(7):1881-1887. doi: 10.1007/s00405-019-05396-7. Epub 2019 Jun 4.

Betts J, Desaix P, Johnson E, Johnson J, Oksana K, Kruse D, Poe B, Wise J, Womble M, Young K. 2023. Anatomy & Physiology. Houston: OpenStax CNX. 22.4 Gas exchange. ISBN 978-1-947172-04-3.

Byun YJ, Patel J, Nguyen SA, Lambert PR. Necrotizing Otitis Externa: A Systematic Review and Analysis of Changing Trends. Otol Neurotol. 2020 Sep;41(8):1004-1011. doi: 10.1097/MAO.0000000000002723. PMID: 32569149.

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Mardassi A, Turki S, Lahiani R, Mbarek H, Benzarti S, Gharsallah H. Is there a real benefit of hyperbaric oxygenotherapy in the treatment of necrotizing otitis externa? Tunis Med. 2016 Dec;94(12):863. PMID: 28994886.

Mathieu D, Marroni A, Kot J. Tenth European Consensus Conference on Hyperbaric Medicine: recommendations for accepted and non-accepted clinical indications and practice of hyperbaric oxygen treatment. Diving Hyperb Med. 2017 Mar;47(1):24-32. doi: 10.28920/dhm47.1.24-32.

Moon RE. Hyperbaric oxygen therapy indications.14th edition. North Palm Beach: Best Publishing Company; 2019.

Philips J, Jones S. Hyperbaric oxygen as an adjuvant treatment for malignant otitis externa (Review). Cochrane Database Syst Rev 2005 Apr 8:(2):CD004617.
doi: 10.1002/14651858.CD004617.pub2.

Sethuraman KN, Smolin R, Henry S. Is There a Place for Hyperbaric Oxygen Therapy? Adv Surg. 2022 Sep;56(1):169-204. doi: 10.1016/j.yasu.2022.02.011. PMID: 36096567.

Takata J, Hopkins M, Alexander V, Bannister O, Dalton L, Harrison L, Groves E, Kanona H, Jones GL, Mohammed H, Andersson MI, Hodgson SH. Systematic review of the diagnosis and management of necrotising otitis externa: Highlighting the need for high-quality research. Clin Otolaryngol. 2023 May;48(3):381-394. doi: 10.1111/coa.14041. Epub 2023 Feb 22. PMID: 36759416.

Gomes P, Cabral D, Costa J, Fernandes T, Camacho O, Penêda J, Duarte D, Viana M. Eur Arch Otorhinolaryngol. 2024 Oct;281(10):5153-5157. doi: 10.1007/s00405-024-08734-6. Epub 2024 May 20.

Appendix

Risk of Bias tables

Risk of bias table for interventions studies (cohort studies based on risk of bias tool by the CLARITY Group at McMaster University)

Author, year	**Selection of participants** **Was selection of exposed and non-exposed cohorts drawn from the same population?**	**Exposure** **Can we be confident in the assessment of exposure?**	**Outcome of interest** **Can we be confident that the outcome of interest was not present at start of study?**	**Confounding-assessment** **Can we be confident in the assessment of confounding factors?**	**Confounding-analysis** **Did the study match exposed and unexposed for all variables that are associated with the outcome of interest or did the statistical analysis adjust for these confounding variables**	**Assessment of outcome** **Can we be confident in the assessment of outcome?**	**Follow up** **Was the follow up of cohorts adequate? In particular, was outcome data complete or imputed?**	**Co-interventions** **Were co-interventions similar between groups?**	**Overall Risk of bias**
Mardassi, 2016	Definitely yes Reason: Participants were selected from a registry	Probably yes	Probably yes	**Definitely no** Reason: counfounding factor were not stated	**Definitely no** Reason: not stated and not taken into account in the multivariate analysis.	Probably yes	**Definitely no** Reason: follow up was not stated	Definitely yes Reason: Additional used medication was balanced between groups	**High : Remission And recurrence**

Table of excluded studies

Reference	Reason for exclusion
Phillips JS, Jones SE. Hyperbaric oxygen as an adjuvant treatment for malignant otitis externa. Cochrane Database Syst Rev. 2013 May 31;2013(5):CD004617. doi: 10.1002/14651858.CD004617.pub3. PMID: 23728650; PMCID: PMC7389256.	Systematic review with no RCT's found, therefore no data
Sandner A, Henze D, Neumann K, Kösling S. Nutzen der HBO bei der Therapie der fortgeschrittenen Schädelbasisosteomyelitis [Value of hyperbaric oxygen in the treatment of advanced skull base osteomyelitis]. Laryngorhinootologie. 2009 Oct;88(10):641-6. German. doi: 10.1055/s-0029-1214394. Epub 2009 Apr 3. PMID: 19347797.	Paper not in English
Amaro CE, Espiney R, Radu L, Guerreiro F. Malignant (necrotizing) externa otitis: the experience of a single hyperbaric centre. Eur Arch Otorhinolaryngol. 2019 Jul;276(7):1881-1887. doi: 10.1007/s00405-019-05396-7. Epub 2019 Jun 4. PMID: 31165255.	Expert opinion
Davis JC, Gates GA, Lerner C, Davis MG Jr, Mader JT, Dinesman A. Adjuvant hyperbaric oxygen in malignant external otitis. Arch Otolaryngol Head Neck Surg. 1992 Jan;118(1):89-93. doi: 10.1001/archotol.1992.01880010093022. PMID: 1728284.	No comparison made
Al Siyabi A, Al Farsi B, Al-Shidhani A, Al Hinai Z, Al Balushi Y, Al Qartoobi H. Management of Malignant Otitis Externa with Hyperbaric Oxygen Therapy: A Case Series of 20 Patients. Oman Med J. 2023 May 31;38(3):e512. doi: 10.5001/omj.2023.19. PMID: 37325261; PMCID: PMC10264722.	No comparison made
Khan MA, Quadri SAQ, Kazmi AS, Kwatra V, Ramachandran A, Gustin A, Farooqui M, Suriya SS, Zafar A. A Comprehensive Review of Skull Base Osteomyelitis: Diagnostic and Therapeutic Challenges among Various Presentations. Asian J Neurosurg. 2018 Oct-Dec;13(4):959-970. doi: 10.4103/ajns.AJNS_90_17. PMID: 30459850; PMCID: PMC6208218.	No comparison made
Narozny W, Kuczkowski J, Stankiewicz C, Kot J, Mikaszewski B, Przewozny T. Value of hyperbaric oxygen in bacterial and fungal malignant external otitis treatment. Eur Arch Otorhinolaryngol. 2006 Jul;263(7):680-4. doi: 10.1007/s00405-006-0033-y. Epub 2006 Apr 22. PMID: 16633825.	Case report
Fischer HG, Gey A, Fischer M, Plontke SK. Hyperbare Sauerstofftherapie : Ausgewählte Indikationen im Fachgebiet HNO-Heilkunde [Hyperbaric oxygen therapy : Selected indications in the discipline of otorhinolaryngology]. HNO. 2022 Nov;70(11):848-	Paper not in english

860. German. doi: 10.1007/s00106-022-01227-0. Epub 2022 Sep 29. PMID: 36173420.	

Literature search strategy

Zoekverantwoording

Algemene informatie

Richtlijn: NVKNO Osteomyelitis Schedelbasis – Maligne Otitis Externa	
Uitgangsvraag: Wat zijn de voor- en nadelen van hyperbare zuurstoftherapie t.o.v. standaard behandeling bij maligne otitis externa?	
Database(s): Ovid/Medline, Embase	Datum: 11-7-2023
Periode: nvt	Talen: nvt
Literatuurspecialist: Ingeborg van Dusseldorp	
BMI zoekblokken: voor verschillende opdrachten wordt (deels) gebruik gemaakt van de zoekblokken van BMI-Online https://blocks.bmi-online.nl/ Bij gebruikmaking van een volledig zoekblok zal naar de betreffende link op de website worden verwezen.	
Toelichting: Voor deze vraag is gezocht met de volgende concepten: Maligne otitis externa EN hyperbare zuurstoftherapie Omdat weinig literatuur wordt gevonden worden alle referenties aangeboden in Rayyan. Het sleutelartikel wordt gevonden	
Te gebruiken voor richtlijnen tekst: In de databases Embase en Ovid/Medline is op met relevante zoektermen gezocht naar studies over hyperbare zuurstoftherapie bij maligne otitis externa. De literatuurzoekactie leverde 143 unieke treffers op.	

Zoekopbrengst

	EMBASE	**OVID/MEDLINE**	**Ontdubbeld**
SRs	11	6	11
Clinical trials RCTs	7	3	7
Observationele studies	30	22	36
Overig	84	38	89
Totaal			143

Zoekstrategie

Embase

No.	Query	Results
#14	#10 OR #11 OR #12 OR #13	132
#13	#3 NOT #10 NOT #11 NOT #12 Overige	84
#12	#3 AND (#8 OR #9) NOT #10 NOT #11 Overige OBS	30
#11	#3 AND #7 NOT #10 Clinical trials, RCts	7
#10	#3 AND #6 SR	11
#9	'case control study'/de OR 'comparative study'/exp OR 'control group'/de OR 'controlled study'/de OR 'controlled clinical trial'/de OR 'crossover procedure'/de OR 'double blind procedure'/de OR 'phase 2 clinical trial'/de OR 'phase 3 clinical trial'/de OR 'phase 4 clinical trial'/de OR 'pretest posttest design'/de OR 'pretest posttest control group design'/de OR 'quasi	14236747

	experimental study'/de OR 'single blind procedure'/de OR 'triple blind procedure'/de OR (((control OR controlled) NEAR/6 trial):ti,ab,kw) OR (((control OR controlled) NEAR/6 (study OR studies)):ti,ab,kw) OR (((control OR controlled) NEAR/1 active):ti,ab,kw) OR 'open label*':ti,ab,kw OR (((double OR two OR three OR multi OR trial) NEAR/1 (arm OR arms)):ti,ab,kw) OR ((allocat* NEAR/10 (arm OR arms)):ti,ab,kw) OR placebo*:ti,ab,kw OR 'sham-control*':ti,ab,kw OR (((single OR double OR triple OR assessor) NEAR/1 (blind* OR masked)):ti,ab,kw) OR nonrandom*:ti,ab,kw OR 'non-random*':ti,ab,kw OR 'quasi-experiment*':ti,ab,kw OR crossover:ti,ab,kw OR 'cross over':ti,ab,kw OR 'parallel group*':ti,ab,kw OR 'factorial trial':ti,ab,kw OR ((phase NEAR/5 (study OR trial)):ti,ab,kw) OR ((case* NEAR/6 (matched OR control*)):ti,ab,kw) OR ((match* NEAR/6 (pair OR pairs OR cohort* OR control* OR group* OR healthy OR age OR sex OR gender OR patient* OR subject* OR participant*)):ti,ab,kw) OR ((propensity NEAR/6 (scor* OR match*)):ti,ab,kw) OR versus:ti OR vs:ti OR compar*:ti OR ((compar* NEAR/1 study):ti,ab,kw) OR (('major clinical study'/de OR 'clinical study'/de OR 'cohort analysis'/de OR 'observational study'/de OR 'cross-sectional study'/de OR 'multicenter study'/de OR 'correlational study'/de OR 'follow up'/de OR cohort*:ti,ab,kw OR 'follow up':ti,ab,kw OR followup:ti,ab,kw OR longitudinal*:ti,ab,kw OR prospective*:ti,ab,kw OR retrospective*:ti,ab,kw OR observational*:ti,ab,kw OR 'cross sectional*':ti,ab,kw OR cross?ectional*:ti,ab,kw OR multicent*:ti,ab,kw OR 'multi-cent*':ti,ab,kw OR consecutive*:ti,ab,kw) AND (group:ti,ab,kw OR groups:ti,ab,kw OR subgroup*:ti,ab,kw OR versus:ti,ab,kw OR vs:ti,ab,kw OR compar*:ti,ab,kw OR 'odds ratio*':ab OR 'relative odds':ab OR 'risk ratio*':ab OR 'relative risk*':ab OR 'rate ratio':ab OR aor:ab OR arr:ab OR rrr:ab OR ((('or' OR 'rr') NEAR/6 ci):ab)))	
#8	'major clinical study'/de OR 'clinical study'/de OR 'case control study'/de OR 'family study'/de OR 'longitudinal study'/de OR 'retrospective study'/de OR 'prospective study'/de OR 'comparative study'/de OR 'cohort analysis'/de OR ((cohort NEAR/1 (study OR studies)):ab,ti) OR (('case control' NEAR/1 (study OR studies)):ab,ti) OR (('follow up' NEAR/1 (study OR studies)):ab,ti) OR (observational NEAR/1 (study OR studies)) OR ((epidemiologic NEAR/1 (study OR studies)):ab,ti) OR (('cross sectional' NEAR/1 (study OR studies)):ab,ti)	6767914
#7	'clinical trial'/exp OR 'randomization'/exp OR 'single blind procedure'/exp OR 'double blind procedure'/exp OR 'crossover procedure'/exp OR 'placebo'/exp OR 'prospective study'/exp OR rct:ab,ti OR random*:ab,ti OR 'single blind':ab,ti OR 'randomised controlled trial':ab,ti OR 'randomized controlled trial'/exp OR placebo*:ab,ti	3302394
#6	'meta analysis'/exp OR 'meta analysis (topic)'/exp OR metaanaly*:ti,ab OR 'meta analy*':ti,ab OR metanaly*:ti,ab OR 'systematic review'/de OR 'cochrane database of systematic reviews'/jt OR prisma:ti,ab OR prospero:ti,ab OR (((systemati* OR scoping OR umbrella OR 'structured literature') NEAR/3 (review* OR overview*)):ti,ab) OR ((systemic* NEAR/1 review*):ti,ab) OR (((systemati* OR literature OR database* OR 'data base*') NEAR/10 search*):ti,ab) OR (((structured OR comprehensive* OR systemic*) NEAR/3 search*):ti,ab) OR (((literature NEAR/3 review*):ti,ab) AND (search*:ti,ab OR database*:ti,ab OR 'data base*':ti,ab)) OR (('data extraction':ti,ab OR 'data source*':ti,ab) AND 'study selection':ti,ab) OR ('search strategy':ti,ab AND 'selection criteria':ti,ab) OR ('data source*':ti,ab AND 'data synthesis':ti,ab) OR medline:ab OR pubmed:ab OR embase:ab OR cochrane:ab OR (((critical OR rapid) NEAR/2 (review* OR overview* OR synthes*)):ti) OR ((((critical* OR rapid*) NEAR/3 (review* OR overview* OR synthes*)):ab) AND (search*:ab OR database*:ab OR 'data base*':ab)) OR metasynthes*:ti,ab OR 'meta synthes*':ti,ab	733409
#5	#3 AND #4 sleutelartikel gevonden	1

#4	'hyperbaric oxygen therapy in malignant otitis externa: a systematic review of the literature'	1
#3	#1 AND #2	124
#2	'hyperbaric oxygen therapy'/exp OR ((hyperbaric NEAR/3 (medicine OR therap* OR treatment OR o2 OR oxygen*)):ti,ab,kw) OR hbot:ti,ab,kw OR ((pressur* NEAR/3 'oxygen therap*'):ti,ab,kw) OR 'hbo therap*':ti,ab,kw OR (((hyperoxygenat* OR 'high oxygen') NEAR/3 (therap* OR treatment)):ti,ab,kw)	23088
#1	'malignant otitis externa'/exp OR (((maligna* OR necroti* OR necros*) NEAR/3 ('otitis externa' OR 'external otitis')):ti,ab,kw) OR ('otitis externa'/mj AND (maligna*:ti,kw OR necroti*:ti,kw OR necrosis:ti,kw)) OR (('osteomyelitis'/exp/mj OR 'osteomyelitis':ti,kw) AND ('skull'/exp/mj OR 'skull disease'/exp/mj OR skull*:ti,ab,kw OR cranial:ti,ab,kw OR cranium:ti,ab,kw))	3354

Ovid/Medline

#	Searches	Results
12	8 or 9 or 10 or 11	69
11	3 not 8 not 9 not 10 Overige	38
10	(3 and (6 or 7)) not 8 not 9 Overige OBS	22
9	(3 and 5) not 8 Clinical trials, RCTs	3
8	3 and 4 SR	6
7	Case-control Studies/ or clinical trial, phase ii/ or clinical trial, phase iii/ or clinical trial, phase iv/ or comparative study/ or control groups/ or controlled before-after studies/ or controlled clinical trial/ or double-blind method/ or historically controlled study/ or matched-pair analysis/ or single-blind method/ or (((control or controlled) adj6 (study or studies or trial)) or (compar* adj (study or studies)) or ((control or controlled) adj1 active) or "open label*" or ((double or two or three or multi or trial) adj (arm or arms)) or (allocat* adj10 (arm or arms)) or placebo* or "sham-control*" or ((single or double or triple or assessor) adj1 (blind* or masked)) or nonrandom* or "non-random*" or "quasi-experiment*" or "parallel group*" or "factorial trial" or "pretest posttest" or (phase adj5 (study or trial)) or (case* adj6 (matched or control*)) or (match* adj6 (pair or pairs or cohort* or control* or group* or healthy or age or sex or gender or patient* or subject* or participant*)) or (propensity adj6 (scor* or match*))).ti,ab,kf. or (confounding adj6 adjust*).ti,ab. or (versus or vs or compar*).ti. or ((exp cohort studies/ or epidemiologic studies/ or multicenter study/ or observational study/ or seroepidemiologic studies/ or (cohort* or 'follow up' or followup or longitudinal* or prospective* or retrospective* or observational* or multicent* or 'multi-cent*' or consecutive*).ti,ab,kf.) and ((group or groups or subgroup* or versus or vs or compar*).ti,ab,kf. or ('odds ratio*' or 'relative odds' or 'risk ratio*' or 'relative risk*' or aor or arr or rrr).ab. or (("OR" or "RR") adj6 CI).ab.))	5464865
6	Epidemiologic studies/ or case control studies/ or exp cohort studies/ or Controlled Before-After Studies/ or Case control.tw. or cohort.tw. or Cohort analy$.tw. or	4482444

	(Follow up adj (study or studies)).tw. or (observational adj (study or studies)).tw. or Longitudinal.tw. or Retrospective*.tw. or prospective*.tw. or consecutive*.tw. or Cross sectional.tw. or Cross-sectional studies/ or historically controlled study/ or interrupted time series analysis/ [Onder exp cohort studies vallen ook longitudinale, prospectieve en retrospectieve studies]	
5	exp clinical trial/ or randomized controlled trial/ or exp clinical trials as topic/ or randomized controlled trials as topic/ or Random Allocation/ or Double-Blind Method/ or Single-Blind Method/ or (clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or controlled clinical trial or randomized controlled trial or multicenter study or clinical trial).pt. or random*.ti,ab. or (clinic* adj trial*).tw. or ((singl* or doubl* or treb* or tripl*) adj (blind$3 or mask$3)).tw. or Placebos/ or placebo*.tw.	2609251
4	meta-analysis/ or meta-analysis as topic/ or (metaanaly* or meta-analy* or metanaly*).ti,ab,kf. or systematic review/ or cochrane.jw. or (prisma or prospero).ti,ab,kf. or ((systemati* or scoping or umbrella or "structured literature") adj3 (review* or overview*)).ti,ab,kf. or (systemic* adj1 review*).ti,ab,kf. or ((systemati* or literature or database* or data-base*) adj10 search*).ti,ab,kf. or ((structured or comprehensive* or systemic*) adj3 search*).ti,ab,kf. or ((literature adj3 review*) and (search* or database* or data-base*)).ti,ab,kf. or (("data extraction" or "data source*") and "study selection").ti,ab,kf. or ("search strategy" and "selection criteria").ti,ab,kf. or ("data source*" and "data synthesis").ti,ab,kf. or (medline or pubmed or embase or cochrane).ab. or ((critical or rapid) adj2 (review* or overview* or synthes*)).ti. or (((critical* or rapid*) adj3 (review* or overview* or synthes*)) and (search* or database* or data-base*)).ab. or (metasynthes* or meta-synthes*).ti,ab,kf.	679922
3	1 and 2	69
2	Hyperbaric Oxygenation/ or (hyperbaric adj3 (medicine or therap* or treatment or o2 or oxygen*)).ti,ab,kf. or hbot.ti,ab,kf. or (pressur* adj3 oxygen therap*).ti,ab,kf. or hbo therap*.ti,ab,kf. or ((hyperoxygenat* or high oxygen) adj3 (therap* or treatment)).ti,ab,kf.	15954
1	((maligna* or necroti* or necrosis) adj3 ('otitis externa' or 'external otitis')).ti,kf. or (exp *Otitis Externa/ and (maligna* or necroti* or necrosis).ti,ab,kf.) or ((exp *Osteomyelitis/ or 'osteomyelitis'.ti,kf.) and (exp Skull/ or skull*.ti,ab,kf. or cranial.ti,ab,kf. or cranium.ti,ab,kf.))	2707

Module 7 – Duration of treatment

Question
What is the optimal duration of treatment for patients with necrotizing otitis externa?

Introduction
The duration of treatment for necrotizing otitis externa varies significantly depending on the region or clinic. For osteomyelitis in long bones or the spine, the standard treatment duration is typically 6 weeks for acute cases and up to 12 weeks or longer for chronic or complicated cases, such as those involving prosthetic joints or hardware (Zimmerli, 2010). While the treatment duration for osteomyelitis in other body parts is broadly similar, the treatment of NOE appears more heterogenous in literature, most probably due to the fact that there is more uncertainty regarding the minimal treatment duration and whether there is a need to individualize the treatment per patient. High-quality research on this topic remains limited.Both conditions can benefit from a combination of clinical, laboratory, and imaging assessments to guide therapy, as long as necessary, but preferrably not longer than necessary.

Search and select
What is the added value of a standard treatment duration compared to basing the treatment duration on clinical parameters?

Table 1. PICO

Patients	Patients with confirmed necrotizing otitis externa
Intervention	Antibiotic treatment for 6 weeks
Control	Standard of care; treatment duration based on clinical parameters
Outcomes	Disease remission, survival, treatment duration, adverse events
Other selection criteria	Study design: systematic reviews and randomized controlled trials, cohort studies [Minimum follow-up: 3 months]

<u>Relevant outcome measures</u>
The guideline panel considered remmision of disease and survival as a **critical** outcome measure for decision making; and length of treatment and adverse events as an **important** outcome measure for decision making.

The guideline panel defined the outcome measures as follows:
- (Disease specific) survival: time to death, caused by the effects of necrotizing otitis externa
- Remission: rate of curation of disease. Defined after prolonged disappearance of the signs and symptoms of a disease.
- Adverse events: an unexpected or harmful medical occurrence after exposure to treatment

The guideline panel defined the following as a minimal clinically (patient) important difference.
- (Disease specific) survival: absolute difference > 5%
- Remission: GRADE standard limits*

Length of treatment: GRADE standard limits*. In case of similar outcome measures for different treatment duration, the guideline panel opts for shorter treatment duration, taking into account side effects, costs, and healthcare burden.

- Adverse events: GRADE standard limits*

* Default thresholds proposed by the international GRADE working group were used: a 25% difference in relative risk (RR) for dichotomous outcomes (RR <0.80 or RR >1.25), or 0.5 standard deviations (SD) for continuous outcomes

Search and select (Methods)

The databases [Medline (via OVID) and Embase (via Embase.com)] were searched using relevant search terms up to July 17, 2023. The detailed search strategy is provided under the tab 'Literature Search Strategy'. The systematic literature search yielded 124 results. Studies were selected based on the following criteria: systematic reviews, randomized controlled trials (RCTs), observational studies, and other non-comparative research on the duration of treatment for necrotizing otitis externa. Eighteen studies were initially selected through title and abstract screening. After full-text review, seventeen studies were excluded (see the exclusion table under the tab 'Evidence Tables'), and one study was included.

Summary of literature

Description of studies

One study was included in the literature analysis. Key study characteristics and results are summarized in Table 2**.** The risk of bias assessment is summarized in the risk of bias tables (under the tab 'Evidence Tables').

Table 2. Characteristics of included studies

Study	Participants (number, age, other important characteristics)	Comparison	Follow-up	Outcome measures	Comments	Risk of bias (per outcome measure)*
Individual study						
Pulcini, 2012	N at baseline Intervention: 19 Control: 13 Age Intervention: 72±13 Control: 76±8 Sex Intervention: 13 males, 5 females Control: 10 males, 3 females	Intervention: Patients received a standard regimen of 3 weeks i.v. ceftazidim + oral ciprofloxacin, followed by 3 weeks of oral ciprofloxacin. Control: Patients received a combination of i.v. ceftazidim followed by oral ciprofloxacin. Duration of both was not set and treatment duration was based on clinical findings (not specified).	14 months (6–21)	Remission: 100% remission in both groups. Length of treatment: 5.8±0.7 weeks in the intervention group. 9.4±3.2 weeks in the control group	Remission is reported in the article as "favourable outcome". What constitutes a favourable outcome is not further discribed in the article.	Remission: high Length of treatment: low

*For further details, see risk of bias table in the appendix.

Results

Survival (critical)

No studies reported survival as an outcome measure.

Remission (critical)

One study reported remission of disease (Pulcini, 2012). However, the authors only describe the outcome as a "favourable outcome", the definition of which is not further explained. Therefore, the following interpretation is based on the assumption that "favourable outcome" is interchangeable with remission of disease. In the intervention group, 19 out of 19 patients achieved a favourable outcome. This is the same rate as in the control group, where 13 out of 13 patients achieved a favourable outcome.

Length of treatment (important)

One study reported on the length of treatment (Pulcini, 2012). With a set number of 6 weeks in the intervention group, the length of treatment was shortened in comparison to the control group. (5.8±0.7 weeks versus 9.4±3.2 weeks; mean difference is 3.60 (95% CI: 2.05 to 5.14).

Adverse events (important)

No studies reported adverse events as an outcome measure.

Summary of Findings

Outcome	**Study results and measurements**	**Absolute effect estimates** 6 weeks treatment	Treament based on clinical parameters	**Certainty of the evidence** (Quality of evidence)	**Summary**
Survival	-	-		-	No evidence was found regarding the effect of a standard 6-weeks treatment on improving survival in patients with necrotizing otitis externa. *(Pucini, 2012)*
Remission	As no events occured it was not possible to provide any indication of either the direction or magnitude of the relative treatment effect, based on 30 participants from one study. In both study arms, no events occured, based on 30 participants from 1 study	-		**Very low** By very serious imprecision[1]	The evidence is unclear regarding the effect of a standard 6-weeks treatment to improving disease remission in patients with necrotizing otitis externa. (*Pulcini, 2012)*

Length of treatment (weeks)	The mean difference (MD) is 3.60 (95% CI: 2.05 to 5.14), based on data from 30 participants in one study.		**Very low** By very serious imprecision[2]	The evidence is very uncertain about the effect of standard 6 weeks treatment to reduce the length of treatment disease control in patients with necrotizing otitis externa *(Pulcini, 2012*)
Adverse events	-		-	No evidence was found regarding the effect of a standard 6-week treatment on reducing adverse events in patients with skull base osteomyelitis. *(Pulcini, 2012)*

1. **Imprecision: very serious.** Low population (<100)
2. **Imprecision: very serious.** Low population (<100)

Considerations – from evidence to recommendation

Balance between desired and undesired effects

The systematic literature review reveals a lack of high-quality comparative studies assessing the optimal treatment duration for necrotizing otitis externa. Only one study (Pulcini, 2012) directly compared different treatment durations: a fixed duration of 6 weeks versus a variable duration (minimum 6 weeks, maximum 12 weeks), based on clinicians' assessment of clinical parameters. However, since both treatment modalities in this study showed a favorable outcome of 100% in both groups, combined with a small sample size (N=19 for the 6-week group, N=13 for the variable-duration group), no clear indication of the optimal treatment regimen can be determined. Notably, the standardized treatment regimen resulted in a shorter treatment duration, with a mean difference (MD) of 3.60 weeks (95% CI: 2.05 to 5.14), which is clinically significant.

Looking at non-comparative studies in the literature, there is a significant variation in the reported treatment durations, combined with varying remission rates of the disease. To illustrate this variability, the results of non-comparative studies from the original systematic literature search are presented in Figure 1. These data are compiled from studies involving 30 or more patients. The cure rate was defined as complete remission of the disease without relapse.

Study, year of publication	N	Length of treatment (mean in weeks) / disease type	Curation rate	Imaging during follw-up?
Dhariwal, 2003	37	6 (fixed) / all definite NOE	73%	-
Hodgson, 2022	84	6 (fixed) / 50/84 definite NOE, 34/84 probable NOE)	94%	-
Jung, 2021	32	16 (variable) / all definite NOE	84%	+
Jacobsen, 2010	51	15 (variable) / all definite NOE	72%	+
Stern Shavit, 2016	88	≥6 (variable, no mean given) / all definite NOE	86%	+/-
Lee, 2008	36	30 (variable) / all definite NOE	74%	+
Franco-Vidal, 2007	46	9.5 (variable) / all definite NOE	96%	+
Soudry, 2007	48	≥6 (variable, no mean given) / all definite NOE	73%	+

These results demonstrate a significant variation in the mean weeks of treatment provided and the corresponding cure rates. This variation can possibly be attributed to substantial differences between cases, including the extent of the disease, causative agents, patient comorbidities, and differences in the definition of necrotizing otitis externa across studies. The guideline committee believes that all these factors play a role in treatment planning. Also, based on the available literature, it is impossible to exclude local practice variation.

In the available literature, and based on the experiences of the working group, the chosen treatment duration seems to roughly fall into two categories: 1) the treatment duration is predetermined and/or adjusted based on clinical findings or 2) the treatment duration is adjusted based on imaging findings during the course of treatment.

The latter, the role of imaging in assessing the effectiveness of therapy, may have had a positive effect on the outcome of NOE (Byun, 2020). Contrast enhanced and functional imaging make it possible to easily determine whether there is a reduction in the severity of the infection. In the Netherlands, this has led to imaging playing an increasingly important role in the decision-making process regarding when to stop treatment. A significant drawback, however, appears to be that clinical recovery does not always align with the normalization of imaging findings: abnormalities in contrast or isotope uptake may occur long after adequate treatment of the infection (Al-Noury 2011, Chhabria 2023, van der Meer 2023). In our view, this seems to be an important factor that could lead to overtreatment (in terms of duration) of patients. Therefore, it is relevant to consider the assessment of symptoms as the cornerstone of the judgment to discontinue treatment. Imaging can guide this judgement.. Additionally, strict follow-up after stopping treatment, with the option to restart in case of deterioration, is another way to prevent overtreatment.

Influence of severity or extent?
The disease severity is reasonably embedded within the definitions, which the working group advises to use (Module 1): definite versus complex NOE, proposed by the UK consensus paper. Several staging protocols have been proposed earlier in the literature, all aimed at guiding the determination of the appropriate treatment (duration). Some studies that use disease extent are mentioned below.

Before the UK consensus paper, the staging system from the textbook *Scott-Brown's Otorhinolaryngology, Head and Neck Surgery* was mostly proposed, which has been modified by Lambor (2013):

- Stage I corresponds to possible NOE (only soft tissue abnormalities and "beyond," without bone erosion of the ear canal on CT).
- Stage II: the above with bone erosion.
- Stage IIIa: the above, including facial nerve involvement.
- Stage IIIb: multiple cranial nerves are involved.
- Stage IV: the above, including intracranial complications.

The staging system by Gleeson is similar but incorporates the use of a bone scan. In the article by Cho, the modified Gleeson staging system is used. The conclusion of the article states that the Gleeson staging system was valuable in assessing the extent of the disease, and all early-stage Gleeson patients had good outcomes. However, patients with higher severity staging on the Gleeson system did not necessarily require prolonged treatment (Cho, 2021).

This may reflect the observation that an advanced infection does not necessarily equate to a difficult-to-treat infection. There is also the possibility that, due to absent or inadequate previous therapy, the infection involves a large volume of tissue but still responds quickly and similarly to an infection in a smaller area.

Another proposed staging system involves stratifying the condition into severe and non-severe. This classification is based on a combination of several clinical and radiological parameters. In the article, it is retrospectively concluded that the treatment duration is, on average, longer in the group with severe NOE (Stevens, 2015). Another article reports similar findings. Here, a distinction is made between a single or a complex spreading pattern based on radiological findings, with patients exhibiting a complex spreading pattern being treated significantly longer (Van der Meer, 2022). The main limitation of these studies is, again, that no fixed endpoints for treatment have been established, making overtreatment difficult to control.

Based on the current literature, it is not possible to identify the difficult-to-treat group, since both good and poor responders are found within the unfavorable groups. On the other hand, extensive bacterial infections other than NOE generally respond well to a 6-week regimen, even including bone or central nervous infections. However, infections with presence of large abscesses or empyema where drainage (which is preferable if feasible) is anatomically not possible may sometimes need longer treatment, often guided by imaging (i.e., in the case of brain abcesses). In the absence of evidence in NOE, similar importance of the presence of undrained abcesses or empyema in determining treatment duration may be assumed.

Based on the available literature, it seems appropriate to treat patients with necrotizing otitis externa (NOE) for 6 weeks. This applies to both the *definite* and *complex* NOE groups according to the UK consensus definition. Evaluate the treatment effect at least based on clinical findings. Imaging appears warranted for therapy evaluation and as an adjunct to clinical assessment, particularly in the *complex* NOE group.

In our view, patients diagnosed with *probable* NOE fall outside the scope of this guideline. In the Dutch context, these patients are classified under the diagnosis of otitis externa, for which short-term antibiotic treatment (≤2 weeks) may be sufficient. Follow-up imaging is not necessary in this patient group (provided they are symptom-free).

Therapy response: symptoms, laboratory results, imaging results
A condition of the aforementioned treatment duration, as guided by the definition, is that the treatment should only be discontinued if the symptoms of otorrhea and otalgia have resolved. If infection parameters were elevated initially, these should also have normalized.

If the function of an affected cranial nerve recovers during the course of treatment, this is a very strong indication of successful therapy. Conversely, if the function has not been restored by the end of the intended treatment (according to the definition), this does not indicate anything about therapy response. Sensorineural hearing loss is by definition irreversible.

The role of imaging has already been mentioned above. In severe infections or infections with an unclear clinical course, imaging can be highly valuable. However, clinical presentation should always guide decision-making. Additionally, the treatment team should be aware that a partial response seen on imaging may lead to overtreatment. This is discussed in module Imaging to monitor treatment response (hyperlink).

Invasive fungal infection
A superficial otomycosis is not uncommon, which merely involves colonization of the ear canal and is treated accordingly. An invasive fungal infection generally occurs only in immunocompromised patients and is a rare life-threatening condition. For a comprehensive rationale regarding the treatment of invasive fungal infections, we refer to the specific guideline (SWAB, 2017), chapter 2.2 & 2.3 (type of therapy), 2.5 (duration), and 2.7). It is stated that duration of therapy is at least 6 to 12 weeks and, in neutropenic patients, not less than 2 weeks after resolution of neutropenia.
This corresponds to the guideline of the Infectious Diseases Society of America for treatment of *Aspergillus* infections recommend a minimum of 6 to 8 weeks of therapy. This range is based upon expert opinion and no systematic literature review or prospective study (Walsh, 2008). A large UK review study reports a median treatment of 13 weeks in cranial invasive aspergillosis patients (Gamaletsou, 2014).

The aforementioned guideline does mention a potential role for surgical debridement in cases of *Aspergillus* osteomyelitis. However, this committee also states that there is no standard role for surgery in osteomyelitis / skull base osteomyelitis caused by invasive aspergillosis.

Follow-up
Follow up should be done regularly, at least until the definition cure is met. The definition cure is set at a minimum period of 3 months after completing antibiotic therapy, without (recurrent) pain or otorrhoea (Hodgson, 2022).

Some authors disscuss the course of each patient in a monthly meeting for the first six months (Hutson, 2021). They suggest continuing follow up every eight weeks for the next six months in order to diagnose reccurences. Recurrence rate of NOE could reach 15- 20%. Recurrence is possible to occur up to 1 year after treatment. It is important to tailor follow-up to the patient's individual profile.

Quality of the evidence
The overall quality of evidence is very low. This means that the estimated effect of the critical outcomes that were found are very uncertain. There was a downgrade due to the following:

- Risk of Bias: methodological limitations
- Inconsistency: inconsistency of the results.

- Indirectness: indirectness of the evidence, due to differences in the use of surrogate outcomes.
- Imprecision: inaccuracy, due to a very small number of events in a small sample size.

Values and preferences of patients (and possibly their caregivers)
As previously stated, NOE can be an extensive infection. The duration of treatment varies but typically consists of a minimum of 6 weeks and may extend to several months. This prolonged therapy can lead to unwanted side effects (discussed in Chapter 9).
When administered intravenously for such a long duration, antibiotics significantly restrict patients' daily activities. Hospitalization further exacerbates these limitations. However, these burdens can be reduced through Outpatient Parenteral Antibiotic Therapy (OPAT).
On the other hand, untreated NOE carries a high mortality risk, justifying the extended treatment duration. A careful balance must be struck between undertreatment and minimizing the severity/side effects of therapy, ideally through shared decision-making between physician and patient.
Ultimately, all patients benefit from the shortest possible antibiotic exposure while maintaining a high likelihood of cure. This underscores the importance of appropriate treatment evaluation.

Costs (resources)
Shorter treatment durations reduce costs. However, undertreatment leading to disease recurrence may result in even higher expenses. To the guideline committee's knowledge, no formal cost-effectiveness analysis has been conducted on this subject.

Equity ((health) equity/equitable)
The guideline committee does not foresee any problems regarding equity.

Acceptability
The guideline committee does not foresee any problems regarding acceptability.

Feasibility
The intervention of long antibiotic treatment seems feasible. Feasibilty rises when OPAT is available.

Recommendations
Rationale of the recommendation: weighing arguments for and against the interventions
Based on the available literature, adjusting treatment duration according to disease extent does not appear to provide significant benefit. A standard 6-week course remains aligned with the core principles of osteomyelitis management. Extended therapy should be considered only in cases of inadequate clinical response, guided by imaging findings, disease severity, and the causative pathogen.

Treat patients with necrotizing otitis externa for 6 weeks.

Evaluate treatment response after 6 weeks and consider successful in case of:
- Resolution of symptoms (otalgia, otorrhea, fever)
- Normalisation of ear canal
- Recovery from previous facial nerve palsy (not mandatory)

If performed, in combination with
- Response on FDG-PET/CT or MRI (complete resolution not mandatory)

Consider prolonging treatment in case of:
- No / partial resolution of symptoms
- Presence of abscesses or empyema which cannot be drainaged
- Fungal cause

If performed, in combination with
- No / partial response seen on 18 FDG PET-CT/MRI

Prolong treatment until criteria of successful treatment are met and follow-up should be at least 3 months.

Knowledge gap
During the development of this module, a systematic search was conducted to find studies that could answer the research question. Through the use of a systematic literature review with an assessment of the strength of evidence, it has become clear that there are still knowledge gaps within this module. The working group believes that further research is desirable to provide clearer answers to practical questions in the future.

Question
Can 18-FDG-PET/CT(or MRI) be used to predict cure of disease in patients with necrotizing otitis externa?

Explanation
As there is a wide variation in the extend of disease between patients with necrotizing otitis externa, the duration of treatment subsequently is varied as well. If there was a sensitive diagnostic tool that could predict when there is cure of disease, overtreatment with antibiotics could be reduced. In this regard, 18-FDG-PET/CT(or MRI) seems to be a promising diagnostic. A study could be performed (RCT or prospective) to further examine this possibility.

Verkeerslicht en (de-)implementatietabel

Toelichting
Met het verkeerslicht worden aanbevelingen gecategoriseerd op basis van formulering en bewijskracht. Als eindproduct wordt bij richtlijnmodules met een sterk geformuleerde en voldoende onderbouwde aanbeveling een implementatietabel opgeleverd. Hierin wordt onder andere opgenomen:
- Een beschrijving van het knelpunt om de module uit te werken of herzien;
- De te verwachten belemmerende en bevorderende factoren voor implementatie;
- Welke partijen van belang zijn bij toepassen van de aanbeveling in de praktijk;
- Een inschatting van de implementatietermijn.

Verkeerslichtanalyse

- **ROOD** = sterk geformuleerde aanbeveling om iets niet te doen, met een GRADE high of moderate
- **ORANJE** = zwak geformuleerde aanbeveling; mogelijk kennishiaat
- **GROEN** = sterk geformuleerde aanbeveling om iets wel te doen, met een GRADE high of moderate
- **LICHT ROOD** of **LICHT GROEN** = sterk geformuleerde aanbevelingen met een GRADE low, very low of geen GRADE *(modules waarin geen studies geïncludeerd konden worden in de literatuursamenvatting of waarin geen literatuursamenvatting werd geschreven zoals modules waarin organisatie van zorg wordt beschreven)*

(Sub)aanbeveling	Sterkte van de aanbeveling	Bewijskracht per uitkomstmaat	Verkeerslicht per (sub)aanbeveling
Treat patients with necrotizing otitis externa for 6 weeks Evaluate treatment response after 6 weeks and consider <u>successful</u> in case of: • Resolution of symptoms (otalgia, otorrhea, fever) • Normalisation of ear canal • Recovery from previous facial nerve palsy (not mandatory) *If performed, in combination with* • Response on FDG-PET/CT or MRI (complete resolution not mandatory) Consider <u>prolonging</u> treatment in case of: • No / partial resolution of symptoms • Presence of abscesses or empyema which cannot be drainaged • Fungal cause *If performed, in combination with* • No / partial response seen on 18 FDG PET-CT/MRI Prolong treatment until criteria of successful treatment are met and follow-up should be at least 3 months	□ Zwak (overweeg)	**Overall bewijskracht** □ **VL** **Range bewijskracht van alle uitkomstmaten** □ **VL**	**LICHT GROEN**

Implementatietabel

Tabel A: (De-)Implementatietabel met impuls analyse

Aanbeveling – 1			
1. Wat was het onderliggende probleem om deze uitgangsvraag uit te werken?	□ **Ongewenste praktijkvariatie**		
2. Maak een inschatting over hoeveel patiënten het ongeveer gaat waar de aanbeveling betrekking op heeft?	□ < **1000**		
3. Maakt de aanbeveling deel uit van een set van interventies voor hetzelfde probleem?	□ **Nee**		
4. Belemmeringen en kansen op verschillende niveaus voor landelijke toepassing van de aanbeveling:	***Voorbeelden***	**Wat zijn mogelijke belemmerende factoren?**	**Wat zijn mogelijke bevorderende factoren?**
a) **Richtlijn/ klinisch traject (innovatie)**	*Voortschrijding/vooruitgang in de praktijk, haalbaarheid, geloofwaardigheid, toegankelijkheid, aantrekkelijkheid*	*Vaak onzekerheid over behandeling, derhalve vaak toch overbehandeling.*	*Mogelijkheid tot ziektemonitoring middels PET scans.*
b) **Zorgverleners (artsen en verpleegkundigen)**	*Bewustzijn, kennis, houding, motivatie om te veranderen, gedragsroutines*	*Vaak onzekerheid over behandeling, derhalve vaak toch overbehandeling.*	-
c) **Patiënt/ cliënt (naasten)**	*Kennis, vaardigheden, houding, compliance*	-	-
d) **Sociale context**	*Mening van collega's, cultuur van het netwerk, samenwerking, leiderschap*	-	-

e) **Organisatorische context**	*Organisatie van zorgprocessen, personeel, capaciteiten, middelen, structuren*	*Indien PET-CT moet deze wel beschikbaar zijn*	-
f) **Economische en politieke context**	*Financiële regelingen, regelgeving, beleid (vergoede zorg, betaaltitel)*	-	-

5. Welke personen/partijen zijn van belang bij het toepassen van de aanbeveling in de praktijk?	**x** Patiënt/ cliënt (naaste) **x** Professional
6. Wat zouden deze personen/ partijen moeten veranderen in hun gedrag of organisatie om de aanbeveling toe te passen?	
7. Binnen welk tijdsbestek moet de aanbeveling zijn geïmplementeerd?	□ < 1 jaar
8. Conclusie: is er extra aandacht nodig voor implementatie van de aanbeveling (anders dan publicatie van deze richtlijnmodule)?	□ **Nee**

**Deze aanbeveling komt in aanmerking voor plaatsing op de Implementatie Agenda van het programma Zorg Evaluatie & Gepast Gebruik (ZE&GG). In het programma ZE&GG werken patiënten, zorgverleners, zorgaanbieders, zorgverzekeraars en overheid samen aan de bewezen beste zorg voor de patiënt. Daarmee is ZE&GG een programma van alle betrokken partijen in de Medisch Specialistische Zorg. FMS is één van deze betrokken partijen.*

De implementatieagenda van ZE&GG bevat onderwerpen over wat de bewezen beste zorg is en die in de dagelijkse zorgpraktijk geïmplementeerd zouden moeten worden. Zorgverzekeraars Nederland (ZN) en de Nederlandse Vereniging voor Ziekenhuizen (NVZ) hebben landelijke afspraken gemaakt over de implementatie van de onderwerpen van de implementatieagenda. Deze afspraken zijn onderdeel van de zorginkoopafspraken tussen zorgverzekeraars en zorgaanbieders.

Vanuit FMS worden sterke, goed onderbouwde aanbevelingen, getoetst op de behoefte aan een implementatie impuls aangedragen. Voor de beoordeling van onderwerpen uit richtlijnen wordt gekeken naar bovenstaande tabel voor een inschatting van de implementatie impuls. Met de ingevulde implementatietabel kunnen we vanuit FMS de andere HLA-MSZ partijen goed informeren om zo samen te beslissen of de aanbeveling daadwerkelijk op de implementatie agenda zal worden geplaatst.

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Dhariwal A, Manjaly JG, Patel B, Morris-Jones S, David K, Khetarpal P, Beale T, Mehta N, Logan S. Management and Clinical Outcomes of 37 Patients with Necrotizing Otitis Externa: Retrospective Review of a Standardized 6-Week Treatment Pathway. J Int Adv Otol. 2023 Jun;19(3):223-227. doi: 10.5152/iao.2023.22637. PMID: 37272640; PMCID: PMC10331632.

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Bijlagen bij module 7

Risk of Bias tables

Risk of bias table for intervention studies (observational: non-randomized clinical trials, cohort and case-control studies)

Study reference (first author, year of publication)	Bias due to a non-representative or ill-defined sample of patients?[1] (unlikely/likely/unclear)	Bias due to insufficiently long, or incomplete follow-up, or differences in follow-up between treatment groups?[2] (unlikely/likely/unclear)	Bias due to ill-defined or inadequately measured outcome ?[3] (unlikely/likely/unclear)	Bias due to inadequate adjustment for all important prognostic factors?[4] (unlikely/likely/unclear)
Pulcini, 2013	Unlikely	Unlikely	likely	Unclear

Table of excluded studies

Reference	Reason for exclusion
Saxena A, Paul BS, Singh G, Ahluwalia A, Paul G. Predicting Outcome in Skull Base Osteomyelitis: An Assessment of Demographic, Clinical, and Pathological Attributes. J Neurosci Rural Pract. 2021 Sep 28;12(4):751-757. doi: 10.1055/s-0041-1735324. PMID: 34737511; PMCID: PMC8559086.	Wrong outcome
van der Meer WL, Bayoumy AB, Otten JJ, Waterval JJ, Kunst HPM, Postma AA. The association between radiological spreading pattern and clinical outcomes in necrotizing external otitis. J Otol. 2022 Jul;17(3):156-163. doi: 10.1016/j.joto.2022.05.002. Epub 2022 Jun 3. PMID: 35847573; PMCID: PMC9270564.	No comparison made
Hodgson SH, Sinclair VJ, Arwyn-Jones J, Oh K, Nucken K, Perenyei M, Sivapathasingam V, Martinez-Devesa P, Pendlebury ST, Ramsden JD, Matthews PC, Pretorius P, Andersson MI. Characteristics, management and outcome of a large necrotising otitis externa case series: need for standardised case definition. J Laryngol Otol. 2022 Jul;136(7):604-610. doi: 10.1017/S002221512100462X. Epub 2022 Jan 19. PMID: 35042578; PMCID: PMC9257435.	No comparison made
Sadé J, Lang R, Goshen S, Kitzes-Cohen R. Ciprofloxacin treatment of malignant external otitis. Am J Med. 1989 Nov 30;87(5A):138S-141S. doi: 10.1016/0002-9343(89)90044-2. PMID: 2589357.	Wrong intervention
Jung DJ, Hong J, Cho HJ, Yoo MH, Lee KY. Clinical outcomes of otogenic skull base osteomyelitis. Eur Arch Otorhinolaryngol. 2021 Aug;278(8):2817-2822. doi: 10.1007/s00405-020-06366-0. Epub 2020 Sep 22. PMID: 32960351.	No comparison made
Chaabouni, M.A., Achour, I., Yousfi, G. et al. Culture-negative necrotizing otitis externa: diagnosis and	No comparison made

management. Egypt J Otolaryngol 39, 30 (2023). https://doi.org/10.1186/s43163-022-00363-2	
Chawdhary G, Pankhania M, Douglas S, Bottrill I. Current management of necrotising otitis externa in the UK: survey of 221 UK otolaryngologists. Acta Otolaryngol. 2017 Aug;137(8):818-822. doi: 10.1080/00016489.2017.1295468. Epub 2017 Mar 16. PMID: 28301961.	No comparison made
Stapleton E, Watson G. Emerging themes in necrotising otitis externa: a scoping review of the literature from 2011 to 2020 and recommendations for future research. J Laryngol Otol. 2022 Jul;136(7):575-581. doi: 10.1017/S0022215121003030. Epub 2021 Oct 20. PMID: 34666847.	No comparison made
Chhabria S, Vishnurag A. Observational Study on Clinical Features and Management of Skull Base Osteomyelitis in Hospitalised Patients at a Tertiary Care Hospital. Indian J Otolaryngol Head Neck Surg. 2023 Apr;75(Suppl 1):635-643. doi: 10.1007/s12070-023-03675-8. Epub 2023 Mar 18. PMID: 37206859; PMCID: PMC10188806.	No comparison made
Durojaiye OC, Slucka A, Kritsotakis EI. Retrospective analysis of outcomes of outpatient parenteral antimicrobial therapy (OPAT) for necrotising otitis externa. Eur J Clin Microbiol Infect Dis. 2022 Jun;41(6):941-949. doi: 10.1007/s10096-022-04455-y. Epub 2022 May 13. PMID: 35556187.	No comparison made
Loh S, Loh WS. Malignant otitis externa: an Asian perspective on treatment outcomes and prognostic factors. Otolaryngol Head Neck Surg. 2013 Jun;148(6):991-6. doi: 10.1177/0194599813482107. Epub 2013 Apr 4. PMID: 23558287.	No comparison made
Dhariwal A, Manjaly JG, Patel B, Morris-Jones S, David K, Khetarpal P, Beale T, Mehta N, Logan S. Management and Clinical Outcomes of 37 Patients with Necrotizing Otitis Externa: Retrospective Review of a Standardized 6-Week Treatment Pathway. J Int Adv Otol. 2023 Jun;19(3):223-227. doi: 10.5152/iao.2023.22637. PMID: 37272640; PMCID: PMC10331632.	No comparison made
Cho WS, Bonduelle Q, Ghasemi A, Baskaran V, O'Connor R, Shah J, Andrewartha F, Fergie N. Prognosticating patients with necrotising otitis externa based on response to treatment. Ann R Coll Surg Engl. 2021 Apr;103(4):285-290. doi: 10.1308/rcsann.2020.7133. Epub 2021 Mar 8. PMID: 33682472; PMCID: PMC10335042.	No comparison made
Frost J, Samson AD. Standardised treatment protocol for necrotizing otitis externa: retrospective case series and systematic literature review. J Glob Antimicrob	No comparison made

Resist. 2021 Sep;26:266-271. doi: 10.1016/j.jgar.2021.06.015. Epub 2021 Jul 14. PMID: 34273591.	
Lang R, Goshen S, Kitzes-Cohen R, Sadé J. Successful treatment of malignant external otitis with oral ciprofloxacin: report of experience with 23 patients. J Infect Dis. 1990 Mar;161(3):537-40. doi: 10.1093/infdis/161.3.537. PMID: 2313132.	No comparison made No comparison made
Djalilian HR, Shamloo B, Thakkar KH, Najme-Rahim M. Treatment of culture-negative skull base osteomyelitis. Otol Neurotol. 2006 Feb;27(2):250-5. doi: 10.1097/01.mao.0000181185.26410.80. PMID: 16436997.	No comparison made

Literature search strategy

Zoekverantwoording

Algemene informatie

Richtlijn: NVKNO Osteomyelitis schedelbasis – Maligne otitis externa	
Uitgangsvraag: Wat is de optimale behandelduur van therapie bij patiënten met maligne otitis externa?	
Database(s): Ovid/Medline, Embase	Datum:17-7-2023
Periode: nvt	Talen: nvt
Literatuurspecialist: Ingeborg van Dusseldorp	
BMI zoekblokken: voor verschillende opdrachten wordt (deels) gebruik gemaakt van de zoekblokken van BMI-Online https://blocks.bmi-online.nl/ Bij gebruikmaking van een volledig zoekblok zal naar de betreffende link op de website worden verwezen.	
Toelichting: Voor deze vraag is gezocht met de volgende concepten: Maligne otitis externa EN antibiotica EN behandelduur Vanwege de kleine aantallen is geen onderscheid gemaakt in studiedesign. NB. Voor deze vraag wordt uitgegaan van de strategie van UV4 dubbeltherapie antibiotica, waarin ook naar alle antibiotica is gezocht. Als er geen evidence wordt gevonden, kan worden overwogen om een volledige update te doen van UV4 en deze opnieuw te selecteren, ook omdat een specifieke behandelduur lastig is te formuleren in een zoekstrategie.	
Te gebruiken voor richtlijnen tekst: In de databases Embase en Ovid/Medline is op 17-7-2023 met relevante zoektermen gezocht naar studies over de behandelduur van therapie bij patiënten met maligne otitis externa. De literatuurzoekactie leverde 124 unieke treffers op.	

Zoekopbrengst

	EMBASE	**OVID/MEDLINE**	**Ontdubbeld**
SRs			
RCTs			
Observationele studies			
Overig	101	31	124
Totaal			

Zoekstrategie

Embase

No.	Query	Results
#48	#38 AND #47	101
#47	'treatment duration'/exp OR '6 week*':ti,ab,kw OR 'six week*':ti,ab,kw OR '6.0':ti,ab,kw OR '6.5':ti,ab,kw OR '6-7':ti,ab,kw OR '6-8':ti,ab,kw OR ((six NEAR/3 week*):ti,ab,kw)	1265464
#46	#42 OR #43 OR #44 OR #45	773
#45	#38 NOT (#42 OR #43 OR #44)	586
#44	#38 AND #41 NOT (#42 OR #43)	146
#43	#38 AND #40 NOT #42	3
#42	#38 AND #39	18
#41	'clinical trial'/exp OR 'randomization'/exp OR 'single blind procedure'/exp OR 'double blind procedure'/exp OR 'crossover procedure'/exp OR 'placebo'/exp OR 'prospective study'/exp OR rct:ab,ti OR random*:ab,ti OR 'single blind':ab,ti OR 'randomised controlled trial':ab,ti OR 'randomized controlled trial'/exp OR placebo*:ab,ti OR 'comparative study'/exp OR 'control group'/de OR 'controlled study'/de OR 'controlled clinical trial'/de OR 'crossover procedure'/de OR 'double blind procedure'/de OR 'phase 2 clinical trial'/de OR 'phase 3 clinical trial'/de OR 'phase 4 clinical trial'/de OR 'pretest posttest design'/de OR 'pretest posttest control group design'/de OR 'quasi experimental study'/de OR 'single blind procedure'/de OR 'triple blind procedure'/de OR (((control OR controlled) NEAR/6 trial):ti,ab,kw) OR (((control OR controlled) NEAR/6 (study OR studies)):ti,ab,kw) OR (((control OR controlled) NEAR/1 active):ti,ab,kw) OR 'open label*':ti,ab,kw OR (((double OR two OR three OR multi OR trial) NEAR/1 (arm OR arms)):ti,ab,kw) OR ((allocat* NEAR/10 (arm OR arms)):ti,ab,kw) OR placebo*:ti,ab,kw OR 'sham-control*':ti,ab,kw OR (((single OR double OR triple OR assessor) NEAR/1 (blind* OR masked)):ti,ab,kw) OR nonrandom*:ti,ab,kw OR 'non-random*':ti,ab,kw OR 'quasi-experiment*':ti,ab,kw OR crossover:ti,ab,kw OR 'cross over':ti,ab,kw OR 'parallel group*':ti,ab,kw OR 'factorial trial':ti,ab,kw OR ((phase NEAR/5 (study OR trial)):ti,ab,kw) OR ((case* NEAR/6 (matched OR control*)):ti,ab,kw) OR ((match* NEAR/6 (pair OR pairs OR cohort* OR control* OR group* OR healthy OR age OR sex OR gender OR patient* OR subject* OR participant*)):ti,ab,kw) OR ((propensity NEAR/6 (scor* OR match*)):ti,ab,kw) OR versus:ti OR vs:ti OR compar*:ti OR ((compar* NEAR/1 study):ti,ab,kw) OR (('major clinical study'/de OR 'clinical study'/de OR 'cohort analysis'/de OR 'observational study'/de OR 'cross-sectional study'/de OR 'multicenter study'/de OR 'correlational study'/de OR 'follow up'/de OR cohort*:ti,ab,kw OR 'follow up':ti,ab,kw OR followup:ti,ab,kw OR longitudinal*:ti,ab,kw OR prospective*:ti,ab,kw OR retrospective*:ti,ab,kw OR observational*:ti,ab,kw OR 'cross sectional*':ti,ab,kw OR cross?ectional*:ti,ab,kw OR multicent*:ti,ab,kw OR 'multi-cent*':ti,ab,kw OR consecutive*:ti,ab,kw) AND (group:ti,ab,kw OR groups:ti,ab,kw OR subgroup*:ti,ab,kw OR versus:ti,ab,kw OR vs:ti,ab,kw OR compar*:ti,ab,kw OR 'odds ratio*':ab OR 'relative odds':ab OR 'risk ratio*':ab OR 'relative risk*':ab OR 'rate ratio':ab OR aor:ab OR arr:ab OR rrr:ab OR ((('or' OR 'rr') NEAR/6 ci):ab))) OR 'major clinical study'/de OR 'clinical study'/de OR 'case control study'/de OR 'family study'/de OR 'longitudinal study'/de OR 'retrospective study'/de OR 'prospective study'/de OR 'comparative study'/de OR 'cohort analysis'/de OR ((cohort NEAR/1 (study OR studies)):ab,ti) OR (('case control' NEAR/1 (study OR studies)):ab,ti) OR (('follow up' NEAR/1 (study OR studies)):ab,ti) OR (observational NEAR/1 (study OR studies)) OR ((epidemiologic NEAR/1 (study OR studies)):ab,ti) OR (('cross sectional' NEAR/1 (study OR studies)):ab,ti)	16360334

#40	'randomized controlled trial'/exp OR random*:ti,ab OR (((pragmatic OR practical) NEAR/1 'clinical trial*'):ti,ab) OR ((('non inferiority' OR noninferiority OR superiority OR equivalence) NEAR/3 trial*):ti,ab) OR rct:ti,ab,kw	1839814
#39	'meta analysis'/exp OR 'meta analysis (topic)'/exp OR metaanaly*:ti,ab OR 'meta analy*':ti,ab OR metanaly*:ti,ab OR 'systematic review'/de OR 'cochrane database of systematic reviews'/jt OR prisma:ti,ab OR prospero:ti,ab OR (((systemati* OR scoping OR umbrella OR 'structured literature') NEAR/3 (review* OR overview*)):ti,ab) OR ((systemic* NEAR/1 review*):ti,ab) OR (((systemati* OR literature OR database* OR 'data base*') NEAR/10 search*):ti,ab) OR (((structured OR comprehensive* OR systemic*) NEAR/3 search*):ti,ab) OR (((literature NEAR/3 review*):ti,ab) AND (search*:ti,ab OR database*:ti,ab OR 'data base*':ti,ab)) OR (('data extraction':ti,ab OR 'data source*':ti,ab) AND 'study selection':ti,ab) OR ('search strategy':ti,ab AND 'selection criteria':ti,ab) OR ('data source*':ti,ab AND 'data synthesis':ti,ab) OR medline:ab OR pubmed:ab OR embase:ab OR cochrane:ab OR (((critical OR rapid) NEAR/2 (review* OR overview* OR synthes*)):ti) OR ((((critical* OR rapid*) NEAR/3 (review* OR overview* OR synthes*)):ab) AND (search*:ab OR database*:ab OR 'data base*':ab)) OR metasynthes*:ti,ab OR 'meta synthes*':ti,ab	733409
#38	#36 AND #37 NOT ('conference abstract'/it OR 'editorial'/it OR 'letter'/it OR 'note'/it) NOT (('animal experiment'/exp OR 'animal model'/exp OR 'nonhuman'/exp) NOT 'human'/exp)	773
#37	'antibiotic therapy'/exp/mj OR 'antibiotic agent'/exp/mj OR 'antifungal agent'/exp/mj OR 'antifungal therapy'/exp/mj OR antibiotic*:ti,kw OR antifung*:ti,ab,kw OR 'anti-biotic*':ti,ab,kw OR 'anti-fung*':ti,ab,kw OR 'cephalosporin'/exp OR 'cefalosporin*':ti,ab,kw OR 'cephalosporin*':ti,ab,kw OR 'penicillin derivative'/exp OR 'penicillin*':ti,ab,kw OR 'carbapenem'/exp OR 'carbapenem':ti,ab,kw OR 'quinoline derived antiinfective agent'/exp OR 'quinolone derivative'/exp OR fluoroquinolon*:ti,ab,kw OR quinolon*:ti,ab,kw OR 'aminoglycoside antibiotic agent'/exp OR 'aminoglycoside'/exp OR aminoglycoside*:ti,ab,kw OR 'aminoglucoside*':ti,ab,kw OR 'meropenem'/exp OR 'meropenem':ti,ab,kw OR merrem:ti,ab,kw OR 'ceftazidime'/exp OR 'ceftazidime':ti,ab,kw OR fortum:ti,ab,kw OR 'tobramycin'/exp OR 'tobramycin*':ti,ab,kw OR 'piperacillin'/exp OR 'piperacillin*':ti,ab,kw OR pipracil:ti,ab,kw OR 'tazobactam'/exp OR 'tazobactam':ti,ab,kw OR 'combination drug therapy'/exp OR (((dual OR mono OR combination* OR combined OR double OR multimodality) NEAR/3 (therap* OR treat*)):ti,ab,kw)	1885018
#36	'malignant otitis externa'/exp/mj OR (((maligna* OR necroti* OR necrosis) NEAR/3 ('otitis externa' OR 'external otitis')):ti,kw) OR ('otitis externa'/mj AND (maligna*:ti,kw OR necroti*:ti,kw OR necrosis:ti,kw)) OR (('osteomyelitis'/exp/mj OR 'osteomyelitis':ti,kw) AND ('skull'/exp/mj OR 'skull disease'/exp/mj OR skull*:ti,ab,kw OR cranial:ti,ab,kw OR cranium:ti,ab,kw))	3086

Ovid/Medline

Search Strategy:

#	Searches	Results
14	4 and 13	31
13	"Duration of Therapy"/ or "6.0".ti,ab,kf. or "6.5".ti,ab,kf. or "6-7".ti,ab,kf. or "6-8".ti,ab,kf. or (six adj3 week*).ti,ab,kf.	1572259
12	4 not 11	374
11	8 or 9 or 10	126
10	(4 and 7) not (8 or 9)	113
9	(4 and 6) not 8	6

8	4 and 5	7
7	exp clinical trial/ or randomized controlled trial/ or exp clinical trials as topic/ or randomized controlled trials as topic/ or Random Allocation/ or Double-Blind Method/ or Single-Blind Method/ or (clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or controlled clinical trial or randomized controlled trial or multicenter study or clinical trial).pt. or random*.ti,ab. or (clinic* adj trial*).tw. or ((singl* or doubl* or treb* or tripl*) adj (blind$3 or mask$3)).tw. or Placebos/ or placebo*.tw. or Epidemiologic studies/ or case control studies/ or exp cohort studies/ or Controlled Before-After Studies/ or Case control.tw. or cohort.tw. or Cohort analy$.tw. or (Follow up adj (study or studies)).tw. or (observational adj (study or studies)).tw. or Longitudinal.tw. or Retrospective*.tw. or prospective*.tw. or consecutive*.tw. or Cross sectional.tw. or Cross-sectional studies/ or historically controlled study/ or interrupted time series analysis/ or Case-control Studies/ or clinical trial, phase ii/ or clinical trial, phase iii/ or clinical trial, phase iv/ or comparative study/ or control groups/ or controlled before-after studies/ or controlled clinical trial/ or double-blind method/ or historically controlled study/ or matched-pair analysis/ or single-blind method/ or (((control or controlled) adj6 (study or studies or trial)) or (compar* adj (study or studies)) or ((control or controlled) adj1 active) or "open label*" or ((double or two or three or multi or trial) adj (arm or arms)) or (allocat* adj10 (arm or arms)) or placebo* or "sham-control*" or ((single or double or triple or assessor) adj1 (blind* or masked)) or nonrandom* or "non-random*" or "quasi-experiment*" or "parallel group*" or "factorial trial" or "pretest posttest" or (phase adj5 (study or trial)) or (case* adj6 (matched or control*)) or (match* adj6 (pair or pairs or cohort* or control* or group* or healthy or age or sex or gender or patient* or subject* or participant*)) or (propensity adj6 (scor* or match*))).ti,ab,kf. or (confounding adj6 adjust*).ti,ab. or (versus or vs or compar*).ti. or ((exp cohort studies/ or epidemiologic studies/ or multicenter study/ or observational study/ or seroepidemiologic studies/ or (cohort* or 'follow up' or followup or longitudinal* or prospective* or retrospective* or observational* or multicent* or 'multi-cent*' or consecutive*).ti,ab,kf.) and ((group or groups or subgroup* or versus or vs or compar*).ti,ab,kf. or ('odds ratio*' or 'relative odds' or 'risk ratio*' or 'relative risk*' or aor or arr or rrr).ab. or (("OR" or "RR") adj6 CI).ab.))	8305718
6	exp randomized controlled trial/ or randomized controlled trials as topic/ or random*.ti,ab. or rct?.ti,ab. or ((pragmatic or practical) adj "clinical trial*").ti,ab,kf. or ((non-inferiority or noninferiority or superiority or equivalence) adj3 trial*).ti,ab,kf.	1628800
5	meta-analysis/ or meta-analysis as topic/ or (metaanaly* or meta-analy* or metanaly*).ti,ab,kf. or systematic review/ or cochrane.jw. or (prisma or prospero).ti,ab,kf. or ((systemati* or scoping or umbrella or "structured literature") adj3 (review* or overview*)).ti,ab,kf. or (systemic* adj1 review*).ti,ab,kf. or ((systemati* or literature or database* or data-base*) adj10 search*).ti,ab,kf. or ((structured or comprehensive* or systemic*) adj3 search*).ti,ab,kf. or ((literature adj3 review*) and (search* or database* or data-base*)).ti,ab,kf. or (("data extraction" or "data source*") and "study selection").ti,ab,kf. or ("search strategy" and "selection criteria").ti,ab,kf. or ("data source*" and "data synthesis").ti,ab,kf. or (medline or pubmed or embase or cochrane).ab. or ((critical or rapid) adj2 (review* or overview* or synthes*)).ti. or (((critical* or rapid*) adj3 (review* or overview* or	680557

	synthes*)) and (search* or database* or data-base*)).ab. or (metasynthes* or meta-synthes*).ti,ab,kf.	
4	3 not (comment/ or editorial/ or letter/ or ((exp animals/ or exp models, animal/) not humans/))	500
3	1 and 2	525
2	exp *Anti-Bacterial Agents/ or exp Antifungal Agents/ or antibiotic*.ti,kf. or antifung*.ti,ab,kf. or 'anti-biotic*'.ti,ab,kf. or 'anti-fung*'.ti,ab,kf. or exp Cephalosporins/ or exp Penicillins/ or exp Carbapenems/ or exp Fluoroquinolones/ or exp Aminoglycosides/ or exp Meropenem/ or exp Ceftazidime/ or exp Tobramycin/ or exp Piperacillin/ or exp Tazobactam/ or 'cefalosporin*'.ti,ab,kf. or 'cephalosporin*'.ti,ab,kf. or 'penicillin*'.ti,ab,kf. or 'carbapenem'.ti,ab,kf. or fluoroquinolon*.ti,ab,kf. or quinolon*.ti,ab,kf. or aminoglycoside*.ti,ab,kf. or 'aminoglucoside*'.ti,ab,kf. or 'meropenem'.ti,ab,kf. or merrem.ti,ab,kf. or 'ceftazidime'.ti,ab,kf. or fortum.ti,ab,kf. or 'tobramycin*'.ti,ab,kf. or 'piperacillin*'.ti,ab,kf. or Pipracil.ti,ab,kf. or 'tazobactam'.ti,ab,kf. or exp Drug Therapy, Combination/ or ((dual or mono or combination* or combined or double or multimodality) adj3 (therap* or treat*)).ti,ab,kf.	1391087
1	((maligna* or necroti* or necrosis) adj3 ('otitis externa' or 'external otitis')).ti,kf. or (exp *Otitis Externa/ and (maligna* or necroti* or necrosis).ti,kf.) or ((exp *Osteomyelitis/ or 'osteomyelitis'.ti,kf.) and (exp Skull/ or skull*.ti,ab,kf. or cranial.ti,ab,kf. or cranium.ti,ab,kf.))	2667

Module 8 – Imaging to monitor treatment response

Question
Which imaging modality (if any) is preferable for the evaluation of treatment response in necrotizing otitis externa?

Introduction
Currently, there is no consensus on how to measure therapy response in necrotizing otitis externa (NOE). Many clinics follow a standard treatment duration or continue therapy until symptoms (otorrhea and otalgia) resolve over a minimum period. Treatment is considered successful if the patient becomes asymptomatic and no abnormalities are found on physical examination. If symptoms recur after discontinuation, therapy is resumed. This represents a purely clinical approach.

However, in some patients, clinical signs are equivocal, necessitating further diagnostic tests. With the availability of MRI and/or [^{18}F]-FDG-PET/CT, there is growing interest in using these imaging modalities to assess treatment success and guide discontinuation. However, their use has not yet been validated, and they have certain limitations.

Evaluating treatment response in NOE through imaging can be challenging due to persistent abnormalities. Both CT and MRI may show ongoing changes (e.g., bone erosions, soft tissue enhancement, or bone marrow signal alterations) even during effective treatment. In such cases, accurately interpreting treatment response remains difficult.

Search and select
A systematic review of the literature was performed to answer the following question(s):
What are the advantages and/or disadvantages of MRI compared to FDG-PET scans in the evaluation of treatment response in necrotizing otitis externa [prognostic/impact question]

Table 1. PICO

Patients	Patients treated/under treatment for necrotizing otitis externa
Intervention	(Dis)Continuation of therapy on basis of MRI
Control	(Dis)Continuation of therapy on basis of FDG-PET/CT scans
Referral	Clinical remission of disease (after stopping treatment)
Outcomes	Remission, duration of treatment
Other selection criteria	Study design: systematic reviews and randomized controlled trials, observational studies

<u>Relevant outcome measures</u>
The guideline panel considered treatment response and recurrence of disease as a **critical** outcome measure for decision making; and duration of treatment as an **important** outcome measure for decision making.

Tthe guideline panel defined the outcome measures as:

- Remission: curation rate, defined as the absence of disease > 3 months.
- Duration of treatment: the length of treatment, preferably in weeks

The guideline development group defined the following as a minimal clinically (patient) important difference:

- Remission: GRADE standard limits
- Duration of treatment: Absolute difference > 5%

* Default thresholds proposed by the international GRADE working group were used: a 25% difference in relative risk (RR) for dichotomous outcomes (RR <0.80 or RR >1.25), or 0.5 standard deviations (SD) for continuous outcomes

Search and select (Methods)
The databases Medline (via OVID) and Embase (via Embase.com) were searched with relevant search terms until 10-11-2023. An additional search was performed on 12-02-2025 by a medical information specialist using the following bibliographic databases: Embase.com and Ovid/Medline. Both databases were searched from inception till 12-2-2025 for systematic reviews, clinical trials and observational studies. Systematic searches were completed using a combination of controlled vocabulary/subject headings (e.g., Emtree-terms, MeSH) wherever they were available and natural language keywords. The overall search strategy was derived from 3 primary search concepts: (1) Osteomyelitis skull base AND ((2) MRI OR (3) PET-CT). Duplicates were removed using EndNote software. After deduplication a total of 233 records were imported for title/abstract screening. The detailed search strategy is listed under the tab 'Literature search strategy'. Initially, 223 studies were selected based on title and abstract screening. After reading the full text, 24 studies were excluded (see the exclusion table under the tab 'Evidence tabellen'), and 4 studies were included.

Summary of literature
Description of studies
A total of 4 studies were included in the analysis of the literature. None of these studies directly compared MRI with FDG-PET/CT. Important study characteristics and results are summarized in table 2. The assessment of the risk of bias is summarized in the risk of bias tables (under the tab 'Evidence tables').

Table 2. Characteristics of included studies

Study	Participants (number, age, other important characteristics)	Comparison	Follow-up	Outcome measures	Comments	Risk of bias (per outcome measure)*
Individual studies						
Shavit, 2018	Type of study: Retrospective analysis. N at baseline Intervention: 12 Control: 12 Mean age was 74 ± 11.5; 10 patients (83%) were male; 10 (83%) After average 16 month follow-up, patients reamained free from disease. Mean duration of treatment was 61 days ± 44. The maximum was 192 days.	For treatment response: The second scan demonstrated no FDG uptake in four patients and substantially reduced FDG uptake in three patients. Hence, treatment was stopped for all seven patients. One patient had significant FDG uptake. The patient completed a second 6-week course of antibiotic treatment until a third scan demonstrated no FDG uptake	Mean follow-up was 16 ± 15 months. Two patients died before the second PET/CT while still treated with antibiotics for active osteomyelitis Two patients were lost to follow-up and did not complete the second scan	Remission	-	Risk of bias for remission in selection and index test
Kulkarni, 2020	Type of study: Retrospective analysis. <u>Inclusion criteria</u>: Patients referred for FDG-PET/CT imaging for suspected skull base osteomyelitis.	For follow up analysis: Intervention: 23 (42.8%) patients had imaging follow up with FDG-PET/CT	The patients were followed in intervals after a duration of 52 ± 9 days. Total follow up was not specified.	Remission	No specification of underlying orgin of disease (only SBO, not only NOE) No recurrence of disease or length of treatment was specified.	When reporting remission, there was risk of Bias for selection and reporting

	Exclusion criteria: Known malignancy (1); Loss for follow up (2); Incomplete data (3) N total at baseline: 83 patients were originally included. 6 were excluded. Of the 77 remaining cases, 56 patients also underwent a MRI. Intervention: 56 Control: 77 Important prognostic factors: *male:female = 56:21; mean age 66.4 ± 9.4 years; range 45–92 years* Groups were comparable at baseline.	Referall: 54 (57.2%) only had clinical follow up. No recurrence of disease or length of treatment was specified. Regarding treatment response. Of the 23 patients with follow up FDG-PET/CT, 14 showed progression of disease and 9 regression. The FDG-PET/CT scan predicted this correctly, according to later clinical findings. (other numbers or not specified. Progression or regression of disease was seen as a increase or decrease respectively in SUVmax,.			Regarding treatment response. Of the 23 patients with follow up FDG-PET/CT, 14 showedprogression of disease and 7 regression. The FDG-PET/CT scan predicted this correctly, according to later clinical findings. (other numbers not specified.)	
Vosbeek, 2023	Type of study: Retrospective analysis.	In 20 cases imaging was used to define	The mean duration of follow-up after	Remission	Patients were divided in 3 groups: 1 group where	When reporting remission, there

	N at baseline Intervention: 24 Important prognostic factors: Mean age was 75 (43–91) years 20 (83%) were male. 20 were diabetic (83%)	treatment response and cessation of treatment. They were devided in groups (zie Comments). Regarding FDG-PET/CT: (other patients had gallium scans) Group 1: 5/5 remission Group 2: 1/1 remission Group 3: 2/1 remission	cessation of IV therapy in the group of cases who achieved remission was 39 months (range 3–83 months; n = 21). For 2 patients, no follow-up time after cessation of therapy was reported since they died outside of the hospital and the date of death was unknown. 1 patient died of another cause before remission was achieved.		resolution of signs of active inflammation on imaging was the cessation point of systemic antibiotic and/or antifungal therapy (n = 9), 1 group where near resolution of active inflammation on imaging was used as the cessation point (n = 3), and a group where other reasons for cessation of therapy were noted while there was no complete resolution on imaging (n = 8)	was risk of Bias for selection and reporting
Thanneru, 2024	Type of study: prospective cohort study N at baseline Intervention: 28 Control: 28 (same patients) Patients characteristics were not described	All patients underwent a FDG-PET/CT (28). 20 patients underwent a scan when cured. The patient was considered clinically cured of the disease when asymptomatic status was maintained without	median follow up time of 20 months. Spread was not described	Remission		When reporting remission, there was risk of Bias for selection and reporting

		any appearance of new signs of the disease for a minimum of three weeks. 8 patients with active disease were also scanned, however the specifics at what time and phase of disease this was performed was not mentioned.				

*For further details, see risk of bias table in the appendix

Results

Treatment response

Shavit (2018) evaluated a small group of 8 patients with a follow-up FDG-PET/CT scan after 6 weeks of treatment with intravenous antibiotics in patients with necrotizing otitis externa. Seven patients showed no FDG uptake or reduced uptake (the method for evaluation of reduction was not specified). One patient showed an increase in FDG uptake, and antibiotic treatment was prolonged for another six weeks. After this second round of antibiotic treatment, this patient showed a decrease in FDG uptake. In all patients showing a decrease in or no FDG uptake after treatment, antibiotics were discontinued. None of these patients showed signs of recurrence of refractory disease after clinical follow-up (mean follow-up time of 16 ± 15 months).

Kulkarni (2020) evaluated a follow-up FDG-PET/CT scan in 23 of the original 77 patients with necrotizing otitis externa. Of the 23 patients with a follow-up FDG-PET/CT scan, 14 showed progression of disease and 9 regression. In all patients, the FDG-PET/CT findings were in accordance with later clinical findings in follow up, making the decision to (dis)continue treatment based on FDG-PET correct.

Vosbeek (2023) assessed treatment (dis)continuation using follow-up FDG-PET/CT or Gallium SPECT/CT in 20 patients divided into 3 groups: complete imaging resolution (no signs of active inflammation/infection) (n=9), near-resolution (n=3), or cessation for other reasons despite residual imaging findings (n=8). FDG-PET/CT (n=8) showed 100% remission in groups 1 (5/5) and 2 (1/1), and 50% (1/2) in group 3.

Thanneru (2024) evaluated FDG-PET/CT scans in 20 patients in clinical remission and 8 patients with clinically active disease. All patients underwent an FDG-PET/CT scan. Among the 20 patients in remission, 17 (85%) showed no increased FDG uptake, while 3 (15%) exhibited residual increased uptake. Of this group, no relapses were mentioned (100% remission rate). In contrast, all eight patients with active disease showed signs of active disease on the follow-up FDG-PET scan. The study did not specify the timing of the scans or the criteria used for evaluation.

Length of treatment

No studies evaluated if imaging modalities could help in determining the length of treatment.

Conclusions

Treatment response FDG PET-CT

Very low GRADE	The evidence is very uncertain about the evaluation of treatment response on FDG-PET/CT in patients with suspected skull base osteomyelitis. *Source: Vosbeek (2023), Kulkarni (2020), Shavit (2018)*

Treatment response MRI

Very low GRADE	No evidence was found about the evaluation of treatment response on MRI in patients with suspected skull base osteomyelitis. *Source: -*

Treatment response MRI vs FDG PET-CT

Very low GRADE	No evidence was found about the evaluation of treatment response on MRI versus FDG-PET-CT in patients with suspected skull base osteomyelitis. *Source: -*

Length of treatment

No GRADE	No evidence was found for using FDG-PET/CT or MRI for determining the length of treatment. *Sources: -*

Considerations – from evidence to recommendation

Balance between desired and undesired effects

After reviewing the literature, we found that none of the studies directly compared MRI with FDG-PET/CT as imaging modality for the follow-up of NOE. Only a few studies evaluated the diagnostic benefits of imaging modalities for treatment follow-up in patients with necrotizing otitis externa. Additionally, no studies were identified regarding the role of imaging in determining treatment duration or predicting disease recurrence. Furthermore, no studies have systematically compared the added value of follow-up imaging versus no imaging at all.

No imaging during follow-up

Clinical follow-up is always the most critical parameter. In patients with limited disease severity/extent who are asymptomatic at the end of treatment, remission is likely. In such cases, follow-up imaging may offer little added value. According to the UK criteria this applies to *probable* and *definite* NOE (Hodgson, 2023).

Pragmatically, imaging for therapy evaluation may be warranted if there is a higher likelihood of post-treatment findings requiring therapy extension—particularly when such findings cannot be adequately monitored based on clinical symptoms alone. These patients typically fall into the category of *NOE with complications* or *complex NOE* (using the same definition).

The committee acknowledges significant practice variations across countries and settings regarding this approach.

Regarding treatment response, we describe the findings and considerations for each imaging modality below:

FDG-PET/CT:

From the systematic literature search, four studies were identified that evaluated FDG-PET/CT as a potential diagnostic tool to guide treatment in patients with necrotizing otitis externa (NOE). High remission rates were observed in patients showing no increased FDG activity or a significant decrease in FDG uptake on follow-up scans. However, these studies were limited by small sample sizes (Shavit 2018, Vosbeek 2023, Thannaru 2024).

In patients with progressive disease (evidenced by increased FDG uptake), FDG-PET/CT results may justify treatment extension. For example, Kulkarni (2020) reported disease progression in 14 patients and regression in 9 based on FDG-PET/CT findings, all of which were later confirmed by clinical follow-up.

Due to the scarcity of high-quality studies, the added value of FDG-PET/CT in assessing treatment response remains uncertain. Nevertheless, its use for this purpose is increasing in NOE, as it remains the optimal modality for visualizing hypermetabolic foci characteristic of infection.

FDG-PET/CT can be reasonably used for treatment response evaluation in NOE, provided:

1) Preferably, a baseline FDG-PET/CT is available for comparison.

2) Recognition that no validated quantitative thresholds currently exist.

While SUVmax may support therapy monitoring (van der Meer 2023), and preliminary data suggest SUVpeak <3.1 as a potential cutoff for treatment cessation (Jansen 2025), robust evidence is still required before quantitative criteria can be standardized.

MRI:

No studies could be included that evaluated the role of MRI in treatment response. However, the literature does suggest that disease extension and progression in follow-up could be monitored by MRI (Lee, 2011). In contrast, other MRI case series describe the persistent absence of normalization in previously affected tissues at 6- and 12-month scans, even after clinically successful treatment (Al-Noury 2011, Chhabria 2023).

Contrast-enhanced MRI is useful for evaluating the anatomic location of NOE / skull base osteomyelitis. During treatment, MRI may show a decrease in the extent or intensity of enhancement. Other sequences – such as T1-weighted imaging (for both bone and soft tissue abnormalities) or diffusion-weighted imaging (DWI) – may also suggest an adequate response. However, most patients show persistent MRI abnormalities after treatment.

For evaluating complex NOE (e.g., cases involving venous thrombosis, abscess, or empyema), MRI is superior to CT for soft tissue evaluation. If MRI is not feasible (due to the patient's clinical condition or contraindications), a contrast-enhanced CT scan or FDG-PET/CT could be considered.

CT:

For completeness, no studies were found that evaluated the role of CT in therapy follow-up. However, the literature suggests that bony erosion may persist even after successful treatment (Kroonenburgh, 2018). Follow-up CT scans can continue to show signs of disease, despite successful treatment (Chabria, 2023; Kroonenburgh, 2018).

In the past, bone scintigraphy (^{99m}Tc-labelled diphosphonates) or galliumscans (^{67}Ga-citrate) were used for infection imaging. However, these techniques are not preferred anymore. Bone scintigraphy is aspecific, depics abnormalities of the bone, and involvement of or extension to the soft tissue cannot be visualized. The uptake of ^{67}Ga-citrate is aspecific. Besides, PET/CT imaging offers better spatial resolution, better sensitivity, and possibilities for quantification.

<u>Quality of the evidence</u>

For MRI, no evidence could be found regarding the role of MRI in therapy evaluation.

The overall quality of evidence for the use of FDG-PET/CT in therapy evaluation is very low. This means we are very uncertain about the estimated effect of the crucial outcomes found. There is downgrading due to very serious:

- Risk of bias: patient selection; index test.
- Imprecision: inaccuracy, due to a very small number of events in a small sample size.

Based on the literature, and despite the very low quality of evidence, when imaging techniques are needed since other diagnostic tests are equivocal, FDG-PET/CT is the first imaging technique of choice to evaluate effect of therapy in patients treated for NOE. No evidence could be found when this FDG-PET/CT should be performed. However, based on other studies in infectious diseases, FDG-PET/CT could show therapy effect after six weeks of antibiotic treatment.

No evidence was found for the use of MRI in therapy evaluation. However, it is known that contrast enhanced MRI can be used to evaluate the extent of infection in the adjacent soft tissues or the adjacent bone marrow in the diagnostic phase. Together with FDG-PET/CT this

could help in determining the exact location of remaining FDG activity in the therapy phase. Therefore, FDG-PET/MRI could be used for this indication, when available.

Values and preferences of patients (and possibly their relatives/caregivers)
Imaging techniques can be used to evaluate treatment response. FDG-PET/CT involves radiation exposure, so patients should be informed of this risk. The ALARA principle (As Low As Reasonably Achievable) must always be followed when using ionizing radiation. Recent advances in camera technology have significantly reduced radiation doses. For younger children, MRI may be challenging due to long scan times, loud noises, and potential difficulties with cooperation.

Cost considerations
FDG-PET/CT is an expensive imaging technique. However, when used to determine whether treatment should be stopped, modified, or prolonged, cost considerations should not be the primary factor. In fact, performing an FDG-PET/CT scan may prove cost-effective if it prevents unnecessary treatment prolongation.

Acceptability, feasibility, and implementation.
Regarding acceptability, feasibility, and implementation, no significant challenges are anticipated since CT, MRI, and FDG-PET/CT are widely available. In situations with limited capacity for one or two modalities, the remaining technique serves as a viable alternative. If local expertise in image interpretation is lacking, referral to a specialized center remains an option.

Recommendations
Rationale of the recommendation: weighing arguments for and against the interventions
Clinical evaluation is the most critical factor in therapy evaluation.

Based on the literature—and despite the very low quality of evidence—if imaging is required due to inconclusive results from other diagnostic tests, FDG-PET/CT is the preferred imaging technique for evaluating therapy response in patients treated for NOE.

In some centers a PET/MRI camera system is available. This could be synergistic, since the metabolic activity of the PET scan can be combined with the soft-tissue characterization of the MRI which is superior over CT. In those center where PET/MRI is available: FDG-PET/MRI is preferred over FDG-PET/CT for this indication.

Be aware that follow-up imaging often reveals residual abnormalities that are impossible to distinguish from persistent disease. In such cases, clinical remission may be decisive.

Final judgment:
Weak recommendaton against imaging for follow-up of Definite NOE. Weak recommendation for imaging in case of complex NOE.

Weak recommendation for FDG-PET as imaging modality to evaluate treatment response.
Weak recommendation for MRI as imaging modality to evaluate complications of NOE (vascular, intracranial).

Clinical findings (physical examination, symptoms) are the most important in treatment evaluation in patients with necrotizing otitis externa. If remission is clearly present, no imaging is necessary.

Use imaging for treatment response when clinical symptoms are equivocal and in case of extensive disease (complex NOE). A baseline scan is then indicated. In case of partial response on imaging, clinical signs may be decisive.

Possible imaging modalities:
1. FDG-PET/CT (or MRI) is the preferred imaging modality for assessing treatment response. Preferably a baseline scan is available.

- If FDG uptake is normal or significantly decreased compared to the baseline scan, therapy can be discontinued.
- If FDG uptake is unchanged / increased, the (microbiological) diagnosis shoud be reconsidered or therapy should be prolonged.

2. MRI

- Contrast-enhanced MRI may demonstrate reduced lesion extent and decreased intensity of enhancement during treatment. Other sequences (e.g., T1, diffusion-weighted imaging) may also suggest an adequate response.
- Most patients exhibit persistent MRI abnormalities post-treatment.

Knowledge gaps
During the development of this module, a systematic search was conducted to find studies that could answer the research question. Through the use of a systematic literature review with an assessment of the strength of evidence, it has become clear that there are still knowledge gaps within this module. The working group believes that further research is desirable to provide clearer answers to practical questions in the future. A prospective study directly comparing FDG-PET/CT with MRI (or directly by means of FDG-PET/MRI) and including baseline and therapy follow-up scans could help in determining the best imaging technique to define treatment response.

Knowledge question
What is the added value of FDG-PET/CT(MRI) and MRI for therapy evaluation in patients with NOE?

Verkeerslicht en (de-)implementatietabel

Toelichting
Met het verkeerslicht worden aanbevelingen gecategoriseerd op basis van formulering en bewijskracht. Als eindproduct wordt bij richtlijnmodules met een sterk geformuleerde en voldoende onderbouwde aanbeveling een implementatietabel opgeleverd. Hierin wordt onder andere opgenomen:

- Een beschrijving van het knelpunt om de module uit te werken of herzien;
- De te verwachten belemmerende en bevorderende factoren voor implementatie;
- Welke partijen van belang zijn bij toepassen van de aanbeveling in de praktijk;
- Een inschatting van de implementatietermijn.

Verkeerslichtanalyse

- **ROOD** = sterk geformuleerde aanbeveling om iets niet te doen, met een GRADE high of moderate
- **ORANJE** = zwak geformuleerde aanbeveling; mogelijk kennishiaat
- **GROEN** = sterk geformuleerde aanbeveling om iets wel te doen, met een GRADE high of moderate
- **LICHT ROOD** of **LICHT GROEN** = sterk geformuleerde aanbevelingen met een GRADE low, very low of geen GRADE *(modules waarin geen studies geïncludeerd konden worden in de literatuursamenvatting of waarin geen literatuursamenvatting werd geschreven zoals modules waarin organisatie van zorg wordt beschreven)*

(Sub)aanbeveling	**Sterkte van de aanbeveling**	**Bewijskracht per uitkomstmaat**	**Verkeerslicht per (sub)aanbeveling**
Aanbeveling 1:	□ Zwak (overweeg)	**Overall bewijskracht** □ **VL** **Range bewijskracht van alle uitkomstmaten** □ **VL**	**LICHT GROEN**

Implementatietabel

Tabel A: (De-)Implementatietabel met impuls analyse

Aanbeveling – 1			
1. Wat was het onderliggende probleem om deze uitgangsvraag uit te werken?	**□ Ongewenste praktijkvariatie** **□ Nieuwe evidentie**		
2. Maak een inschatting over hoeveel patiënten het ongeveer gaat waar de aanbeveling betrekking op heeft?	**□ < 1000**		
3. Maakt de aanbeveling deel uit van een set van interventies voor hetzelfde probleem?	**□ Nee**		
4. Belemmeringen en kansen op verschillende niveaus voor landelijke toepassing van de aanbeveling:	***Voorbeelden***	**Wat zijn mogelijke belemmerende factoren?**	**Wat zijn mogelijke bevorderende factoren?**
a) **Richtlijn/ klinisch traject (innovatie)**	*Voortschrijding/vooruitgang in de praktijk, haalbaarheid, geloofwaardigheid, toegankelijkheid, aantrekkelijkheid*	Geen	Geen
b) **Zorgverleners (artsen en verpleegkundigen)**	*Bewustzijn, kennis, houding, motivatie om te veranderen, gedragsroutines*	Expertise van radioloog verschilt per modaliteit; soms voorkeur voor 1 modaliteit t.o.v. anderen. Dit wisselt ook per kliniek.	Gezien kleine verschillen tussen modaliteiten lijkt er ruimte te zijn per specialist welke beeldvorming zij willen gebruiken. De richtlijn laat dit ook toe.
c) **Patiënt/ cliënt (naasten)**	*Kennis, vaardigheden, houding, compliance*	Geen	Geen
d) **Sociale context**	*Mening van collega's, cultuur van het netwerk, samenwerking, leiderschap*	Geen	Geen

e) **Organisatorische context**	*Organisatie van zorgprocessen, personeel, capaciteiten, middelen, structuren*	Toegang tot PET scanner indien gewenst	Klinieken hebben contracten met klinieken om daar evt. PET scan te verrichten
f) **Economische en politieke context**	*Financiële regelingen, regelgeving, beleid (vergoede zorg, betaaltitel)*	Geen	Geen

5. Welke personen/partijen zijn van belang bij het toepassen van de aanbeveling in de praktijk?	**x** Patiënt/ cliënt (naaste) **x** Professional
6. Wat zouden deze personen/ partijen moeten veranderen in hun gedrag of organisatie om de aanbeveling toe te passen?	Dit kan reeds worden toegepast, geen aanpassingen hoeven te worden gemaakt.
7. Binnen welk tijdsbestek moet de aanbeveling zijn geïmplementeerd?	□ < 1 jaar
8. Conclusie: is er extra aandacht nodig voor implementatie van de aanbeveling (anders dan publicatie van deze richtlijnmodule)?	□ **Nee**

**Deze aanbeveling komt in aanmerking voor plaatsing op de Implementatie Agenda van het programma Zorg Evaluatie & Gepast Gebruik (ZE&GG). In het programma ZE&GG werken patiënten, zorgverleners, zorgaanbieders, zorgverzekeraars en overheid samen aan de bewezen beste zorg voor de patiënt. Daarmee is ZE&GG een programma van alle betrokken partijen in de Medisch Specialistische Zorg. FMS is één van deze betrokken partijen.*

De implementatieagenda van ZE&GG bevat onderwerpen over wat de bewezen beste zorg is en die in de dagelijkse zorgpraktijk geïmplementeerd zouden moeten worden. Zorgverzekeraars Nederland (ZN) en de Nederlandse Vereniging voor Ziekenhuizen (NVZ) hebben landelijke afspraken gemaakt over de implementatie van de onderwerpen van de implementatieagenda. Deze afspraken zijn onderdeel van de zorginkoopafspraken tussen zorgverzekeraars en zorgaanbieders.

Vanuit FMS worden sterke, goed onderbouwde aanbevelingen, getoetst op de behoefte aan een implementatie impuls aangedragen. Voor de beoordeling van onderwerpen uit richtlijnen wordt gekeken naar bovenstaande tabel voor een inschatting van de implementatie impuls. Met de ingevulde implementatietabel kunnen we vanuit FMS de andere HLA-MSZ partijen goed informeren om zo samen te beslissen of de aanbeveling daadwerkelijk op de implementatie agenda zal worden geplaatst.

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Lee JE, Song JJ, Oh SH, Chang SO, Kim CH, Lee JH. Prognostic value of extension patterns on follow-up magnetic resonance imaging in patients with necrotizing otitis externa. Arch Otolaryngol Head Neck Surg. 2011 Jul;137(7):688-93. doi: 10.1001/archoto.2011.98. PMID: 21768413.

van der Meer WL, Mitea C, Waterval JJ, Kunst HPM, Mottaghy FM, Postma AA. The Role of F18-FDG PET-MRI in Necrotising External Otitis Follow-Up: A Single Centre Experience. Ann Otolaryngol Rhinol 2023; 10(2): 1313

Stern Shavit S, Bernstine H, Sopov V, Nageris B, Hilly O. FDG-PET/CT for diagnosis and follow-up of necrotizing (malignant) external otitis. Laryngoscope. 2019 Apr;129(4):961-966. doi: 10.1002/lary.27526. Epub 2018 Dec 14. PMID: 30549258.

Thanneru S, Sikka K, Bhalla AS, Tripathi M, Thakar A, Singh A, Singh CA, Verma H. Deciding treatment end point in necrotizing otitis externa: validation of a standardized clinical response assessment strategy with positron emission tomography findings. Eur Arch Otorhinolaryngol. 2025 Mar;282(3):1171-1177. doi: 10.1007/s00405-024-09006-z. Epub 2024 Oct 11. PMID: 39394331.

Vosbeek EGM, Straatman LV, Braat AJAT, de Keizer B, Thomeer HGXM, Smit AL. Management and Outcomes of Necrotizing Otitis Externa: A Retrospective Cohort Study in a Tertiary Referral Center. Otol Neurotol Open. 2023 Nov 22;3(4):e042. doi: 10.1097/ONO.0000000000000042. PMID: 38516544; PMCID: PMC10950167.

Bijlagen bij module 8

Risk of Bias tables
Risk of bias assessment diagnostic accuracy studies (QUADAS II, 2011)

Study reference (first author, publication year)	**Patient selection**	**Index test**	**Reference standard**	**Flow and timing**	**Comments wioth respect to applicability**
Kulkarni, 2020	Was a consecutive or random sample of patients enrolled? Yes, due to single-center tertiary centre study a selection bias occured Was a case-control design avoided? yes Did the study avoid inappropriate exclusions? yes	Were the index test results interpreted without knowledge of the results of the reference standard? yes If a threshold was used, was it pre-specified? No threshold was used	Is the reference standard likely to correctly classify the target condition? Probably Were the reference standard results interpreted without knowledge of the results of the index test? no	Was there an appropriate interval between index test(s) and reference standard? yes Did all patients receive a reference standard? Because of the reference standard being multifactorial all patient recieved one or multiple factors Did patients receive the same reference standard? no Were all patients included in the analysis? yes	Are there concerns that the included patients do not match the review question? no Are there concerns that the index test, its conduct, or interpretation differ from the review question? no Are there concerns that the target condition as defined by the reference standard does not match the review question? no
Shavit, 2018	Was a consecutive or random sample of patients enrolled? Yes, due to single-center tertiary centre study a selection bias occured Was a case-control design avoided? yes Did the study avoid inappropriate exclusions? yes	Were the index test results interpreted without knowledge of the results of the reference standard? yes If a threshold was used, was it pre-specified? No threshold was used	Is the reference standard likely to correctly classify the target condition? Probably Were the reference standard results interpreted without knowledge of the results of the index test? no	Was there an appropriate interval between index test(s) and reference standard? yes Did all patients receive a reference standard? Because of the reference standard being multifactorial all patient recieved one or multiple factors Did patients receive the same reference standard? no Were all patients included in the analysis? yes	Are there concerns that the included patients do not match the review question? no Are there concerns that the index test, its conduct, or interpretation differ from the review question? no Are there concerns that the target condition as defined by the reference standard does not match the review question? no

Vosbeek, 2023	Was a consecutive or random sample of patients enrolled? Yes, due to single-center tertiary centre study a selection bias occured Was a case-control design avoided? yes Did the study avoid inappropriate exclusions? no	Were the index test results interpreted without knowledge of the results of the reference standard? yes If a threshold was used, was it pre-specified? No threshold was used	Is the reference standard likely to correctly classify the target condition? yes Were the reference standard results interpreted without knowledge of the results of the index test? no	Was there an appropriate interval between index test(s) and reference standard? yes Did all patients receive a reference standard? Because of the reference standard being multifactorial all patient recieved one or multiple factors Did patients receive the same reference standard? no Were all patients included in the analysis? yes	Are there concerns that the included patients do not match the review question? no Are there concerns that the index test, its conduct, or interpretation differ from the review question? no Are there concerns that the target condition as defined by the reference standard does not match the review question? no
Thanneru, 2024	Was a consecutive or random sample of patients enrolled? Yes, due to single-center tertiary centre study a selection bias occured Was a case-control design avoided? yes Did the study avoid inappropriate exclusions? no	Were the index test results interpreted without knowledge of the results of the reference standard? yes If a threshold was used, was it pre-specified? No threshold was used	Is the reference standard likely to correctly classify the target condition? yes Were the reference standard results interpreted without knowledge of the results of the index test? no	Was there an appropriate interval between index test(s) and reference standard? yes Did all patients receive a reference standard? Because of the reference standard being multifactorial all patient recieved one or multiple factors Did patients receive the same reference standard? no Were all patients included in the analysis? yes	Are there concerns that the included patients do not match the review question? no Are there concerns that the index test, its conduct, or interpretation differ from the review question? no Are there concerns that the target condition as defined by the reference standard does not match the review question? no

Randomization: generation of allocation sequences have to be unpredictable, for example computer generated random-numbers or drawing lots or envelopes. Examples of inadequate procedures are generation of allocation sequences by alternation, according to case record number, date of birth or date of admission.
Allocation concealment: refers to the protection (blinding) of the randomization process. Concealment of allocation sequences is adequate if patients and enrolling investigators cannot foresee assignment, for example central randomization (performed at a site remote from trial location). Inadequate procedures are all procedures based on inadequate randomization procedures or open allocation schedules..
Blinding: neither the patient nor the care provider (attending physician) knows which patient is getting the special treatment. Blinding is sometimes impossible, for example when comparing surgical with non-surgical treatments, but this should not affect the risk of bias judgement. Blinding of those assessing and collecting outcomes prevents that the knowledge of patient assignment influences the process of outcome assessment or data collection (detection or information bias). If a study has hard (objective) outcome measures, like death, blinding of outcome assessment is usually not necessary. If a study has "soft" (subjective) outcome measures, like the assessment of an X-ray, blinding of outcome assessment is necessary. Finally, data analysts should be blinded to patient assignment to prevents that knowledge of patient assignment influences data analysis.
Lost to follow-up: If the percentage of patients lost to follow-up or the percentage of missing outcome data is large, or differs between treatment groups, or the reasons for loss to follow-up or missing outcome data differ between treatment groups, bias is likely unless the proportion of missing

outcomes compared with observed event risk is not enough to have an important impact on the intervention effect estimate or appropriate imputation methods have been used.
Selective outcome reporting: Results of all predefined outcome measures should be reported; if the protocol is available (in publication or trial registry), then outcomes in the protocol and published report can be compared; if not, outcomes listed in the methods section of an article can be compared with those whose results are reported.
Other biases: Problems may include: a potential source of bias related to the specific study design used (e.g., lead-time bias or survivor bias); trial stopped early due to some data-dependent process (including formal stopping rules); relevant baseline imbalance between intervention groups; claims of fraudulent behavior; deviations from intention-to-treat (ITT) analysis; (the role of the) funding body (see also downgrading due to industry funding https://kennisinstituut.viadesk.com/do/document?id=1607796-646f63756d656e74). Note: The principles of an ITT analysis implies that (a) participants are kept in the intervention groups to which they were randomized, regardless of the intervention they actually received, (b) outcome data are measured on all participants, and (c) all randomized participants are included in the analysis.
Overall judgement of risk of bias per study and per outcome measure, including predicted direction of bias (e.g., favors experimental, or favors comparator). Note: the decision to downgrade the certainty of the evidence for a particular outcome measure is taken based on the body of evidence, i.e., considering potential bias and its impact on the certainty of the evidence in all included studies reporting on the outcome.

Table of excluded studies

Reference	Reason for exclusion
Auinger AB, Dahm V, Stanisz I, Schwarz-Nemec U, Arnoldner C. The challenging diagnosis and follow-up of skull base osteomyelitis in clinical practice. Eur Arch Otorhinolaryngol. 2021 Dec;278(12):4681-4688. doi: 10.1007/s00405-020-06576-6. Epub 2021 Jan 28. PMID: 33511482; PMCID: PMC8553694.	Wrong outcome
Maramattom BV, Ram SA, Viswam V, Nair S. Central Skull Base Osteomyelitis: Multimodality Imaging and Clinical Findings from a Large Indian Cohort. Neurol India. 2022 Sep-Oct;70(5):1911-1919. doi: 10.4103/0028-3886.359218. PMID: 36352587.	Wrong outcome
Takata J, Hopkins M, Alexander V, Bannister O, Dalton L, Harrison L, Groves E, Kanona H, Jones GL, Mohammed H, Andersson MI, Hodgson SH. Systematic review of the diagnosis and management of necrotising otitis externa: Highlighting the need for high-quality research. Clin Otolaryngol. 2023 May;48(3):381-394. doi: 10.1111/coa.14041. Epub 2023 Feb 22. PMID: 36759416.	Wrong outcome
Chhabria S, Vishnurag A. Observational Study on Clinical Features and Management of Skull Base Osteomyelitis in Hospitalised Patients at a Tertiary Care Hospital. Indian J Otolaryngol Head Neck Surg. 2023 Apr;75(Suppl 1):635-643. doi: 10.1007/s12070-023-03675-8. Epub 2023 Mar 18. PMID: 37206859; PMCID: PMC10188806.	Case report
Ismail H, Hellier WP, Batty V. Use of magnetic resonance imaging as the primary imaging modality in the diagnosis and follow-up of malignant external otitis. J Laryngol Otol. 2004 Jul;118(7):576-9. doi: 10.1258/0022215041615100. PMID: 15318971.	Wrong outcome
Lee JE, Song JJ, Oh SH, Chang SO, Kim CH, Lee JH. Prognostic value of extension patterns on follow-up magnetic resonance imaging in patients with necrotizing otitis externa. Arch Otolaryngol Head Neck Surg. 2011 Jul;137(7):688-93. doi: 10.1001/archoto.2011.98. PMID: 21768413.	Small case series

Literature search strategy

Zoekverantwoording

Algemene informatie

Cluster/richtlijn: NVKNO Osteomyelitis schedelbasis	
Uitgangsvraag/modules: Wat zijn de voor- en nadelen van MRI t.o.v. PET-CT voor de evaluatie van het therapie-effect? [prognose/impact vraag]	
Database(s): Embase.com, Ovid/Medline	Datum: 10-11-2023,12-2-2025
Periode: vanaf nvt	Talen: geen restrictie
Literatuurspecialist:Ingeborg van Dusseldorp	Rayyan review: https://rayyan.ai/reviews/839938
BMI-zoekblokken: voor verschillende opdrachten wordt (deels) gebruik gemaakt van de zoekblokken van BMI-Online https://blocks.bmi-online.nl/ Bij gebruikmaking van een volledig zoekblok zal naar de betreffende link op de website worden verwezen.	
Toelichting: **12-2-2025** Op verzoek is de strategie PET-CT toegevoegd. Daarmee verandert de vraag in: Wat zijn de voor- en nadelen van MRI of PET CT voor de evaluatie van therapie en is gezocht met de volgende 3 concepten: 1. Osteomyelitis skull base 2. MRI 3. PET-CT 10-11-2023 Voor deze vraag is gezocht op de concepten: Osteomyelitis schedelbasis EN MRI Het sleutelartikel van Kulkarni wordt gevonden. Het artikel van vader Meer wordt niet gevonden omdat het tijdschrift niet in de databases is opgenomen.	
Te gebruiken voor richtlijntekst: A systematic literature search was performed by a medical information specialist using the following bibliographic databases: Embase.com and Ovid/Medline. Both databases were searched from inception to12-2-2025 for systematic reviews, clinical trials and observational studies. Systematic searches were completed using a combination of controlled vocabulary/subject headings (e.g., Emtree-terms, MeSH) wherever they were available and natural language keywords. The overall search strategy was derived from 3 primary search concepts: (1) Osteomyelitis skull base AND ((2) MRI OR (3) PET-CT). Duplicates were removed using EndNote software. After deduplication a total of 233 records were imported for title/abstract screening. Initially, XXX studies were selected based on title and abstract screening. After reading the full text, XXX studies were excluded (see the exclusion table under the tab 'Evidence tabellen'), and XXX studies were included.	

Zoekopbrengst

	EMBASE	**OVID/MEDLINE**	**Ontdubbeld t.o.v. Rayyan**
SR	26	15	7
RCT	16	3	11

Observationele studies	130	121	55
Totaal	172	139	***233**
	EMBASE	**OVID/MEDLINE**	**Ontdubbeld**
SR	18	12	23
RCT	6	2	8
Observationele studies	82	83	129
Totaal	106	97	***160**

in Rayyan

Zoekstrategie

Embase.com

12-2-2025

No.	Query	Results
#1	'positron emission tomography-computed tomography'/exp OR 'pet-ct scanner'/exp OR (('positron*emission' NEAR/2 ('computed tomography' OR 'computer assisted' OR 'tomography computed' OR 'tomography-computed' OR 'computed tomography')):ti,ab,kw) OR (('pet' NEAR/1 'ct' NEAR/2 ('scan*' OR 'system')):ti,ab,kw)	99282
#2	'malignant otitis externa'/exp OR (((maligna* OR necroti* OR necrosis) NEAR/3 ('otitis externa' OR 'external otitis')):ti,ab,kw) OR ('otitis externa'/mj AND (maligna*:ti,kw OR necroti*:ti,kw OR necrosis:ti,kw)) OR (('osteomyelitis'/exp/mj OR 'osteomyelit*':ti,ab,kw OR osteitis:ti,ab,kw) AND ('skull'/exp/mj OR 'skull disease'/exp/mj OR skull*:ti,ab,kw OR cranial:ti,ab,kw OR cranium:ti,ab,kw)) OR 'skull base malignant osteomyelitis':ti,ab,kw	4864
#3	'nuclear magnetic resonance imaging'/exp OR 'mri scanner'/exp OR ('magnetic resonance':ab,ti AND (image:ab,ti OR images:ab,ti OR imaging:ab,ti)) OR mri:ab,ti OR mris:ab,ti OR nmr:ab,ti OR mra:ab,ti OR mras:ab,ti OR zeugmatograph*:ab,ti OR 'mr tomography':ab,ti OR 'mr tomographies':ab,ti OR 'mr tomographic':ab,ti OR 'mr imag*':ti,ab,kw OR 'proton spin':ab,ti OR ((magneti*:ab,ti OR 'chemical shift':ab,ti) AND imaging:ab,ti) OR fmri:ab,ti OR fmris:ab,ti OR rsfmri:ti,ab,kw	1577837
#4	#2 AND (#1 OR #3)	697
#5	#4 NOT ('conference abstract'/it OR 'editorial'/it OR 'letter'/it OR 'note'/it) NOT (('animal'/exp OR 'animal experiment'/exp OR 'animal model'/exp OR 'nonhuman'/exp) NOT 'human'/exp)	549
#6	'meta analysis'/exp OR 'meta analysis (topic)'/exp OR metaanaly*:ti,ab OR 'meta analy*':ti,ab OR metanaly*:ti,ab OR 'systematic review'/de OR 'cochrane database of systematic reviews'/jt OR prisma:ti,ab OR prospero:ti,ab OR (((systemati* OR scoping OR umbrella OR 'structured literature') NEAR/3 (review* OR overview*)):ti,ab) OR ((systemic* NEAR/1 review*):ti,ab) OR (((systemati* OR literature OR database* OR 'data base*') NEAR/10 search*):ti,ab) OR (((structured OR comprehensive* OR systemic*) NEAR/3 search*):ti,ab) OR (((literature NEAR/3 review*):ti,ab) AND (search*:ti,ab OR database*:ti,ab OR 'data base*':ti,ab)) OR (('data extraction':ti,ab OR 'data source*':ti,ab) AND 'study selection':ti,ab) OR ('search strategy':ti,ab AND 'selection criteria':ti,ab) OR ('data source*':ti,ab AND 'data synthesis':ti,ab) OR medline:ab OR pubmed:ab OR embase:ab OR cochrane:ab OR (((critical OR rapid) NEAR/2 (review* OR overview* OR synthes*)):ti) OR ((((critical* OR rapid*) NEAR/3 (review* OR overview* OR synthes*)):ab) AND (search*:ab OR	976433

	database*:ab OR 'data base*':ab)) OR metasynthes*:ti,ab OR 'meta synthes*':ti,ab	
#7	'clinical trial'/exp OR 'randomization'/exp OR 'single blind procedure'/exp OR 'double blind procedure'/exp OR 'crossover procedure'/exp OR 'placebo'/exp OR 'prospective study'/exp OR rct:ab,ti OR random*:ab,ti OR 'single blind':ab,ti OR 'randomised controlled trial':ab,ti OR 'randomized controlled trial'/exp OR placebo*:ab,ti	3911098
#8	'major clinical study'/de OR 'clinical study'/de OR 'case control study'/de OR 'family study'/de OR 'longitudinal study'/de OR 'retrospective study'/de OR 'prospective study'/de OR 'comparative study'/de OR 'cohort analysis'/de OR ((cohort NEAR/1 (study OR studies)):ab,ti) OR (('case control' NEAR/1 (study OR studies)):ab,ti) OR (('follow up' NEAR/1 (study OR studies)):ab,ti) OR (observational NEAR/1 (study OR studies)) OR ((epidemiologic NEAR/1 (study OR studies)):ab,ti) OR (('cross sectional' NEAR/1 (study OR studies)):ab,ti)	7922528
#9	'case control study'/de OR 'comparative study'/exp OR 'control group'/de OR 'controlled study'/de OR 'controlled clinical trial'/de OR 'crossover procedure'/de OR 'double blind procedure'/de OR 'phase 2 clinical trial'/de OR 'phase 3 clinical trial'/de OR 'phase 4 clinical trial'/de OR 'pretest posttest design'/de OR 'pretest posttest control group design'/de OR 'quasi experimental study'/de OR 'single blind procedure'/de OR 'triple blind procedure'/de OR (((control OR controlled) NEAR/6 trial):ti,ab,kw) OR (((control OR controlled) NEAR/6 (study OR studies)):ti,ab,kw) OR (((control OR controlled) NEAR/1 active):ti,ab,kw) OR 'open label*':ti,ab,kw OR (((double OR two OR three OR multi OR trial) NEAR/1 (arm OR arms)):ti,ab,kw) OR ((allocat* NEAR/10 (arm OR arms)):ti,ab,kw) OR placebo*:ti,ab,kw OR 'sham-control*':ti,ab,kw OR (((single OR double OR triple OR assessor) NEAR/1 (blind* OR masked)):ti,ab,kw) OR nonrandom*:ti,ab,kw OR 'non-random*':ti,ab,kw OR 'quasi-experiment*':ti,ab,kw OR crossover:ti,ab,kw OR 'cross over':ti,ab,kw OR 'parallel group*':ti,ab,kw OR 'factorial trial':ti,ab,kw OR ((phase NEAR/5 (study OR trial)):ti,ab,kw) OR ((case* NEAR/6 (matched OR control*)):ti,ab,kw) OR ((match* NEAR/6 (pair OR pairs OR cohort* OR control* OR group* OR healthy OR age OR sex OR gender OR patient* OR subject* OR participant*)):ti,ab,kw) OR ((propensity NEAR/6 (scor* OR match*)):ti,ab,kw) OR versus:ti OR vs:ti OR compar*:ti OR ((compar* NEAR/1 study):ti,ab,kw) OR (('major clinical study'/de OR 'clinical study'/de OR 'cohort analysis'/de OR 'observational study'/de OR 'cross-sectional study'/de OR 'multicenter study'/de OR 'correlational study'/de OR 'follow up'/de OR cohort*:ti,ab,kw OR 'follow up':ti,ab,kw OR followup:ti,ab,kw OR longitudinal*:ti,ab,kw OR prospective*:ti,ab,kw OR retrospective*:ti,ab,kw OR observational*:ti,ab,kw OR 'cross sectional*':ti,ab,kw OR cross?ectional*:ti,ab,kw OR multicent*:ti,ab,kw OR 'multi-cent*':ti,ab,kw OR consecutive*:ti,ab,kw) AND (group:ti,ab,kw OR groups:ti,ab,kw OR subgroup*:ti,ab,kw OR versus:ti,ab,kw OR vs:ti,ab,kw OR compar*:ti,ab,kw OR 'odds ratio*':ab OR 'relative odds':ab OR 'risk ratio*':ab OR 'relative risk*':ab OR 'rate ratio':ab OR aor:ab OR arr:ab OR rrr:ab OR (('or' OR 'rr') NEAR/6 ci):ab)))	14563337
#10	#5 AND #6	26
#11	#5 AND #7 NOT #10	16
#12	#5 AND (#8 OR #9) NOT #10 NOT #11	130
#13	#10 OR #11 OR #12	172
#14	'in the evaluation of patients with skull base osteomyelitis, does':ti	1
#15	#13 AND #14	1

10-11-2023

No.	Query	Results
#2	'malignant otitis externa'/exp/mj OR (((maligna* OR necroti* OR necrosis) NEAR/3 ('otitis externa' OR 'external otitis')):ti,kw) OR ('otitis externa'/mj AND	3456

	(maligna*:ti,kw OR necroti*:ti,kw OR necrosis:ti,kw)) OR (('osteomyelitis'/exp/mj OR 'osteomyelitis':ti,kw OR osteitis:ti,kw) AND ('skull'/exp/mj OR 'skull disease'/exp/mj OR skull*:ti,ab,kw OR cranial:ti,ab,kw OR cranium:ti,ab,kw))	
#3	'nuclear magnetic resonance imaging'/exp OR 'mri scanner'/exp OR ('magnetic resonance':ab,ti AND (image:ab,ti OR images:ab,ti OR imaging:ab,ti)) OR mri:ab,ti OR mris:ab,ti OR nmr:ab,ti OR mra:ab,ti OR mras:ab,ti OR zeugmatograph*:ab,ti OR 'mr tomography':ab,ti OR 'mr tomographies':ab,ti OR 'mr tomographic':ab,ti OR 'mr imag*':ti,ab,kw OR 'proton spin':ab,ti OR ((magneti*:ab,ti OR 'chemical shift':ab,ti) AND imaging:ab,ti) OR fmri:ab,ti OR fmris:ab,ti OR rsfmri:ti,ab,kw	1577837
#4	#2 AND #3	605
#5	#4 NOT ('conference abstract'/it OR 'editorial'/it OR 'letter'/it OR 'note'/it) NOT (('animal'/exp OR 'animal experiment'/exp OR 'animal model'/exp OR 'nonhuman'/exp) NOT 'human'/exp)	484
#6	'meta analysis'/exp OR 'meta analysis (topic)'/exp OR metaanaly*:ti,ab OR 'meta analy*':ti,ab OR metanaly*:ti,ab OR 'systematic review'/de OR 'cochrane database of systematic reviews'/jt OR prisma:ti,ab OR prospero:ti,ab OR (((systemati* OR scoping OR umbrella OR 'structured literature') NEAR/3 (review* OR overview*)):ti,ab) OR ((systemic* NEAR/1 review*):ti,ab) OR (((systemati* OR literature OR database* OR 'data base*') NEAR/10 search*):ti,ab) OR (((structured OR comprehensive* OR systemic*) NEAR/3 search*):ti,ab) OR (((literature NEAR/3 review*):ti,ab) AND (search*:ti,ab OR database*:ti,ab OR 'data base*':ti,ab)) OR (('data extraction':ti,ab OR 'data source*':ti,ab) AND 'study selection':ti,ab) OR ('search strategy':ti,ab AND 'selection criteria':ti,ab) OR ('data source*':ti,ab AND 'data synthesis':ti,ab) OR medline:ab OR pubmed:ab OR embase:ab OR cochrane:ab OR (((critical OR rapid) NEAR/2 (review* OR overview* OR synthes*)):ti) OR ((((critical* OR rapid*) NEAR/3 (review* OR overview* OR synthes*)):ab) AND (search*:ab OR database*:ab OR 'data base*':ab)) OR metasynthes*:ti,ab OR 'meta synthes*':ti,ab	976433
#7	'clinical trial'/exp OR 'randomization'/exp OR 'single blind procedure'/exp OR 'double blind procedure'/exp OR 'crossover procedure'/exp OR 'placebo'/exp OR 'prospective study'/exp OR rct:ab,ti OR random*:ab,ti OR 'single blind':ab,ti OR 'randomised controlled trial':ab,ti OR 'randomized controlled trial'/exp OR placebo*:ab,ti	3911098
#8	'major clinical study'/de OR 'clinical study'/de OR 'case control study'/de OR 'family study'/de OR 'longitudinal study'/de OR 'retrospective study'/de OR 'prospective study'/de OR 'comparative study'/de OR 'cohort analysis'/de OR ((cohort NEAR/1 (study OR studies)):ab,ti) OR (('case control' NEAR/1 (study OR studies)):ab,ti) OR (('follow up' NEAR/1 (study OR studies)):ab,ti) OR (observational NEAR/1 (study OR studies)) OR ((epidemiologic NEAR/1 (study OR studies)):ab,ti) OR (('cross sectional' NEAR/1 (study OR studies)):ab,ti)	7922528
#9	'case control study'/de OR 'comparative study'/exp OR 'control group'/de OR 'controlled study'/de OR 'controlled clinical trial'/de OR 'crossover procedure'/de OR 'double blind procedure'/de OR 'phase 2 clinical trial'/de OR 'phase 3 clinical trial'/de OR 'phase 4 clinical trial'/de OR 'pretest posttest design'/de OR 'pretest posttest control group design'/de OR 'quasi experimental study'/de OR 'single blind procedure'/de OR 'triple blind procedure'/de OR (((control OR controlled) NEAR/6 trial):ti,ab,kw) OR (((control OR controlled) NEAR/6 (study OR studies)):ti,ab,kw) OR (((control OR controlled) NEAR/1 active):ti,ab,kw) OR 'open label*':ti,ab,kw OR (((double OR two OR three OR multi OR trial) NEAR/1 (arm OR arms)):ti,ab,kw) OR ((allocat* NEAR/10 (arm OR arms)):ti,ab,kw) OR placebo*:ti,ab,kw OR 'sham-control*':ti,ab,kw OR (((single OR double OR triple OR assessor) NEAR/1 (blind* OR masked)):ti,ab,kw) OR nonrandom*:ti,ab,kw OR 'non-random*':ti,ab,kw OR	14563337

	'quasi-experiment*':ti,ab,kw OR crossover:ti,ab,kw OR 'cross over':ti,ab,kw OR 'parallel group*':ti,ab,kw OR 'factorial trial':ti,ab,kw OR ((phase NEAR/5 (study OR trial)):ti,ab,kw) OR ((case* NEAR/6 (matched OR control*)):ti,ab,kw) OR ((match* NEAR/6 (pair OR pairs OR cohort* OR control* OR group* OR healthy OR age OR sex OR gender OR patient* OR subject* OR participant*)):ti,ab,kw) OR ((propensity NEAR/6 (scor* OR match*)):ti,ab,kw) OR versus:ti OR vs:ti OR compar*:ti OR ((compar* NEAR/1 study):ti,ab,kw) OR (('major clinical study'/de OR 'clinical study'/de OR 'cohort analysis'/de OR 'observational study'/de OR 'cross-sectional study'/de OR 'multicenter study'/de OR 'correlational study'/de OR 'follow up'/de OR cohort*:ti,ab,kw OR 'follow up':ti,ab,kw OR followup:ti,ab,kw OR longitudinal*:ti,ab,kw OR prospective*:ti,ab,kw OR retrospective*:ti,ab,kw OR observational*:ti,ab,kw OR 'cross sectional*':ti,ab,kw OR cross?ectional*:ti,ab,kw OR multicent*:ti,ab,kw OR 'multi-cent*':ti,ab,kw OR consecutive*:ti,ab,kw) AND (group:ti,ab,kw OR groups:ti,ab,kw OR subgroup*:ti,ab,kw OR versus:ti,ab,kw OR vs:ti,ab,kw OR compar*:ti,ab,kw OR 'odds ratio*':ab OR 'relative odds':ab OR 'risk ratio*':ab OR 'relative risk*':ab OR 'rate ratio':ab OR aor:ab OR arr:ab OR rrr:ab OR ((('or' OR 'rr') NEAR/6 ci):ab)))	
#10	#5 AND #6 SR	18
#11	#5 AND #7 NOT #10 Clinical trials	6
#12	#5 AND (#8 OR #9) NOT #10 NOT #11 OBS	82
#13	#10 OR #11 OR #12	106
#14	'in the evaluation of patients with skull base osteomyelitis, does'sleutelartikel	1
#15	#13 AND #14 sleutelartikel gevonden	1
#16	'annals of otolaryngology and rhinology' Tijdschrift niet in Embase	0

Ovid/Medline
12-2-2025

#	Searches	Results
1	((maligna* or necroti* or necrosis) adj3 (otitis externa or external otitis)).ti,ab,kf. or (exp Otitis Externa/ and (maligna* or necroti* or necrosis).ti,ab,kf.) or ((exp Osteomyelitis/ or osteomyelitis.ti,ab,kf. or osteitis.ti,ab,kf.) and (exp Skull/ or skull*.ti,ab,kf. or cranial.ti,ab,kf. or cranium.ti,ab,kf.))	4480
2	exp *magnetic resonance imaging/ or ("magnetic resonance" and (image or images or imaging)).ti,ab,kf. or mri.ti,ab,kf. or mris.ti,ab,kf. or nmr.ti,ab,kf. or mra.ti,ab,kf. or mras.ti,ab,kf. or zeugmatograph*.ti,ab,kf. or "mr tomography".ti,ab,kf. or "mr tomographies".ti,ab,kf. or "mr tomographic".ti,ab,kf. or "proton spin".ti,ab,kf. or ((magneti* or "chemical shift") and imaging).ti,ab,kf. or fmri.ti,ab,kf. or fmris.ti,ab,kf. or (imag* adj3 modalit*).ti,ab,kf.	914939
3	Positron Emission Tomography Computed Tomography/ or (positron* emission adj2 (computed tomography or computer assisted or tomography computed or computed tomography)).ti,ab,kf. or (pet adj1 ct).ti,ab,kf.	54746
4	1 and (2 or 3)	373
5	4 not ((exp animals/ or exp models, animal/) not humans/) not (letter/ or comment/ or editorial/)	365
6	meta-analysis/ or meta-analysis as topic/ or (metaanaly* or meta-analy* or metanaly*).ti,ab,kf. or systematic review/ or cochrane.jw. or (prisma or prospero).ti,ab,kf. or ((systemati* or scoping or umbrella or "structured literature") adj3 (review* or overview*)).ti,ab,kf. or (systemic* adj1 review*).ti,ab,kf. or ((systemati* or literature or database* or data-base*) adj10 search*).ti,ab,kf. or	808514

	((structured or comprehensive* or systemic*) adj3 search*).ti,ab,kf. or ((literature adj3 review*) and (search* or database* or data-base*)).ti,ab,kf. or (("data extraction" or "data source*") and "study selection").ti,ab,kf. or ("search strategy" and "selection criteria").ti,ab,kf. or ("data source*" and "data synthesis").ti,ab,kf. or (medline or pubmed or embase or cochrane).ab. or ((critical or rapid) adj2 (review* or overview* or synthes*)).ti. or (((critical* or rapid*) adj3 (review* or overview* or synthes*)) and (search* or database* or data-base*)).ab. or (metasynthes* or meta-synthes*).ti,ab,kf.	
7	exp clinical trial/ or randomized controlled trial/ or exp clinical trials as topic/ or randomized controlled trials as topic/ or Random Allocation/ or Double-Blind Method/ or Single-Blind Method/ or (clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or controlled clinical trial or randomized controlled trial or multicenter study or clinical trial).pt. or random*.ti,ab. or (clinic* adj trial*).tw. or ((singl* or doubl* or treb* or tripl*) adj (blind$3 or mask$3)).tw. or Placebos/ or placebo*.tw.	2845064
8	Epidemiologic studies/ or case control studies/ or exp cohort studies/ or Controlled Before-After Studies/ or Case control.tw. or cohort.tw. or Cohort analy$.tw. or (Follow up adj (study or studies)).tw. or (observational adj (study or studies)).tw. or Longitudinal.tw. or Retrospective*.tw. or prospective*.tw. or consecutive*.tw. or Cross sectional.tw. or Cross-sectional studies/ or historically controlled study/ or interrupted time series analysis/ [Onder exp cohort studies vallen ook longitudinale, prospectieve en retrospectieve studies]	4959968
9	Case-control Studies/ or clinical trial, phase ii/ or clinical trial, phase iii/ or clinical trial, phase iv/ or comparative study/ or control groups/ or controlled before-after studies/ or controlled clinical trial/ or double-blind method/ or historically controlled study/ or matched-pair analysis/ or single-blind method/ or (((control or controlled) adj6 (study or studies or trial)) or (compar* adj (study or studies)) or ((control or controlled) adj1 active) or "open label*" or ((double or two or three or multi or trial) adj (arm or arms)) or (allocat* adj10 (arm or arms)) or placebo* or "sham-control*" or ((single or double or triple or assessor) adj1 (blind* or masked)) or nonrandom* or "non-random*" or "quasi-experiment*" or "parallel group*" or "factorial trial" or "pretest posttest" or (phase adj5 (study or trial)) or (case* adj6 (matched or control*)) or (match* adj6 (pair or pairs or cohort* or control* or group* or healthy or age or sex or gender or patient* or subject* or participant*)) or (propensity adj6 (scor* or match*))).ti,ab,kf. or (confounding adj6 adjust*).ti,ab. or (versus or vs or compar*).ti. or ((exp cohort studies/ or epidemiologic studies/ or multicenter study/ or observational study/ or seroepidemiologic studies/ or (cohort* or 'follow up' or followup or longitudinal* or prospective* or retrospective* or observational* or multicent* or 'multi-cent*' or consecutive*).ti,ab,kf.) and ((group or groups or subgroup* or versus or vs or compar*).ti,ab,kf. or ('odds ratio*' or 'relative odds' or 'risk ratio*' or 'relative risk*' or aor or arr or rrr).ab. or (("OR" or "RR") adj6 CI).ab.))	5907260
10	4 and 6	15
11	(4 and 7) not 10	3
12	(4 and (8 or 9)) not 10 not 11	121
13	10 or 11 or 12	139

10-11-2023

#	Searches	Results
1	((maligna* or necroti* or necrosis) adj3 ('otitis externa' or 'external otitis')).ti,kf. or (exp *Otitis Externa/ and (maligna* or necroti* or necrosis).ti,kf.) or ((exp *Osteomyelitis/ or 'osteomyelitis'.ti,kf. or osteitis.ti,kf.) and (exp Skull/ or skull*.ti,ab,kf. or cranial.ti,ab,kf. or cranium.ti,ab,kf.))	3139
2	exp *magnetic resonance imaging/ or ("magnetic resonance" and (image or images or imaging)).ti,ab,kf. or mri.ti,ab,kf. or mris.ti,ab,kf. or nmr.ti,ab,kf. or mra.ti,ab,kf. or mras.ti,ab,kf. or zeugmatograph*.ti,ab,kf. or "mr tomography".ti,ab,kf. or "mr tomographies".ti,ab,kf. or "mr tomographic".ti,ab,kf. or "proton spin".ti,ab,kf. or ((magneti* or "chemical shift") and imaging).ti,ab,kf. or fmri.ti,ab,kf. or fmris.ti,ab,kf. or (imag* adj3 modalit*).ti,ab,kf.	849591
3	1 and 2	251
4	3 not ((exp animals/ or exp models, animal/) not humans/) not (letter/ or comment/ or editorial/)	247
5	meta-analysis/ or meta-analysis as topic/ or (metaanaly* or meta-analy* or metanaly*).ti,ab,kf. or systematic review/ or cochrane.jw. or (prisma or prospero).ti,ab,kf. or ((systemati* or scoping or umbrella or "structured literature") adj3 (review* or overview*)).ti,ab,kf. or (systemic* adj1 review*).ti,ab,kf. or ((systemati* or literature or database* or data-base*) adj10 search*).ti,ab,kf. or ((structured or comprehensive* or systemic*) adj3 search*).ti,ab,kf. or ((literature adj3 review*) and (search* or database* or data-base*)).ti,ab,kf. or (("data extraction" or "data source*") and "study selection").ti,ab,kf. or ("search strategy" and "selection criteria").ti,ab,kf. or ("data source*" and "data synthesis").ti,ab,kf. or (medline or pubmed or embase or cochrane).ab. or ((critical or rapid) adj2 (review* or overview* or synthes*)).ti. or (((critical* or rapid*) adj3 (review* or overview* or synthes*)) and (search* or database* or data-base*)).ab. or (metasynthes* or meta-synthes*).ti,ab,kf.	705919
6	exp clinical trial/ or randomized controlled trial/ or exp clinical trials as topic/ or randomized controlled trials as topic/ or Random Allocation/ or Double-Blind Method/ or Single-Blind Method/ or (clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or controlled clinical trial or randomized controlled trial or multicenter study or clinical trial).pt. or random*.ti,ab. or (clinic* adj trial*).tw. or ((singl* or doubl* or treb* or tripl*) adj (blind$3 or mask$3)).tw. or Placebos/ or placebo*.tw.	2654379
7	Epidemiologic studies/ or case control studies/ or exp cohort studies/ or Controlled Before-After Studies/ or Case control.tw. or cohort.tw. or Cohort analy$.tw. or (Follow up adj (study or studies)).tw. or (observational adj (study or studies)).tw. or Longitudinal.tw. or Retrospective*.tw. or prospective*.tw. or consecutive*.tw. or Cross sectional.tw. or Cross-sectional studies/ or historically controlled study/ or interrupted time series analysis/ [Onder exp cohort studies vallen ook longitudinale, prospectieve en retrospectieve studies]	4576875
8	Case-control Studies/ or clinical trial, phase ii/ or clinical trial, phase iii/ or clinical trial, phase iv/ or comparative study/ or control groups/ or controlled before-after studies/ or controlled clinical trial/ or double-blind method/ or historically controlled study/ or matched-pair analysis/ or single-blind method/ or (((control or controlled) adj6 (study or studies or trial)) or (compar* adj (study or studies)) or ((control or	5552579

	controlled) adj1 active) or "open label*" or ((double or two or three or multi or trial) adj (arm or arms)) or (allocat* adj10 (arm or arms)) or placebo* or "sham-control*" or ((single or double or triple or assessor) adj1 (blind* or masked)) or nonrandom* or "non-random*" or "quasi-experiment*" or "parallel group*" or "factorial trial" or "pretest posttest" or (phase adj5 (study or trial)) or (case* adj6 (matched or control*)) or (match* adj6 (pair or pairs or cohort* or control* or group* or healthy or age or sex or gender or patient* or subject* or participant*)) or (propensity adj6 (scor* or match*))).ti,ab,kf. or (confounding adj6 adjust*).ti,ab. or (versus or vs or compar*).ti. or ((exp cohort studies/ or epidemiologic studies/ or multicenter study/ or observational study/ or seroepidemiologic studies/ or (cohort* or 'follow up' or followup or longitudinal* or prospective* or retrospective* or observational* or multicent* or 'multi-cent*' or consecutive*).ti,ab,kf.) and ((group or groups or subgroup* or versus or vs or compar*).ti,ab,kf. or ('odds ratio*' or 'relative odds' or 'risk ratio*' or 'relative risk*' or aor or arr or rrr).ab. or (("OR" or "RR") adj6 CI).ab.))	
9	3 and 5SR	12
10	(3 and 6) not 9 Clinical trials	2
11	(3 and (7 or 8)) not 9 not 10 OBS	83
12	9 or 10 or 11	97
13	"The role of F18-FDG PET-MRI in necrotizing external otitis follow-up" [Article Title]	0
14	"Annals of Otolaryngology and Rhinology$" [Journal Name]	0

Module 9 – Additional conditions and optimizing care

Question

1. What is the added value of intensifying diabetes regulation, or detecting/correcting deficiencies, in the treatment of necrotizing otitis externa?
2. Which conditions should be met in the organization around patients with NOE?

Introduction

The development of necrotizing otitis externa is the result of a combination of factors. In the majority of patients, comorbidities are present. The most well-known and common of those is diabetes mellitus, which in itself leads to immune dysfunction, especially if poorly regulated. There are also other causes of immune dyfunction, some of which may be easily correctable such as iron or vitamin defiencies, which may increase the likelihood of developing NOE. Because treatment of NOE can be challenging and outcomes are often poor, addressing the potentially underlying causes should be considerered. This approach could also help prevent potential relapses.

Many patients will often already receive treatment for these underlying causes. Additionally, there is an added burden on healthcare systems to detect relevant deficiencies. The question is whether optimizing the treatment of known comorbidities, as well as detecting and treating new conditions, will lead to better patient outcomes and whether this justifies the additional use of healthcare resources.

The diagnosis and management of NOE implies a multidisciplinary approach. Taking into consideration a long trajectory of the patient with NOE until recovery, it is essential to discuss the possibility of therapy in an ambulatory setting. This could have a positive influence on the associated healthcare costs and occupancy of beds.

Search and select

What is the effect of intensifying diabetes treatment and/or detecting and correcting deficiencies

Table 1. PICO

Patients	Patients with proven necrotizing otitis externa
Intervention	Optimization of the immune system (referral to an internist for diabetes control/referral to a doctor who can address deficiencies)
Control	No referral/standard of care
Outcomes	Remission, length of treatment, mortality
Other selection criteria	Study design: systematic reviews and randomized controlled trials, cohort studies and other comparative research [Minimal follow-up: 3 months]

<u>Relevant outcome measures</u>

The guideline panel considered remission, length of treatment and mortality as **critical** outcome measures for decision making;

The guideline panel defined the outcome measures as follows:

- Remission: rate of curation of disease. Defined after prolonged disappearance of the signs and symptoms of a disease.

- Length of treatment: Days/weeks until the treatment for NOE was stopped
- (Disease specific) Mortality: number of deaths, caused by the effects of necrotizing otitis externa

The guideline panel defined the following as a minimal clinically important difference.

- Remission: GRADE standard limits*
- Length of treatment: GRADE standard limits*
- Mortality: GRADE standard limits*

Search and select (Methods)

The databases [Medline (via OVID) and Embase (via Embase.com)] were searched with relevant search terms until 30 september 2024. The detailed search strategy is listed under the tab 'Literature search strategy'. The systematic literature search resulted in 982 hits. Studies were selected based on the following criteria: Systematic reviews, RCTs, observational and other studies on the added value of intensifying diabetes regulation, or detecting/correcting deficiencies, in the treatment of malignant otitis externa. One hundred and twenty-eight studies were initially selected based on title and abstract screening. After reading the full text, 128 studies were excluded (see the exclusion table under the tab 'Evidence tabellen'), and no studies were included.

Summary of literature

There were no studies found in the systemic search of literature that complied with the PICO. Therefore, no systemic review of literature could be performed. However, relevant studies were found, wich will be discussed within the considerations.

Considerations – from evidence to decision

Balance between desired and undesired effects

Necrotizing otitis externa is an infectious disease. Curation of disease therefore depends on the immune system of the patient, in combination with antimicrobial therapy. Deficiencies in the immune system thereforecould lead to worse outcomes in the treatment of NOE.

Diabetes mellitus

It is generally accepted that people with diabetes mellitus are at an increased risk of serious infections, representing a significant burden on public health. A large, matched cohort study on the risk of infection in general among patients with type 1 and type 2 diabetes showed that diabetic patients had higher rates of all infections, particularly bone and joint infections, sepsis, and cellulitis (Carey, 2018). The authors estimated that 6% of infection-related hospitalizations and 12% of infection-related deaths were attributable to diabetes.

The typical profile of a patient with NOE is an elderly man with diabetes mellitus. Diabetes is the most frequently reported risk factor for NOE and is present in 84% of patients (Takata, 2023). Poorly controlled glycemic status leads to decreased cellular innate immunity, worsened microcirculation (Geerlings, 1999), and impaired neutrophil function, including chemotaxis, adherence to vascular endothelium, opsonization, and phagocytosis. Cell-mediated immunity is also affected; the methylglyoxal-glycation pathway inhibits the production of inflammatory mediators such as IL-10, IFN-gamma, and TNF-alpha from T-cells. Microvascular complications, resulting in localized ischemia due to diabetes, may hinder the penetration and absorption of antibiotics at the infection site. In the external auditory canal, the origin of the infection, the pH levels of cerumen are significantly higher, creating a favorable environment for pathogens such as *Pseudomonas aeruginosa* (Driscoll, 1993).

It could be theorized that better control of diabetes, most often in the form of glycemic control, results in better outcomes for patients with necrotizing otitis externa. However, the literature shows conflicting results regarding this matter, and it is important to note that these studies often involve small numbers of patients. Some studies indicate that there is no correlation between HbA1c levels and outcomes such as cure rates or length of treatment (Loh, 2012; Lee, 2017). In one study, high HbA1c levels were not considered a risk factor, but the duration of diabetes was associated with worse outcomes (Lee, 2018). The authors concluded that the most likely explanation was the microvascular complications developed over time. On the other hand, other studies suggest a positive correlation between HbA1c levels and outcomes (Verim, 2014; Hudson, 2019). Joshua et al. is frequently cited in other studies for reporting a correlation between a history of diabetes-related complications and longer treatment durations, as well as reduced survival rates in NOE patients. One study intensified glucose regulation in hospitalized patients with NOE and diabetes and found that intensifying diabetes therapy significantly shortened the duration of hospital stays (Peled, 2022).
In conclusion, there is insufficient evidence to support clear recommendations on diabetes management with the goal to enhance the immune response during treatment for NOE. However, it is well-known that uncontrolled diabetes leads to a worse prognosis in infections overall. Given the potential severity of NOE, optimizing glycemic control should be encouraged. The guideline panel advises blood glucose tests to identify patients with undiagnosed diabetes mellitus. For patients with known diabetes, assessing glycemic control via HbA1c testing should be considered. In cases of moderately or severely uncontrolled diabetes, consultation with an internal medicine specialist for the optimization of diabetes management is recommended.

Other (immuno)defiencies
The literature shows that immunodeficiencies other than diabetes are found in less than 10% of NOE cases (Byun, 2020; Takata, 2023). In addition to diabetes mellitus, immune dysfunction can be caused by other conditions, such as uncontrolled HIV infection, the natural aging process, or the use of immunosuppressants (e.g., medications for transplantations, autoimmune diseases, or hematologic malignancies). In cases involving immunosuppressive medication, it is important to consider possible treatment adjustments in consultation with the physician managing the underlying condition. Depending on the situation, this may involve temporarily discontinuing (some) immunosuppressants, reducing the dosage, or postponing the initiation of immunosuppressive therapy.

Another category of vulnerable patients includes those with vitamin or iron deficiencies, malnutrition, significant unintentional weight loss, or alcoholism. People with nutritional deficiencies are generally considered more susceptible to infections. Over the past two decades, numerous articles have been published on the correlation between vitamin D deficiency and the risk of infections in general. Vitamin D plays an immunomodulatory role, among other functions (De Haan, 2014). Iron is involved in erythropoiesis and the proper functioning of the immune system, but it is also essential for microbial growth (Jonker, 2014). Chronic alcoholism interferes with the normal sequences of the immune response, including both cell-mediated and humoral responses. Additionally, it affects multiple organs, making these patients more susceptible to complicated disease courses or multiple side effects, especially when prolonged antibiotic treatment is required. Unintentional weight loss can be caused by various underlying conditions and warrants further investigation.
We did not identify articles looking for nutritional deficiencies as a risk factor for (complicated) NOE. However, given their established role in predisposing individuals to infections in general, the working group advises consultation of an internal medicine specialist and/or dietitian if

any of the above-mentioned conditions are suspected. A search for nutritional deficiencies and subsequent treatment is encouraged at the time of diagnosis (anemia, vitamin B1, B12, D and folic acid deficiency).

Monitoring side effects of treatment
NOE requires long term antimicrobial therapy, during which allergic reactions or various side effects may occur. One of the most frequent adverse reactions are the following (not exhaustive): diarrea with *Clostridium difficile*, renal failure, long QT syndrome with possible torsades de pointes, liver test abnormalities, cytopenia. There are also more specifically adverse events: e.g., tendon rupture due to long-term ciprofloxacine-use. If there are many or severe side effects under voriconazole, it could be because of CYP2C19 polymorphism in slow metabolizers. Voriconazol is also known to have multiple drug-drug interactions as it is an inhibitor of CYP3A4, CYP2C19 and CYP2C9.).
Standard lab tests should be performed every 1-2 weeks. Consider contacting an internal medicine specialist in case of using glycopeptides, aminoglycosides or azoles for specific advice.

Outpatient healthcare (OPAT)
Given the long duration of systemic antibiotic treatment, outpatient parenteral antimicrobial therapy (OPAT) could be a useful option to reduce healthcare costs, decrease hospital bed occupancy, and improve patient comfort. OPAT has been already used for many infections in the daily practice in order to decrease the burden of the hospital without endangering the efficiency of the therapy.
OPAT is indicated when oral therapy is not suitable due to antimicrobial resistance, drug interactions, intolerance, poor adherence, or poor oral absorption. A recent study focused on NOE (Durojaiye, 2022) investigated factors associated with treatment response. OPAT failure and prolonged intravenous (IV) antimicrobial therapy were recorded in 9 (19.6%) and 23 (50.0%) episodes, respectively. OPAT failure (implied as failure of treatment or the impossibility/impracticality of treatment outside of the hospital) was associated with facial nerve involvement, dementia, Charlson comorbidity score, and peak CRP levels. Prolonged duration of IV antimicrobial therapy was correlated with the extent of disease (based on imaging findings), facial nerve involvement, and peak CRP levels.
The guideline panel recommends the use of OPAT for patients requiring IV therapy, considering the long duration of NOE treatment and the positive outcomes observed in daily practice for various infections.

<u>Quality of the evidence</u>
As the systemic search of literature found no studies that reported the selected outcomes, considerations and recommendations were based on expert opinion and known literature. the overall quality of evidence is therefore very low.

<u>Values and preferences of patients (and possibly their relatives/caregivers)</u>
As previously mentioned, OPAT significantly decreases hospital stay and has therefore an often positive effect on patient comfort.

<u>Costs</u>
The opinion of internal medicine specialists (or other specialists who prescribe immunossupressive therapy or treat underlying diseases) could be asked for during multidisciplinary disscussions. A referral to such a specialist is not always necessary. Optimizing diabetes medication could be done sometimes by GP - general practioner. No studies on cost-effectiveness were identified for NOE. However, extrapolating from

experience with other infections, costs during OPAT are supposed to be lower than costs during hospitalization.

Equity
The guideline panel expects no problems with health equity with regard to medical treatment of necrotizing otitis externa.

Acceptibility
Diabetes mellitus and other immunodeficiencies are reported to increase the susceptibility for infections in general.
OPAT has been already used for many infections in the daily practice.

Feasibility
The feasibility of OPAT depends on outpatient healthcare system in each country.

Recommendation(s)
Rationale of the recommendation: weighing arguments for and against the interventions
Recommendation-1
Every patient should have baseline bloodtests, inclusively blood cell count, eGFR, liver tests, CRP/ESR and an HbA1c check performed at diagnosis. The cost of these tests are low especially in the context of difficult to treat infections, with potential life-threatening course. Periodical bloodtests every 1-2 weeks for side effects or evolution of disease and awareness of possible complications are needed. If the infection parameters are elevated at the start of treatment, it appears advisable to monitor them throughout the course of the treatment as an additional indicator of treatment success.
A suboptimal control of diabetes could jeopardize the good course of NOE because diabetes leads to microangiopathy and impaired polymorphonuclear and T cell function. Because of the poor microcirculation secondary to small vessel obliteration, the antibiotics penetrate less in these areas. Various forms of immunosupression are generally accepted as risk factors for complicated evolutions of infections.
Seeing the possible severe complications of NOE, e.g., skull base osteomyelitis with life threatening course, a special attention should be given both to immediate diagnosis and management of NOE itself and also to controlling associated diseases (diabetes, immunosuppression).
Referral to internal medicine or other specialties could generate higher costs. It is still encouraged mostly if underlying disease is not under control or if bloodtests identifies new underlying clinical entity (important side effects, nutritional deficiencies, other diseases) In case of immunosuppressants, it is adviced to evaluate the pros en cons of adjusting this treatment with the responsible treating physicianuntil the resolution of NOE.

Assess general blood values, including blood cell count, eGFR, liver function, HbA1c, CRP/ESR in every patient with necrotizing otitis externa at diagnosis (and during follow up if indicated). Consider consulting an internal medicine specialist (or physician in charge of treatment underlying disease), in case of underlying (immuno)defiencies, dysregulated diabetes mellitus or a complicated course.

Recommendation-2
Outpatient parenteral antimicrobial therapy (OPAT) has been shown to be a safe and effective alternative to hospitalisation for treatment of a wide range of infections, but there are little

studies on NOE patients. Selected patients can receive oral antibiotica. If is not feasible, OPAT could be taken into consideration in order to decrease healthcare burden (costs, occupancy of beds) and to increase the quality of life of these patients.
OPAT requires close monitoring by a specialized team of nurses and also patients who can recognize alarm symptoms. Periodical bloodtests every 1-2 weeks for side effects or evolution of disease and proactive questions to detect the these issues are needed. Some antibiotical or antifungal regimens impose controle bloodtests more frequently. A personalized plan should be discussed depending on medical history of patients and extension of NOE.

Consider outpatient parenteral antimicrobial therapy (OPAT) as a safe and efficient alternative for hospitalized intravenous therapy.

Knowledge gap
During the development of this module, a systematic search for studies addressing the research question was conducted. Through a systematic literature analysis and evidence assessment, it became clear that there are still knowledge gaps within this module. The working group believes that further research is necessary to provide clearer answers to practical questions in the future.

Question
What is the added value of intensifying diabetes regulation, or detecting/correcting deficiencies, in the treatment of necrotizing otitis externa?

Explanation
As no studies were found, that clearly answered the original search question, it should be further researched. Preferrably by a randomized control study.

Verkeerslicht en (de-)implementatietabel

Toelichting
Met het verkeerslicht worden aanbevelingen gecategoriseerd op basis van formulering en bewijskracht. Als eindproduct wordt bij richtlijnmodules met een sterk geformuleerde en voldoende onderbouwde aanbeveling een implementatietabel opgeleverd. Hierin wordt onder andere opgenomen:

- Een beschrijving van het knelpunt om de module uit te werken of herzien;
- De te verwachten belemmerende en bevorderende factoren voor implementatie;
- Welke partijen van belang zijn bij toepassen van de aanbeveling in de praktijk;
- Een inschatting van de implementatietermijn.

Verkeerslichtanalyse

- **ROOD** = sterk geformuleerde aanbeveling om iets niet te doen, met een GRADE high of moderate
- **ORANJE** = zwak geformuleerde aanbeveling; mogelijk kennishiaat
- **GROEN** = sterk geformuleerde aanbeveling om iets wel te doen, met een GRADE high of moderate
- **LICHT ROOD** of **LICHT GROEN** = sterk geformuleerde aanbevelingen met een GRADE low, very low of geen GRADE *(modules waarin geen studies geïncludeerd konden worden in de literatuursamenvatting of waarin geen literatuursamenvatting werd geschreven zoals modules waarin organisatie van zorg wordt beschreven)*

(Sub)aanbeveling	Sterkte van de aanbeveling	Bewijskracht per uitkomstmaat	Verkeerslicht per (sub)aanbeveling
Aanbeveling 1: Assess general blood values, including blood cell count, eGFR, liver function, HbA1c, CRP/ESR in every patient with NOE at diagnosis (and during follow up if indicated). Consider consulting an internal medicine specialist (or physician in charge of treatment underlying disease), in case of underlying (immuno)defiencies, dysregulated diabetes mellitus or a complicated course.	□ Zwak (overweeg)	**NG** **Range bewijskracht van alle uitkomstmaten** **NG** **OF** □ **voor de (sub)uitgangsvraag is geen systematische literatuur analyse uitgevoerd**	**LICHT GROEN**
Aanbeveling 2 Consider outpatient parenteral antimicrobial therapy (OPAT) as a safe and efficient alternative for hospitalized intravenous therapy.	Zwak (overweeg)	**voor de (sub)uitgangsvraag is geen systematische literatuur analyse uitgevoerd**	**LICHT GROEN**

Implementatietabel

Tabel A: (De-)Implementatietabel met impuls analyse

Aanbeveling – 1			
1. Wat was het onderliggende probleem om deze uitgangsvraag uit te werken?	□ **Ongewenste praktijkvariatie**		
2. Maak een inschatting over hoeveel patiënten het ongeveer gaat waar de aanbeveling betrekking op heeft?	□ **< 1000**		
3. Maakt de aanbeveling deel uit van een set van interventies voor hetzelfde probleem?	□ **Nee**		
4. Belemmeringen en kansen op verschillende niveaus voor landelijke toepassing van de aanbeveling:	***Voorbeelden***	**Wat zijn mogelijke belemmerende factoren?**	**Wat zijn mogelijke bevorderende factoren?**
a) **Richtlijn/ klinisch traject (innovatie)**	*Voortschrijding/vooruitgang in de praktijk, haalbaarheid, geloofwaardigheid, toegankelijkheid, aantrekkelijkheid*	-	Makkelijk haalbaar, testen zijn toegankelijk
b) **Zorgverleners (artsen en verpleegkundigen)**	*Bewustzijn, kennis, houding, motivatie om te veranderen, gedragsroutines*	-	-
c) **Patiënt/ cliënt (naasten)**	*Kennis, vaardigheden, houding, compliance*	-	-
d) **Sociale context**	*Mening van collega's, cultuur van het netwerk, samenwerking, leiderschap*	Indien geen goede samenwerking tussen specialismen, kan een	Deze richtlijn kan al houvast geven.

		internist eventueel niet in consult gevraagd	
e) **Organisatorische context**	*Organisatie van zorgprocessen, personeel, capaciteiten, middelen, structuren*	Probleem met druk op zorg indien dit tot veel verwijzingen leidt. Te veel consulten interne geneeskunde bijv.	Goed concretiseren wanneer een consult nodig lijkt, dit staat ook geformuleerd in de overwegingen
f) **Economische en politieke context**	*Financiële regelingen, regelgeving, beleid (vergoede zorg, betaaltitel)*	-	-

5. Welke personen/partijen zijn van belang bij het toepassen van de aanbeveling in de praktijk?	**x** Patiënt/ cliënt (naaste) **x** Professional
6. Wat zouden deze personen/ partijen moeten veranderen in hun gedrag of organisatie om de aanbeveling toe te passen?	*Gebeurt reeds vaak, zal dus niet een directe aanpassing noodzakelijk zijn.* *Mogelijk dat ze het in eigen ziekenhuisprotocollen moeten opnemen*
7. Binnen welk tijdsbestek moet de aanbeveling zijn geïmplementeerd?	□ < 1 jaar
8. Conclusie: is er extra aandacht nodig voor implementatie van de aanbeveling (anders dan publicatie van deze richtlijnmodule)?	□ **Nee**

Aanbeveling – 2	
1. Wat was het onderliggende probleem om deze uitgangsvraag uit te werken?	□ **Ongewenste praktijkvariatie**
2. Maak een inschatting over hoeveel patiënten het ongeveer gaat waar de aanbeveling betrekking op heeft?	□ < **1000**

3. Maakt de aanbeveling deel uit van een set van interventies voor hetzelfde probleem?	**□ Nee**		
4. Belemmeringen en kansen op verschillende niveaus voor landelijke toepassing van de aanbeveling:	***Voorbeelden***	**Wat zijn mogelijke belemmerende factoren?**	**Wat zijn mogelijke bevorderende factoren?**
a) **Richtlijn/ klinisch traject (innovatie)**	*Voortschrijding/vooruitgang in de praktijk, haalbaarheid, geloofwaardigheid, toegankelijkheid, aantrekkelijkheid*	*Kost initieel meer moeite OPAT om te regelen*	*Scheelt lange ziekenhuis opname*
b) **Zorgverleners (artsen en verpleegkundigen)**	*Bewustzijn, kennis, houding, motivatie om te veranderen, gedragsroutines*	*Kost initieel meer moeite OPAT om te regelen*	*Scheelt lange ziekenhuis opname*
c) **Patiënt/ cliënt (naasten)**	*Kennis, vaardigheden, houding, compliance*	*Is wel enige zelfzorg voor nodig, mogelijk belemmerend.*	*Goede thuiszorg*
d) **Sociale context**	*Mening van collega's, cultuur van het netwerk, samenwerking, leiderschap*	-	-
e) **Organisatorische context**	*Organisatie van zorgprocessen, personeel, capaciteiten, middelen, structuren*	*Geen goede OPAT organisatie binnen kliniek. Geen ondersteunend personeel hiervoor bijvoorbeeld.*	*Vaak kan het aantrekken van verpleegkundig specialisten de orginisatie al bevorderderen. Samen met een transferverpleegkundige. Zij kunnen inventariseren en regelen welke zaken en nodig zijn voor het OPAT.*
f) **Economische en politieke context**	*Financiële regelingen, regelgeving, beleid (vergoede zorg, betaaltitel)*	-	-

**Deze aanbeveling komt in aanmerking voor plaatsing op de Implementatie Agenda van het programma Zorg Evaluatie & Gepast Gebruik (ZE&GG). In het programma ZE&GG werken patiënten, zorgverleners, zorgaanbieders, zorgverzekeraars en overheid samen aan de bewezen beste zorg voor de patiënt. Daarmee is ZE&GG een programma van alle betrokken partijen in de Medisch Specialistische Zorg. FMS is één van deze betrokken partijen.*

De implementatieagenda van ZE&GG bevat onderwerpen over wat de bewezen beste zorg is en die in de dagelijkse zorgpraktijk geïmplementeerd zouden moeten worden. Zorgverzekeraars Nederland (ZN) en de Nederlandse Vereniging voor Ziekenhuizen (NVZ) hebben landelijke afspraken gemaakt over de implementatie van de onderwerpen van de implementatieagenda. Deze afspraken zijn onderdeel van de zorginkoopafspraken tussen zorgverzekeraars en zorgaanbieders.

Vanuit FMS worden sterke, goed onderbouwde aanbevelingen, getoetst op de behoefte aan een implementatie impuls aangedragen. Voor de beoordeling van onderwerpen uit richtlijnen wordt gekeken naar bovenstaande tabel voor een inschatting van de implementatie impuls. Met de ingevulde implementatietabel kunnen we vanuit FMS de andere HLA-MSZ partijen goed informeren om zo samen te beslissen of de aanbeveling daadwerkelijk op de implementatie agenda zal worden geplaatst.

Literature

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Verim A, Naiboğlu B, Karaca Ç, Seneldir L, Külekçi S, Oysu Ç. Clinical outcome parameters for necrotizing otitis externa. Otol Neurotol. 2014 Feb;35(2):371-6. doi: 10.1097/MAO.0000000000000249. PMID: 24448298.

Bijlagen bij module 9

Risk of Bias tables
Not applicable

Table of excluded studies

Reference	Reason for exclusion
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Chin R, Roche P, Sigston E, Valance N. Malignant otitis externa: an Australian case series. Surgeon. 2012 Oct;10(5):273-7. doi: 10.1016/j.surge.2011.09.004. Epub 2011 Oct 26. PMID: 22032882.	Observational study, without intervention (No comparison made)
Hutson KH, Watson GJ. Malignant otitis externa, an increasing burden in the twenty-first century: review of cases in a UK teaching hospital, with a proposed algorithm for diagnosis and management. J Laryngol Otol. 2019 May;133(5):356-362. doi: 10.1017/S0022215119000604. Epub 2019 Apr 12. PMID: 30975233.	Observational study, without intervention (No comparison made)
Jamshidi A, Zonnour A, Dabiri S, Hasibi M, Tajdini A, Karrabi N, Yazdani N. Predictive role of facial nerve palsy improvement in malignant external otitis. Eur Arch Otorhinolaryngol. 2024 Mar;281(3):1253-1258. doi: 10.1007/s00405-023-08230-3. Epub 2023 Sep 19. PMID: 37725133.	Observational study, without intervention (No comparison made)

Krawiec E, Brenet E, Truong F, Nguyen Y, Papthanassiou D, Labrousse M, Dubernard X. Epidemiology and risk factors for extension of necrotizing otitis externa. Eur Arch Otorhinolaryngol. 2024 May;281(5):2383-2394. doi: 10.1007/s00405-024-08549-5. Epub 2024 Mar 18. Erratum in: Eur Arch Otorhinolaryngol. 2024 Jun;281(6):3317-3318. doi: 10.1007/s00405-024-08638-5. PMID: 38499694.	Wrong outcome
Lee SK, Lee SA, Seon SW, Jung JH, Lee JD, Choi JY, Kim BG. Analysis of Prognostic Factors in Malignant External Otitis. Clin Exp Otorhinolaryngol. 2017 Sep;10(3):228-235. doi: 10.21053/ceo.2016.00612. Epub 2016 Sep 27. PMID: 27671716; PMCID: PMC5545692.	Observational study, without intervention (No comparison made),
Loh S, Loh WS. Malignant otitis externa: an Asian perspective on treatment outcomes and prognostic factors. Otolaryngol Head Neck Surg. 2013 Jun;148(6):991-6. doi: 10.1177/0194599813482107. Epub 2013 Apr 4. PMID: 23558287.	Wrong outcome
Mahdyoun P, Pulcini C, Gahide I, Raffaelli C, Savoldelli C, Castillo L, Guevara N. Necrotizing otitis externa: a systematic review. Otol Neurotol. 2013 Jun;34(4):620-9. doi: 10.1097/MAO.0b013e3182804aee. PMID: 23598690.	Observational study, without intervention (No comparison made)
MULLAPUDI, H., and S. AV. “MALIGNANT OTITIS EXTERNA – OUR EXPERIENCE”. Asian Journal of Pharmaceutical and Clinical Research, vol. 15, no. 4, Apr. 2022, pp. 61-62, doi:10.22159/ajpcr.2022.v15i4.43974.	Observational study, without intervention (No comparison made)
Peled C, Sadeh R, El-Saied S, Novack V, Kaplan DM. Diabetes and glycemic control in necrotizing otitis externa (NOE). Eur Arch Otorhinolaryngol. 2022 Mar;279(3):1269-1275. doi: 10.1007/s00405-021-06772-y. Epub 2021 Apr 1. PMID: 33792784.	Observational study, without intervention (No comparison made)
Saidha PK, Kakkar V, Das P, Kapoor S. Malignant Otitis Externa: Association of Biochemical Markers with Staging of the Disease and Emergence of Methicillin Resistant Staphylococcus aureus as a Causative Agent. Int J Otorhinolaryngol Clin 2023; 15 (1):14-18.	Wrong outcome
Saxena A, Paul BS, Singh G, Ahluwalia A, Paul G. Predicting Outcome in Skull Base Osteomyelitis: An Assessment of Demographic, Clinical, and Pathological Attributes. J Neurosci Rural Pract. 2021 Sep 28;12(4):751-757. doi: 10.1055/s-0041-1735324. PMID: 34737511; PMCID: PMC8559086.	Observational study, without intervention (No comparison made)
Sekar R, Raja K, Ganesan S, Alexander A, Saxena SK. Clinical and Current Microbiological Profile with Changing Antibiotic Sensitivity in Malignant Otitis Externa. Indian J Otolaryngol Head Neck Surg. 2022 Dec;74(Suppl 3):4422-4427. doi: 10.1007/s12070-021-	Observational study, without intervention (No comparison made)

03068-9. Epub 2022 Jan 22. PMID: 36742648; PMCID: PMC9895493.	
Tsilivigkos C, Avramidis K, Ferekidis E, Doupis J. Malignant External Otitis: What the Diabetes Specialist Should Know-A Narrative Review. Diabetes Ther. 2023 Apr;14(4):629-638. doi: 10.1007/s13300-023-01390-9. Epub 2023 Mar 10. PMID: 36897495; PMCID: PMC10064349.	Observational study, without intervention (No comparison made)
Upreti G, Thomas R, Sundaresan R, Rebekah G, Rupali P, Jasper A. Clinico-Radiological Evaluation for Longitudinal Assessment in Central Skull Base Osteomyelitis: Proposal of Novel Scoring System. Indian J Otolaryngol Head Neck Surg. 2023 Dec;75(4):3553-3564. doi: 10.1007/s12070-023-03956-2. Epub 2023 Jul 4. PMID: 37974699; PMCID: PMC10646027.	Overview of literature
Verim A, Naiboğlu B, Karaca Ç, Seneldir L, Külekçi S, Oysu Ç. Clinical outcome parameters for necrotizing otitis externa. Otol Neurotol. 2014 Feb;35(2):371-6. doi: 10.1097/MAO.0000000000000249. PMID: 24448298.	Observational study, without intervention (No comparison made)
Zonnour A, Jamshidi A, Dabiri S, Hasibi M, Tajdini A, Karrabi N, Yazdani N. Predictive factors in treatment response of malignant external otitis. Eur Arch Otorhinolaryngol. 2023 Jan;280(1):159-166. doi: 10.1007/s00405-022-07478-5. Epub 2022 Jun 25. PMID: 35751693.	Observational study, without intervention (No comparison made)
Al-Noury K, Lotfy A. Computed tomography and magnetic resonance imaging findings before and after treatment of patients with malignant external otitis. Eur Arch Otorhinolaryngol. 2011 Dec;268(12):1727-34. doi: 10.1007/s00405-011-1552-8. Epub 2011 Mar 15. PMID: 21400256.	Wrong outcome

Literature search strategy

Zoekverantwoording

Algemene informatie

Cluster/richtlijn: Osteomyelitis schedelbasis - UV9 Medicamenteuze behandeling	
Uitgangsvraag/modules: Wat is de meerwaarde van intensiveren van diabetesregulatie, danwel opsporen/ aanvullen van deficiënties, in de behandeling maligne otitis externa?	
Database(s): Embase.com, Ovid/Medline	Datum: 30 september 2024
Periode: geen restrictie	Talen: geen restrictie
Literatuurspecialist: Esther van der Bijl	Rayyan review: https://rayyan.ai/reviews/1173104
BMI-zoekblokken: voor verschillende opdrachten wordt (deels) gebruik gemaakt van de zoekblokken van BMI-Online https://blocks.bmi-online.nl/ Deduplication: voor het ontdubbelen is gebruik gemaakt van http://dedupendnote.nl/	

Toelichting: Voor deze vraag is gezocht op de elementen maligne otitis externa EN optimalisatie immuunsysteem (verwijzing naar internist voor diabetes controle/verwijzing naar arts die deficiënties op kan lossen). Er waren geen sleutelartikelen voor deze search opgegeven.
Te gebruiken voor richtlijntekst: In de databases Embase.com en Ovid/Medline is op 30 september 2024 systematisch gezocht naar systematische reviews, RCTs, observationele - en overige studies over de meerwaarde van intensiveren van diabetesregulatie, danwel opsporen/ aanvullen van deficiënties, in de behandeling maligne otitis externa. De literatuurzoekactie leverde 982 unieke treffers op.

Zoekopbrengst 30 september 2024

	EMBASE	OVID/MEDLINE	Ontdubbeld
SR	40	25	41
RCT	32	7	36
Observationele studies	224	69	240
Overige studies	573	446	665
Totaal	869	547	**982***

in Rayyan

Zoekstrategie Embase.com 30 september 2024

No.	Query	Results
#1	'malignant otitis externa'/exp OR (((maligna* OR necroti* OR necrosis) NEAR/3 ('otitis externa' OR 'external otitis')):ti,ab,kw) OR ('otitis externa' AND (maligna*:ti,ab,kw OR necroti*:ti,ab,kw OR necrosis:ti,ab,kw)) OR (('osteomyelitis'/exp OR 'osteomyelitis':ti,ab,kw) AND ('skull'/exp OR 'skull disease'/exp OR skull*:ti,ab,kw OR cranial:ti,ab,kw OR cranium:ti,ab,kw))	6958
#2	'patient referral'/exp OR 'internal medicine'/exp OR 'internist'/exp OR 'diabetes mellitus'/exp OR 'insulin dependent diabetes mellitus'/exp OR 'non insulin dependent diabetes mellitus'/exp OR 'glycated hemoglobin'/exp OR 'hemoglobin a1c'/exp OR 'hemoglobin a1c test kit'/exp OR 'glycemic control'/exp OR ((dm NEAR/3 (1 OR 'type 1' OR 'type i' OR 2 OR 'type 2' OR 'type ii')):ti,ab,kw) OR (((doctor* OR physician* OR practitioner* OR clinical*) NEAR/3 (visit* OR exam*)):ti,ab,kw) OR (((haemoglobin* OR hb OR hba OR hemoglobin*) NEAR/3 (a1c OR 'a1' OR 1c OR aic OR 'alpha 1')):ti,ab,kw) OR (((clia OR a1c OR 1c) NEAR/3 (kit* OR test*)):ti,ab,kw) OR ((('blood glucose*' OR glycemic*) NEAR/3 (control* OR test* OR level*)):ti,ab,kw) OR (((glycated OR glycosyl OR glycosylated OR glycosylised OR glycoside OR glycosylation) NEAR/1 (haemoglobin* OR hemoglobin*)):ti,ab,kw) OR gatekeep*:ti,ab,kw OR referral*:ti,ab,kw OR consultation*:ti,ab,kw OR 'internal* medicine*':ti,ab,kw OR 'internist*':ti,ab,kw OR diabetes:ti,ab,kw OR diabetic*:ti,ab,kw OR diabets:ti,ab,kw OR iddm:ti,ab,kw OR iddm1:ti,ab,kw OR iddmi:ti,ab,kw OR t1dm:ti,ab,kw OR tidm:ti,ab,kw OR t2dm:ti,ab,kw OR tiidm:ti,ab,kw OR niddm:ti,ab,kw OR niddm2:ti,ab,kw OR niddmii:ti,ab,kw OR hba1c:ti,ab,kw OR 'dca vantage analy*':ti,ab,kw OR glycohaemoglobin*:ti,ab,kw OR	2641309

	glycohemoglobin*:ti,ab,kw OR glycosylhaemoglobin*:ti,ab,kw OR glycosylhemoglobin*:ti,ab,kw	
#3	#1 AND #2	1171
#4	#3 NOT ('conference abstract'/it OR 'editorial'/it OR 'letter'/it OR 'note'/it) NOT (('animal'/exp OR 'animal experiment'/exp OR 'animal model'/exp OR 'nonhuman'/exp) NOT 'human'/exp)	869
#5	'meta analysis'/exp OR 'meta analysis (topic)'/exp OR metaanaly*:ti,ab OR 'meta analy*':ti,ab OR metanaly*:ti,ab OR 'systematic review'/de OR 'cochrane database of systematic reviews'/jt OR prisma:ti,ab OR prospero:ti,ab OR (((systemati* OR scoping OR umbrella OR 'structured literature') NEAR/3 (review* OR overview*)):ti,ab) OR ((systemic* NEAR/1 review*):ti,ab) OR (((systemati* OR literature OR database* OR 'data base*') NEAR/10 search*):ti,ab) OR (((structured OR comprehensive* OR systemic*) NEAR/3 search*):ti,ab) OR (((literature NEAR/3 review*):ti,ab) AND (search*:ti,ab OR database*:ti,ab OR 'data base*':ti,ab)) OR (('data extraction':ti,ab OR 'data source*':ti,ab) AND 'study selection':ti,ab) OR ('search strategy':ti,ab AND 'selection criteria':ti,ab) OR ('data source*':ti,ab AND 'data synthesis':ti,ab) OR medline:ab OR pubmed:ab OR embase:ab OR cochrane:ab OR (((critical OR rapid) NEAR/2 (review* OR overview* OR synthes*)):ti) OR ((((critical* OR rapid*) NEAR/3 (review* OR overview* OR synthes*)):ab) AND (search*:ab OR database*:ab OR 'data base*':ab)) OR metasynthes*:ti,ab OR 'meta synthes*':ti,ab	1065368
#6	'clinical trial'/exp OR 'randomization'/exp OR 'single blind procedure'/exp OR 'double blind procedure'/exp OR 'crossover procedure'/exp OR 'placebo'/exp OR 'prospective study'/exp OR rct:ab,ti OR random*:ab,ti OR 'single blind':ab,ti OR 'randomised controlled trial':ab,ti OR 'randomized controlled trial'/exp OR placebo*:ab,ti	4115353
#7	'major clinical study'/de OR 'clinical study'/de OR 'case control study'/de OR 'family study'/de OR 'longitudinal study'/de OR 'retrospective study'/de OR 'prospective study'/de OR 'comparative study'/de OR 'cohort analysis'/de OR ((cohort NEAR/1 (study OR studies)):ab,ti) OR (('case control' NEAR/1 (study OR studies)):ab,ti) OR (('follow up' NEAR/1 (study OR studies)):ab,ti) OR (observational NEAR/1 (study OR studies)) OR ((epidemiologic NEAR/1 (study OR studies)):ab,ti) OR (('cross sectional' NEAR/1 (study OR studies)):ab,ti)	8424623
#8	'case control study'/de OR 'comparative study'/exp OR 'control group'/de OR 'controlled study'/de OR 'controlled clinical trial'/de OR 'crossover procedure'/de OR 'double blind procedure'/de OR 'phase 2 clinical trial'/de OR 'phase 3 clinical trial'/de OR 'phase 4 clinical trial'/de OR 'pretest posttest design'/de OR 'pretest posttest control group design'/de OR 'quasi experimental study'/de OR 'single blind procedure'/de OR 'triple blind procedure'/de OR (((control OR controlled) NEAR/6 trial):ti,ab,kw) OR (((control OR controlled) NEAR/6 (study OR studies)):ti,ab,kw) OR (((control OR controlled) NEAR/1 active):ti,ab,kw) OR 'open label*':ti,ab,kw OR (((double OR two OR three OR multi OR trial) NEAR/1 (arm OR arms)):ti,ab,kw) OR ((allocat* NEAR/10 (arm OR arms)):ti,ab,kw) OR placebo*:ti,ab,kw OR 'sham-control*':ti,ab,kw OR (((single OR double OR triple OR assessor) NEAR/1 (blind* OR masked)):ti,ab,kw) OR nonrandom*:ti,ab,kw OR 'non-random*':ti,ab,kw OR 'quasi-experiment*':ti,ab,kw OR crossover:ti,ab,kw OR 'cross over':ti,ab,kw OR 'parallel group*':ti,ab,kw OR 'factorial trial':ti,ab,kw OR ((phase NEAR/5 (study OR trial)):ti,ab,kw) OR ((case* NEAR/6 (matched OR control*)):ti,ab,kw) OR ((match* NEAR/6 (pair OR pairs OR cohort* OR control* OR group* OR healthy OR age OR sex OR gender OR patient* OR subject* OR participant*)):ti,ab,kw) OR ((propensity NEAR/6 (scor* OR match*)):ti,ab,kw) OR versus:ti OR vs:ti OR compar*:ti OR ((compar* NEAR/1 study):ti,ab,kw) OR (('major clinical study'/de OR 'clinical study'/de OR 'cohort analysis'/de OR 'observational study'/de OR 'cross-sectional study'/de OR 'multicenter study'/de OR 'correlational study'/de	15424750

	OR 'follow up'/de OR cohort*:ti,ab,kw OR 'follow up':ti,ab,kw OR followup:ti,ab,kw OR longitudinal*:ti,ab,kw OR prospective*:ti,ab,kw OR retrospective*:ti,ab,kw OR observational*:ti,ab,kw OR 'cross sectional*':ti,ab,kw OR cross?ectional*:ti,ab,kw OR multicent*:ti,ab,kw OR 'multi-cent*':ti,ab,kw OR consecutive*:ti,ab,kw) AND (group:ti,ab,kw OR groups:ti,ab,kw OR subgroup*:ti,ab,kw OR versus:ti,ab,kw OR vs:ti,ab,kw OR compar*:ti,ab,kw OR 'odds ratio*':ab OR 'relative odds':ab OR 'risk ratio*':ab OR 'relative risk*':ab OR 'rate ratio':ab OR aor:ab OR arr:ab OR rrr:ab OR ((('or' OR 'rr') NEAR/6 ci):ab)))	
#9	#4 AND #5 - SR	40
#10	#4 AND #6 NOT #9 - RCT	32
#11	#4 AND (#7 OR #8) NOT (#9 OR #10) - Observationeel	224
#12	#4 NOT (#9 OR #10 OR #11) - Overig	573
#13	#9 OR #10 OR #11 OR #12 - Totaal	869

Zoekstrategie Ovid/Medline 30 september 2024

#	Searches	Results
1	((maligna* or necroti* or necrosis) adj3 ('otitis externa' or 'external otitis')).ti,ab,kf. or (exp *Otitis Externa/ and (maligna* or necroti* or necrosis).ti,ab,kf.) or ((exp *Osteomyelitis/ or 'osteomyelitis'.ti,ab,kf.) and (exp Skull/ or skull*.ti,ab,kf. or cranial.ti,ab,kf. or cranium.ti,ab,kf.))	3370
2	exp "Referral and Consultation"/ or exp Internal Medicine/ or exp Diabetes Mellitus/ or exp Glycated Hemoglobin/ or exp Glycemic Control/ or (dm adj3 ("1" or type 1 or type i or "2" or type 2 or type ii)).ti,ab,kf. or ((doctor* or physician* or practitioner* or clinical*) adj3 (visit* or exam*)).ti,ab,kf. or ((haemoglobin* or hb or hba or hemoglobin*) adj3 (a1c or a1 or 1c or aic or alpha 1)).ti,ab,kf. or ((clia or a1c or 1c) adj3 (kit* or test*)).ti,ab,kf. or ((blood glucose* or glycemic*) adj3 (control* or test* or level*)).ti,ab,kf. or ((glycated or glycosyl or glycosylated or glycosylised or glycoside or glycosylation) adj1 (haemoglobin* or hemoglobin*)).ti,ab,kf. or gatekeep*.ti,ab,kf. or referral*.ti,ab,kf. or consultation*.ti,ab,kf. or internal* medicine*.ti,ab,kf. or internist*.ti,ab,kf. or diabetes.ti,ab,kf. or diabetic*.ti,ab,kf. or diabets.ti,ab,kf. or iddm.ti,ab,kf. or iddm1.ti,ab,kf. or iddmi.ti,ab,kf. or t1dm.ti,ab,kf. or tidm.ti,ab,kf. or t2dm.ti,ab,kf. or tiidm.ti,ab,kf. or niddm.ti,ab,kf. or niddm2.ti,ab,kf. or niddmii.ti,ab,kf. or hba1c.ti,ab,kf. or dca vantage analy*.ti,ab,kf. or glycohaemoglobin*.ti,ab,kf. or glycohemoglobin*.ti,ab,kf. or glycosylhaemoglobin*.ti,ab,kf. or glycohemoglobin*.ti,ab,kf. or glycosylhaemoglobin*.ti,ab,kf. or glycosylhemoglobin*.ti,ab,kf.	1492419
3	1 and 2	563
4	3 not (comment/ or editorial/ or letter/) not ((exp animals/ or exp models, animal/) not humans/)	547
5	meta-analysis/ or meta-analysis as topic/ or (metaanaly* or meta-analy* or metanaly*).ti,ab,kf. or systematic review/ or cochrane.jw. or (prisma or prospero).ti,ab,kf. or ((systemati* or scoping or umbrella or "structured literature") adj3 (review* or overview*)).ti,ab,kf. or (systemic* adj1 review*).ti,ab,kf. or ((systemati* or literature or database* or data-base*) adj10 search*).ti,ab,kf. or ((structured or comprehensive* or systemic*) adj3 search*).ti,ab,kf. or ((literature adj3 review*) and (search* or database* or data-base*)).ti,ab,kf. or (("data extraction" or "data source*") and "study selection").ti,ab,kf. or ("search strategy" and "selection criteria").ti,ab,kf. or ("data source*" and "data synthesis").ti,ab,kf. or (medline or pubmed or embase or cochrane).ab. or ((critical or rapid) adj2 (review* or overview* or synthes*)).ti. or (((critical* or rapid*) adj3 (review* or overview* or synthes*)) and (search* or database* or data-base*)).ab. or (metasynthes* or meta-synthes*).ti,ab,kf.	778200
6	exp clinical trial/ or randomized controlled trial/ or exp clinical trials as topic/ or randomized controlled trials as topic/ or Random Allocation/ or Double-Blind	2783743

	Method/ or Single-Blind Method/ or (clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or controlled clinical trial or randomized controlled trial or multicenter study or clinical trial).pt. or random*.ti,ab. or (clinic* adj trial*).tw. or ((singl* or doubl* or treb* or tripl*) adj (blind$3 or mask$3)).tw. or Placebos/ or placebo*.tw.	
7	Epidemiologic studies/ or case control studies/ or exp cohort studies/ or Controlled Before-After Studies/ or Case control.tw. or cohort.tw. or Cohort analy$.tw. or (Follow up adj (study or studies)).tw. or (observational adj (study or studies)).tw. or Longitudinal.tw. or Retrospective*.tw. or prospective*.tw. or consecutive*.tw. or Cross sectional.tw. or Cross-sectional studies/ or historically controlled study/ or interrupted time series analysis/ [Onder exp cohort studies vallen ook longitudinale, prospectieve en retrospectieve studies]	4839638
8	Case-control Studies/ or clinical trial, phase ii/ or clinical trial, phase iii/ or clinical trial, phase iv/ or comparative study/ or control groups/ or controlled before-after studies/ or controlled clinical trial/ or double-blind method/ or historically controlled study/ or matched-pair analysis/ or single-blind method/ or (((control or controlled) adj6 (study or studies or trial)) or (compar* adj (study or studies)) or ((control or controlled) adj1 active) or "open label*" or ((double or two or three or multi or trial) adj (arm or arms)) or (allocat* adj10 (arm or arms)) or placebo* or "sham-control*" or ((single or double or triple or assessor) adj1 (blind* or masked)) or nonrandom* or "non-random*" or "quasi-experiment*" or "parallel group*" or "factorial trial" or "pretest posttest" or (phase adj5 (study or trial)) or (case* adj6 (matched or control*)) or (match* adj6 (pair or pairs or cohort* or control* or group* or healthy or age or sex or gender or patient* or subject* or participant*)) or (propensity adj6 (scor* or match*))).ti,ab,kf. or (confounding adj6 adjust*).ti,ab. or (versus or vs or compar*).ti. or ((exp cohort studies/ or epidemiologic studies/ or multicenter study/ or observational study/ or seroepidemiologic studies/ or (cohort* or 'follow up' or followup or longitudinal* or prospective* or retrospective* or observational* or multicent* or 'multi-cent*' or consecutive*).ti,ab,kf.) and ((group or groups or subgroup* or versus or vs or compar*).ti,ab,kf. or ('odds ratio*' or 'relative odds' or 'risk ratio*' or 'relative risk*' or aor or arr or rrr).ab. or (("OR" or "RR") adj6 CI).ab.))	5796137
9	4 and 5 - SR	25
10	(4 and 6) not 9 - RCT	7
11	(4 and (8 or 9)) not (9 or 10) - Observationeel	69
12	4 not (9 or 10 or 11) - Overig	446
13	9 or 10 or 11 or 12 - Totaal	547

Appendices

Appendix 1 – Schriftelijke knelpunteninventarisatie

Terugkoppeling schriftelijke knelpunteninventarisatie richtlijn Osteomyelitis schedelbasis – maligne otitis externa (NVKNO)

Datum uitnodiging verstuurd: 14 maart 2022
Uiterste reactiedatum: 29 april 2022

Organisatie	Opmerking	1. Zijn er wat u betreft knelpunten rondom osteomyelitis van de schedelbasis/maligne otitis externa die nog niet geadresseerd worden in het raamwerk?	2. Zijn er concept uitgangsvragen opgenomen in het raamwerk waar u zich niet in kan vinden?	3. Welke 3 concept uitgangsvragen hebben voor u de hoogste prioriteit?	Reactie werkgroep
NVZ (Nederlandse Vereniging van Ziekenhuizen)	De knelpuntenanalyse is vooral medisch inhoudelijk. De NVZ heeft daarop geen aanvullend commentaar maar wordt wel graag betrokken bij het vervolg en geeft alvast de volgende aandachtspunten mee: De richtlijn dient organisatorisch, juridisch en financieel uitvoerbaar te zijn voor alle organisaties voor medisch specialistische zorg (algemene, categorale, topklinische ziekenhuizen,	-	-	-	Hartelijk dank voor uw reactie. We nemen uw aandachtspunten mee bij de ontwikkeling van deze richtlijn. Bij elke richtlijn wordt een financiële raming opgesteld in het kader van de Wkkgz, waarin wordt aangegeven of er wel of geen financiële gevolgen zijn van de aanbevelingen. We zullen de conceptrichtlijn aan jullie

Organisatie	Opmerking	1. Zijn er wat u betreft knelpunten rondom osteomyelitis van de schedelbasis/maligne otitis externa die nog niet geadresseerd worden in het raamwerk?	2. Zijn er concept uitgangsvragen opgenomen in het raamwerk waar u zich niet in kan vinden?	3. Welke 3 concept uitgangsvragen hebben voor u de hoogste prioriteit?	Reactie werkgroep
	revalidatie-instellingen), zonder ingrijpende consequenties op deze gebieden. Tevens dient rekening gehouden te worden met het verminderen van de regeldruk, evaluatie van de huidige zorg en eventuele andere algemene richtlijnen die de betreffende richtlijn raken. Dit maakt een bijhorend implementatieplan met inzicht in financiële, juridische en organisatorische consequenties noodzakelijk. In de samenvatting van de richtlijn dient het onderdeel organisatie van zorg ook terug te komen. Het is daarbij van belang om ook inzicht te geven in het verschil tussen de huidige situatie en de nieuwe situatie om de impact te kunnen beoordelen. Bij eventuele consequenties en/of knelpunten op het gebied van de				voorleggen ter commentaar.

Organisatie	Opmerking	1. Zijn er wat u betreft knelpunten rondom osteomyelitis van de schedelbasis/maligne otitis externa die nog niet geadresseerd worden in het raamwerk?	2. Zijn er concept uitgangsvragen opgenomen in het raamwerk waar u zich niet in kan vinden?	3. Welke 3 concept uitgangsvragen hebben voor u de hoogste prioriteit?	Reactie werkgroep
	implementatie en de uiteindelijke naleving van de richtlijn dienen aspecten zoals kosten, veranderde inzet van FTE, IT zaken of anderszins concreet te worden uitgewerkt voor alle soorten organisaties op het gebied van medisch specialistische zorg. Daarbij dient de governance-afspraak van 2019 te worden nagegaan, waarbij nieuwe en te wijzigen richtlijnen worden gecategoriseerd naar impact (categorie 1, 2 of 3) voor de haalbaarheid. Afhankelijk van de categorie dient eventueel een BIA te worden uitgevoerd, met als doel dat alle organisaties de richtlijn kunnen naleven zodra daar toezicht op wordt gehouden. Wij worden graag betrokken bij het vervolg en verzoeken u daarbij				

Organisatie	Opmerking	1. Zijn er wat u betreft knelpunten rondom osteomyelitis van de schedelbasis/maligne otitis externa die nog niet geadresseerd worden in het raamwerk?	2. Zijn er concept uitgangsvragen opgenomen in het raamwerk waar u zich niet in kan vinden?	3. Welke 3 concept uitgangsvragen hebben voor u de hoogste prioriteit?	Reactie werkgroep
	een overzicht te verstrekken van de verschillen tussen de huidige en de nieuwe situatie om de impact beter te kunnen inschatten.				
Nederlandse Internisten Vereniging	-	Vraag 3: suggestie voor toevoegen subvraag:"Welke diagnostiek moet plaatsvinden voor het starten van antimicrobiele therapie, of waarbij deze tijdelijk gestaakt is?" Vraag 4 en 5 en 8: suggestie om deze vragen te combineren, bijvoorbeeld: "welke antimicrobiele behandeling, zowel qua type, toedieningsvorm,	nee	1. vraag 4 (medicamenteuze behandeling), waarbij we het voorstel hebben gedaan deze te combineren met vraag 5 en 8, zodat het gaat over type antimicrobieel middel, toedieningsvorm, dosis en duur. 2. vraag 3 (microbiologische diagnostiek) 3. vraag 9 (evalueren/monitoren effect)	Dank voor u reactie. Er zijn naar aanleiding hiervan vragen samengevoegd. Zoals reeds voorgesteld zijn dit vraag 4 & 5. Vraag 7 is op zichzelf een vraagstuk geworden over hyperbare zuurstoftherapie. Er is een nieuwe module toegevoegd, over additionele voorwaarden. De uitgangsvraag van deze module is: Wat is de meerwaarde van intensiveren van diabetesregulatie, danwel aanvullen van deficiënties,

Organisatie	Opmerking	1. Zijn er wat u betreft knelpunten rondom osteomyelitis van de schedelbasis/maligne otitis externa die nog niet geadresseerd worden in het raamwerk?	2. Zijn er concept uitgangsvragen opgenomen in het raamwerk waar u zich niet in kan vinden?	3. Welke 3 concept uitgangsvragen hebben voor u de hoogste prioriteit?	Reactie werkgroep
		dosis en behandelduur, draagt bij aan een gunstig beloop van maligne otitis externa/schedeloste omyelitis?" Vraag 7: suggestie om deze vraag anders te formuleren, namelijk: ' Additionele therapieen: welke waarde hebben additionele therapieen zoals hyperbare zuurstoftherapie, betere regulatie diabetes en behandeling van deficienties zoals ijzertekort voor de			in de behandeling maligne otitis externa?

Organisatie	Opmerking	1. Zijn er wat u betreft knelpunten rondom osteomyelitis van de schedelbasis/maligne otitis externa die nog niet geadresseerd worden in het raamwerk?	2. Zijn er concept uitgangsvragen opgenomen in het raamwerk waar u zich niet in kan vinden?	3. Welke 3 concept uitgangsvragen hebben voor u de hoogste prioriteit?	Reactie werkgroep
		behandeling van otitis externa/schedeloste omyelitis?" Vraag 9 en 10: suggestie deze te combineren.			

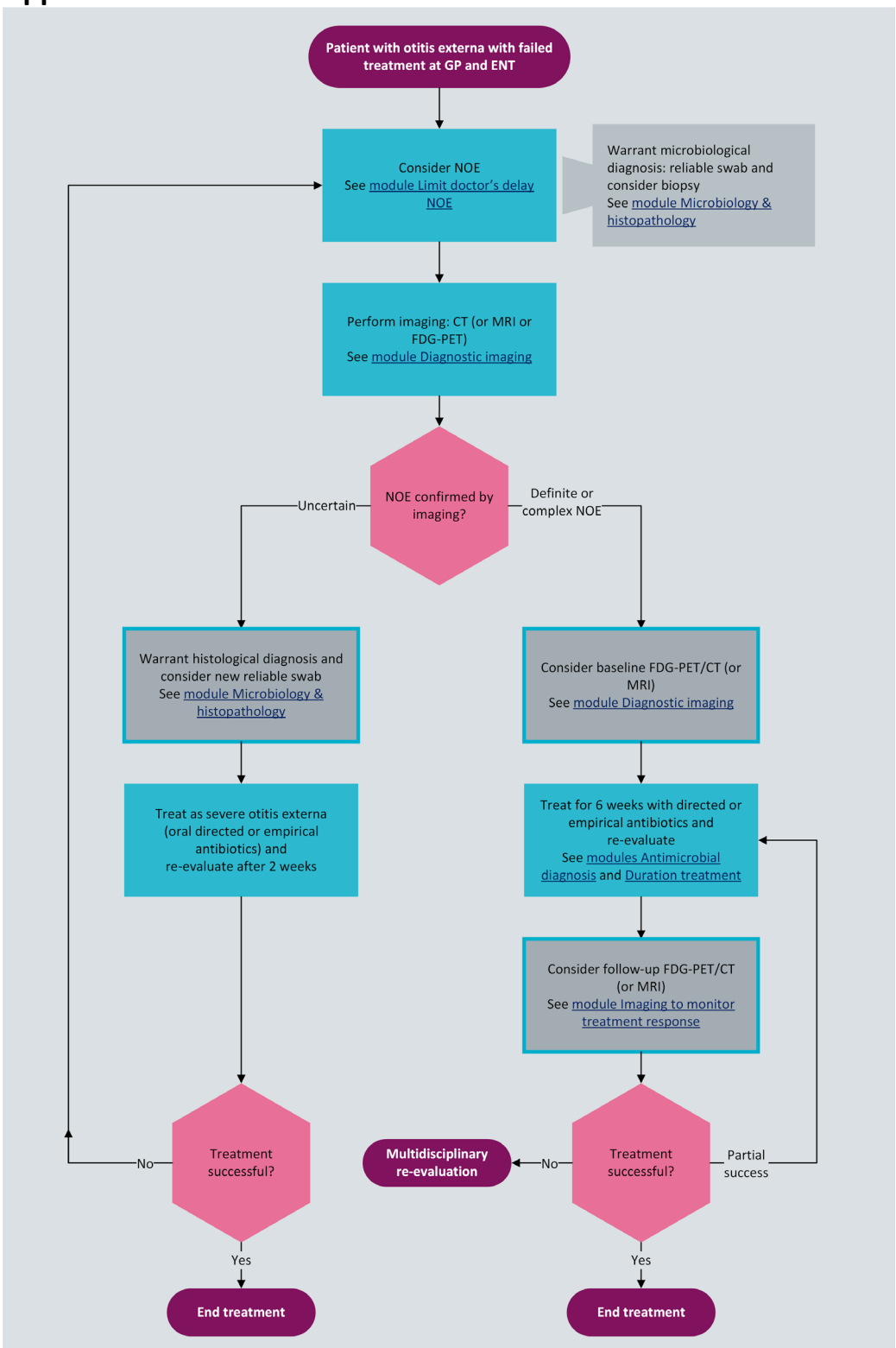
Organisatie	Opmerking	1. Zijn er wat u betreft knelpunten rondom osteomyelitis van de schedelbasis/maligne otitis externa die nog niet geadresseerd worden in het raamwerk?	2. Zijn er concept uitgangsvragen opgenomen in het raamwerk waar u zich niet in kan vinden?	3. Welke 3 concept uitgangsvragen hebben voor u de hoogste prioriteit?	Reactie werkgroep
Nederlandse Vereniging voor Nucleaire Geneeskunde		nee	nee; wel voor mij wat onduidelijk wat bedoeld wordt bij doel van de richtlijn met statische en dynamische beeldvormende technieken. Kijkend naar de FDG-PET/CT scan, wat waarschijnlijk bedoeld wordt met dynamisch, dan klopt dat niet, we maken eigenlijk een statisch plaatje 60 minuten na injectie van FDG. Er zijn wel mogelijkheden tot dynamisch scannen natuurlijk, maar dat wordt niet gebruikt in de reguliere klinische praktijk. Verder verzoek om uitgangsvraag 2 te veranderen in welke beeldvormende diagnostiek…	1. Uitgangsvraag 2 diagnostiek 2. Uitgangsvraag 10 duur behandeling 3.Nvt	Hartelijk dank voor uw reactie. Terugkomend op statisch en dynamisch; dit klopt hetgeen u zegt. Dit zal worden aangepast naar statisch. De uitgangsvraag bij module 2 is aangepast naar ‘Welke beeldvormende diagnostiek is relevant voor het stellen van de diagnose maligne otitis externa?’.

Organisatie	Opmerking	1. Zijn er wat u betreft knelpunten rondom osteomyelitis van de schedelbasis/maligne otitis externa die nog niet geadresseerd worden in het raamwerk?	2. Zijn er concept uitgangsvragen opgenomen in het raamwerk waar u zich niet in kan vinden?	3. Welke 3 concept uitgangsvragen hebben voor u de hoogste prioriteit?	Reactie werkgroep
IGJ (Inspectie Gezondheidszorg en Jeugd)	Geen knelpunten.	-	-	-	Hartelijk dank voor uw reactie.
NHG (Nederlands Huisartsen Genootschap	Geen knelpunten.	-	-	-	Hartelijk dank voor uw reactie.
Patiëntenfederatie Nederland	Geen knelpunten, Stichting Hoormij is voldoende aan patienteninbreng.	-	-	-	Hartelijk dank voor uw reactie.
V&VN (Verpleegkundigen & Verzorgenden Nederland)	Geen knelpunten.	-	-	-	Hartelijk dank voor uw reactie.
ZiNL (Zorginstituut Nederland)	Geen knelpunten.	-	-	-	Hartelijk dank voor uw reactie.
ZKN (Zelfstandige Klinieken Nederland)	Geen knelpunten.	-	-	-	Hartelijk dank voor uw reactie.
ZN (Zorgverzekeraars Nederland)	Geen knelpunten, te specialistisch	-	-	-	Hartelijk dank voor uw reactie.

Organisatie	Opmerking	1. Zijn er wat u betreft knelpunten rondom osteomyelitis van de schedelbasis/maligne otitis externa die nog niet geadresseerd worden in het raamwerk?	2. Zijn er concept uitgangsvragen opgenomen in het raamwerk waar u zich niet in kan vinden?	3. Welke 3 concept uitgangsvragen hebben voor u de hoogste prioriteit?	Reactie werkgroep
Nederlandse Vereniging voor Radiologie	Geen reactie ontvangen.				
Stichting Hoormij	Geen reactie ontvangen.				
NFU (Nederlandse Federatie van Universitair Medische Centra)	Geen reactie ontvangen.				
Nederlandse Vereniging voor Medische Microbiologie	Geen reactie ontvangen.				
STZ (Samenwerkende Topklinische opleidingsZiekenhuizen)	Geen reactie ontvangen.				
Nederlandse Vereniging van Ziekenhuis Apothekers	Geen reactie ontvangen.				

Organisatie	Opmerking	1. Zijn er wat u betreft knelpunten rondom osteomyelitis van de schedelbasis/maligne otitis externa die nog niet geadresseerd worden in het raamwerk?	2. Zijn er concept uitgangsvragen opgenomen in het raamwerk waar u zich niet in kan vinden?	3. Welke 3 concept uitgangsvragen hebben voor u de hoogste prioriteit?	Reactie werkgroep
NAPA (Nederlandse Associatie Physician Assistants)	Geen reactie ontvangen.				
Nederlandse Vereniging voor Keel-Neus-Oorheelkunde en Heelkunde van het Hoofd-Halsgebied	Geen reactie ontvangen.				

Appendix 2 – Flowchart



Abbreviations

CT	computed tomography
ENT	ear, nose and throat surgery
FDG	fluorodeoxyglucose
GP	general practioner
MRI	magnetic resonance imaging
NOE	necrotizing otitis externa
PET	positron emission tomography

Initiating association

Note 1: This flowchart is part of guideline 'Necrotizing otitis externa'. Always read the considerations and recommendations for nuances, possible deviating situations and additional

Note 2: Involve the patient in decision-making.

Federatie Medisch Specialisten

Developed by the Knowledge Institute of the Federation of Medical Specialists

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