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A systematic review of antimicrobial treatment regimens and their outcomes in necrotising otitis externa

Sirat Lodhi, Sara Timms and Emma Stapleton

Department of Otolaryngology, Manchester Royal Infirmary, Oxford Road, Manchester, UK

Review Article

Emma Stapleton takes responsibility for the integrity of the content of the paper

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Corresponding author: Emma Stapleton; Email: emmastapleton@doctors.org.uk

Abstract

Background. Necrotising otitis externa is a serious infection with minimal evidence underpinning its management. This review aims to synthesise published evidence of antimicrobial therapies and their outcomes in necrotising otitis externa.

Methods. The review was PROSPERO registered (CRD42022353244) and conducted according to Preferred Reporting Items for Systematic Review and Meta-Analyses ('PRISMA') guidelines. A robust search strategy filtered 28 manuscripts into the final review. Antimicrobial therapy and clinical outcome data were extracted and analysed.

Results. Published studies are heterogeneous, with high risk of bias and low certainty. Reporting of outcomes is poor and extremely variable. First-line therapy is most commonly in-patient (95 per cent) empiric fluoroquinolone (68 per cent) delivered intravenously (82 per cent). The lack of granular data and poor outcome reporting mean it is impossible to correlate treatment strategies with clinical outcomes.

Conclusion. Robust, consistent outcome reporting with reference to treatments administered is mandatory, to inform clinical management and optimise future research. Optimal antimicrobial choices and treatment strategies require clarification through prospective clinical trials.

Introduction

Necrotising otitis externa is a serious infective condition originating from the external auditory canal, largely but not exclusively in patients with recognised risk factors.[1] The first report of necrotising otitis externa appears in the literature in 1830,[2] with the first case series described by Chandler in 1968.[3] Necrotising otitis externa has a profound effect on patients' quality of life[4] and carries potentially fatal complications.[5]

Necrotising otitis externa has attracted considerable interest from researchers due to its apparent rising incidence between 2002 and 2018[6] with theories for this phenomenon including increasing prevalence of diabetes mellitus,[7] antibiotic resistance,[8,9] ageing population, and increased clinician awareness of the condition.[6]

In patients with diabetes mellitus, microangiopathy and hypoperfusion are thought to contribute to the pathogenesis of necrotising otitis externa.[10,11] However, non-diabetic and non-immuno-compromised cases are appearing in the literature.[12,13] *Pseudomonas aeruginosa* remains the most common pathogen isolated in necrotising otitis externa.[14] Pseudomonal resistance has been attributed to the increased use of fluoroquinolones, and the formation of biofilms.[15,16]

There is a paucity of evidence regarding the diagnostic criteria, management and monitoring of necrotising otitis externa.[14] Although consensus definitions have been recommended,[17] standardised diagnostic criteria, treatment recommendations and outcomes measures remain elusive. The resulting heterogeneity in data prevents best practice from being defined.[18] The management of necrotising otitis externa therefore remains a challenge.

Several reviews[14,18] summarise antibiotic regimens used to manage necrotising otitis externa in published case series and highlight variation within these, but detailed analysis of these regimens and their outcomes is yet to be performed. This systematic review explores antimicrobial therapies and outcomes reported in published case series, aiming to identify the most effective approach to antimicrobial therapy in terms of medication choice, delivery method, dual versus single therapy, and empiric versus culture-guided therapy. This review also addresses reported outcomes regarding treatment efficacy and safety profiles of antimicrobial therapies.

Methods

The review was conducted according to the Preferred Reporting Items for Systematic Review and Meta-Analyses ('PRISMA') guidelines.[19] The review was pre-registered on the PROSPERO database (ID CRD42022353244).

The search terms used are outlined in Table 1. These include all variations of 'necrotising otitis externa' identified through a pilot search. Electronic literature searches were performed in PubMed (9 October 2022; 1945–2022), Embase via OVID (7 October 2022; 1974–2022), CINAHL Plus (9 October 2022, no date limitations) and the Cochrane Library databases (9 October 2022; no date limitations; English-only publications).

Eligible studies included the use of diagnostic criteria for necrotising otitis externa and included at least one outcome measure in the context of patients receiving antimicrobial therapy for necrotising otitis externa. Studies were limited to adult patients. Randomised, controlled trials, case control studies, and multi- and single-centre case series with 10 or more patients were included. Case reports and case series with fewer than 10 patients were excluded, as were review articles, opinion pieces and paediatric and animal studies.

Two researchers independently screened all abstracts and full-text papers, with review by a third author in the event of non-agreement. Duplicates were removed. Titles and abstracts were screened using the inclusion and exclusion criteria. If further information was needed to determine whether abstracts were eligible, full texts were also screened. Short-listed studies underwent full text assessment to exclude ineligible studies. Of the studies selected for full text assessment, reference lists were screened to identify relevant studies not detected by the search. Additional papers were also identified using the Google search engine free text search. Data were extracted from full manuscripts for analysis (summarised in Table 2). Statistical analysis included calculating the total number of patients and/or the percentage of patients pertaining to each data item, where appropriate. If this was not possible, the total number of studies addressing each variable of interest was calculated. The average total duration of treatment across studies was calculated.

Risk-of-bias assessments were completed using the Risk of Bias Assessment of Non-randomised Studies (RoBANS) criteria. Certainty of evidence was assessed using the Grading of Recommendations, Assessments, Development and Evaluation (GRADE) criteria.

Table 1. Search terms used to complete literature searches

Database(s)	Search terms
PubMed and the Cochrane Library	1. invasive otitis externa (all fields) 2. invasive external otitis (all fields) 3. malignant otitis externa (all fields) 4. malignant external otitis (all fields) 5. necrotising otitis externa (all fields) 6. necrotising otitis externa (all fields) 7. necrotising external otitis (all fields) 8. necrotising external otitis (all fields) 9. skull base osteomyelitis (all fields) 10. cranial base osteomyelitis (all fields) 11. temporal osteomyelitis (all fields) 12. 1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8 OR 9 OR 10 OR 11
Embase via Ovid®	1. invasive otitis externa.mp. 2. invasive external otitis.mp. 3. exp malignant otitis externa/ 4. malignant external otitis.mp. 5. necrotising otitis externa.mp. 6. necrotising otitis externa.mp. 7. necrotising external otitis.mp. 8. necrotising external otitis.mp. 9. skull base osteomyelitis.mp. 10. cranial base osteomyelitis.mp. 11. temporal osteomyelitis.mp. 12. 1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8 OR 9 OR 10 OR 11

Results

A four-phase Preferred Reporting Items for Systematic Review and Meta-Analyses ('PRISMA') flow diagram displays the literature search (Figure 1). Of the 548 records that were identified, 393 abstracts were screened and 72 articles were assessed for eligibility. Twenty-eight articles were included in the final synthesis.

Study characteristics

The characteristics of each study, including the first author, year of publication, study type and number of patients, are outlined in Table 3. Four cohort studies, 19 case series, one descriptive study, two quasi-experimental studies and two retrospective case reviews were identified.

Risk-of-bias assessment

The risk-of-bias assessment for each study is outlined in Table 4. All studies rated 'high' for selection bias in participant selection due to the lack of control groups. All studies also rated 'high' for intervention measurements due to the nature of necrotising otitis externa diagnosis (lack of best-evidence guidelines) and retrospective diagnosis. With the exception of a study by Franco-Vidal *et al.*,[42] studies also rated 'high' for selection bias in confounding variable control. The majority of studies rate 'low' for detection and attrition bias because, although studies did not have blinding, the outcome measures were deemed unlikely to be influenced by this, and reasons for missing data were provided. Reporting bias ratings were variable. In studies with a 'high' rating for reporting bias, outcomes were reported incompletely. As a result, meta-analysis could not be performed.

Certainty of assessment

Sixty-one per cent (17/28) of studies were deemed to have 'low' overall certainty, meaning that the true effect is likely to be markedly different from the presented effect (Table 5).

Table 2. Data items for extraction from selected studies

Data item category	Data item for extraction
Antibiotic regimen	Antibiotic name Antibiotic class Route of administration (oral, intravenous, oral and intravenous) Monotherapy and multitherapy use Setting (in-patient or out-patient) Basis for treatment (empiric, culture guided, or empiric then culture guided) Antibiotic treatment duration Criteria for antibiotic treatment cessation
Outcome	Side effects Side effects reported to occur due to antibiotic treatment Number of total deaths Number of deaths reported to occur due to necrotising otitis externa Progressive disease Relapses Reports of participants needing at least one readmission to hospital

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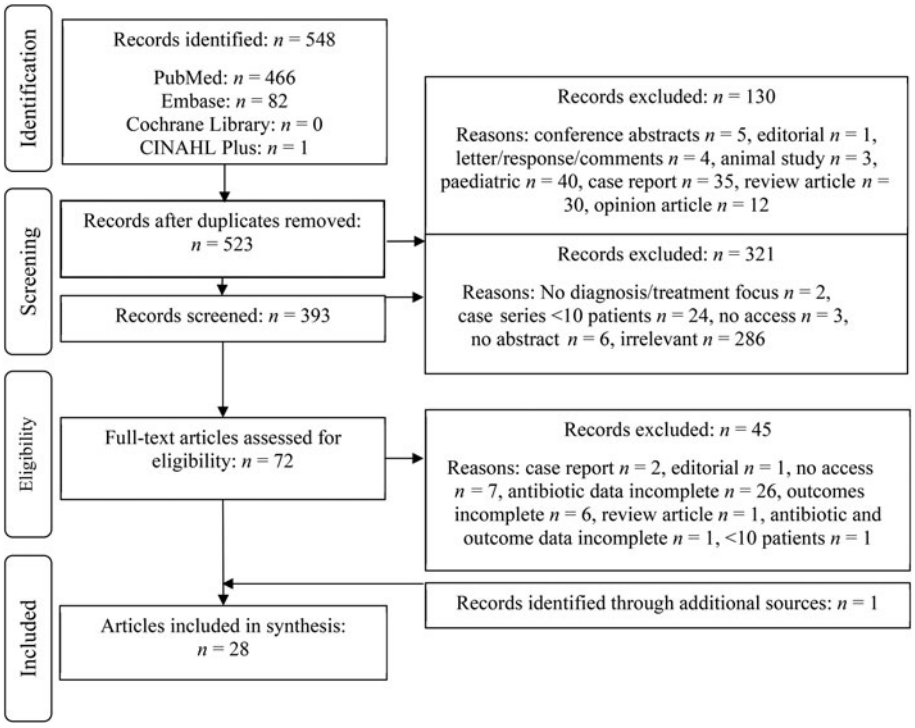

Figure 1. Preferred Reporting Items for Systematic Review and Meta-Analyses ('PRISMA') flow diagram displaying the systematic search methodology. CINAHL = Cumulative Index to Nursing and Allied Health Literature

Thirty-six per cent (10/28) of studies were deemed to have 'moderate' overall certainty, meaning that the true effect is likely to be close to the presented effect. One study was deemed to have 'very low' overall certainty, meaning that the true effect is likely to be markedly different from the presented effect.

Antibiotic classifications

Seventeen different antibiotic classes were identified in the included studies (Table 6). Fluoroquinolones were the most prescribed antibiotic class (68 per cent), with ciprofloxacin the most used antibiotic (64 per cent).

Antifungal therapy

Antifungal therapies are mentioned in several studies, delivered empirically in cases of non-response to antibiotic therapy[36,41] or guided by positive fungal culture.[5,9] However, outcome reporting was inconsistent, therefore outcomes could not be compared, particularly because patients often received a variety of therapies during their treatment.

Antimicrobial combinations

Due to incomplete and heterogeneous reporting of data, exact antimicrobial combinations could not be identified in all studies (Table 7). Most patients received dual therapy first line (57 per cent), and monotherapy second line (23 per cent).

Route of antimicrobial delivery

Most patients received intravenous therapy first line (82 per cent), and oral therapy second line (31 per cent), as summarised in Table 8.

Setting of antimicrobial delivery

Antimicrobials were delivered most often in the in-patient setting (50 per cent). In 45 per cent of participants, this was followed by the out-patient setting (Table 9).

Basis for antimicrobial delivery

Half of the studies (50 per cent) involved empirical antimicrobial prescription, with regimens amended based on culture results, as outlined in Table 10.

Treatment duration

The mean duration of total antimicrobial treatment was 65 days, based on treatment duration detail provided by 10 studies (Table 11). There was wide variation, with mean treatment durations ranging from 21 to 122 days across the included studies.

Criteria for cessation of antimicrobial treatment

Ten studies reported on criteria used for cessation of antibiotic treatment (Table 12). These varied across the included studies, but most included clinical and radiological markers.

Side effects

Seven studies reported side effects of antimicrobial therapy for necrotising otitis externa (Table 13). Of 196 patients in studies where side effects were reported, the most common were allergy (9 per cent), renal impairment (9 per cent), hepatotoxicity (7 per cent) and leukopenia (6 per cent), with only one published study focusing on the complications of antimicrobial therapy for necrotising otitis externa.[23]

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Table 3. Characteristics of studies included in the final synthesis

Author	Year of publication	Study type	Number of patients
Chaabouni[20]	2023	Retrospective case series	25
Danjou[21]	2022	Retrospective observational cohort study	66
Durojaiye[22]	2022	Retrospective cohort	46
Ijaz[23]	2022	Retrospective cohort	63
Hodgson[24]	2022	Retrospective case series	92
Kamalden[25]	2022	Retrospective descriptive study	49
Van Der Meer[26]	2022	Retrospective case series	41
Ozer[27]	2021	Retrospective case series	32
Auinger[28]	2021	Retrospective case series	30
Faizal[29]	2020	Prospective cohort study	51
Jung[30]	2020	Retrospective case series	32
Amaro[31]	2019	Retrospective observational study	17
Honnurappa[32]	2019	Retrospective case series	51
Hutson[33]	2019	Prospective case series	16
Marina[34]	2019	Retrospective case series	14
Carlton[35]	2017	Retrospective case series	12
Hasibi[36]	2017	Prospective observational study	224
Bhasker[37]	2017	Retrospective case series	11
Glikson[38]	2017	Retrospective case series	25
Bhat[39]	2016	Retrospective study case series	15
Verim[40]	2014	Retrospective case series	14
Soudry[41]	2011	Retrospective case series	57
Franco-Vidal[42]	2007	Retrospective case series	46
Lang[43]	1990	Quasi experimental	23
Sade[44]	1989	Quasi experimental	23
Kraus[45]	1988	Case series	19
Salit[46]	1985	Case series	12
Doroghazi[47]	1981	Case series	21

Deaths

Of the 20 studies reporting mortality ($n = 708$ patients), 19 per cent of patients died ($n = 131/708$) within the variable stated follow-up periods. Five per cent of deaths were attributed to necrotising otitis externa (34/708). No deaths were attributed to complications of antimicrobial therapy.

Disease progression, relapse and readmission

Seven studies reported disease progression ($n = 280$ patients). Fourteen per cent of patients (40/280) experienced disease progression whilst receiving antibiotic therapy. In the 16 studies reporting relapse ($n = 702$ patients), 7 per cent (51/702) of patients experienced at least one relapse following cessation of antibiotic therapy. In the five studies reporting on readmission ($n = 153$ patients), 34 per cent (52/153 patients) of patients required at least one readmission to hospital after discharge.

Correlation between antimicrobial therapy and outcomes

Due to the heterogeneity of reported data regarding antimicrobial therapy and outcomes, in addition to the results of the bias and certainty assessments, it was not possible to form any conclusion regarding optimal treatment regimen or strategy in the treatment of necrotising otitis externa.

Discussion

The aim of this systematic review was to summarise antimicrobial regimens used to manage necrotising otitis externa reported in published literature, and to identify most effective and safe antimicrobial regimens and strategies. Due to insufficient and heterogeneous variable reporting, the most efficacious and safe regimens could not be determined, and an accepted process for treatment cessation could not be identified.

Complete antimicrobial therapy details could not be identified due to underreporting of drug combinations, doses used and the reasons for these. Nevertheless, this review identified that fluoroquinolones were the most prescribed antimicrobial (68 per cent), with ciprofloxacin being most used. Most patients received dual therapy first line (57 per cent), and monotherapy second line (23 per cent).

Prior to the introduction of ciprofloxacin, patients with necrotising otitis externa traditionally were treated with

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Table 4. Risk of bias assessment results for studies included in the final analysis

Study	Selection bias: participant selection	Selection bias: confounding variables	Performance bias: intervention measurement	Detection bias: outcome blinding	Attrition bias: incomplete outcome data	Reporting bias: selective outcome reporting
Chaabouni[20]	High	High	High	Low	Low	High
Danjou[21]	High	High	High	Low	Low	High
Durojaiye[22]	High	High	High	Low	Low	High
Ijaz[23]	High	High	High	Low	Low	Low
Hodgson[24]	High	High	High	Low	Low	Low
Kamalden[25]	High	High	High	Low	Low	Low
Van Der Meer[26]	High	High	High	Low	High	Low
Ozer[27]	High	High	High	Low	Low	Low
Auinger[28]	High	High	High	Low	Low	Low
Faizal[29]	High	High	High	Low	Low	Low
Jung[30]	High	High	High	Low	Low	High
Amaro[31]	High	High	High	Low	Low	Low
Honnurappa[32]	High	High	High	Low	Low	Unclear
Hutson[33]	High	High	High	Low	Low	Low
Marina[34]	High	High	High	Low	Low	High
Carlton[35]	High	High	High	Low	Low	Low
Hasibi[36]	High	High	High	Low	Low	Low
Bhasker[37]	High	High	High	High	Low	Unclear
Glikson[38]	High	High	High	Low	Low	High
Bhat[39]	High	High	High	Low	Low	High
Verim[40]	High	High	High	Low	Low	High
Soudry[41]	High	High	High	Low	Low	High
Franco-Vidal[42]	High	Low	High	Low	Low	Low
Lang[43]	High	High	High	Low	Low	Low
Sade[44]	High	High	High	Low	Low	Low
Kraus[45]	High	High	High	Low	Low	Low
Salit[46]	High	High	High	Low	Low	Unclear
Doroghazi[47]	High	High	High	Low	Low	Low

in-patient intravenous dual therapy, consisting of an aminoglycoside and semisynthetic penicillin.[16] Since the introduction of ciprofloxacin in the 1980s, patients have been treated largely with ciprofloxacin as a first-line choice.[43,44] Increasingly, dual therapy with both ciprofloxacin and an additional antibiotic to cover ciprofloxacin-resistant strains of pseudomonas is chosen as a first-line treatment.[16] Notably, Pulcini *et al.* reported better prognosis with dual therapy, in comparison to monotherapy.[48]

The incidence of ciprofloxacin-resistant strains of pseudomonas in aural swabs has remained stable at 7–20 per cent over the past two decades.[6]

Regarding delivery method, most patients received intravenous (82 per cent) therapy first line, and oral (31 per cent) therapy second line. Treatment tended to be initiated in the in-patient setting (95 per cent) and continued in the out-patient setting (50 per cent). Since the introduction of ciprofloxacin, which has good oral bioavailability, increasing numbers of patients are managed in the out-patient setting.[43,44] However, evidence to support decisions regarding intravenous versus oral treatment, or switch between the two, is lacking. There are no studies that directly compare the efficacy of oral and intravenous antibiotic treatment. Nevertheless, early studies report that in comparison to intravenous ciprofloxacin, oral ciprofloxacin is associated with fewer side effects.[44] Moreover, studies suggest that intravenous monotherapy produces comparable outcomes to co-administration of antipseudomonal penicillin and aminoglycoside antibiotics.[44,49] Future research could usefully focus on comparing monotherapy, dual therapy, and oral and intravenous antibiotic treatment through double-blind prospective clinical trials.

Necrotising otitis externa patients tend to be frail, immunosuppressed, and have medical co-morbidities.[1] Necrotising otitis externa patients also tend to receive prolonged parenteral antimicrobial treatment. It is therefore unsurprising that 95 per cent of studies in this review involved delivery of at least initial courses of treatment in an in-patient setting. Non-in-patient settings identified in this review were variable. In 45 per cent of studies, in-patient treatment was followed by treatment in the out-patient setting, and in one study (5 per cent),

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Table 5. Certainty assessment results for studies included in the final analysis

Study	Risk of bias	Imprecision of results	Inconsistency of results	Indirectness of results	Publication bias	Overall certainty
Chaabouni[20]	High	High	Low	High	High	Low
Danjou[21]	High	Low	Low	High	High	Low
Durojaiye[22]	High	High	Low	High	High	Very low
Ijaz[23]	High	Low	Low	High	Low	Moderate
Hodgson[24]	Low	Low	Low	High	Low	Moderate
Kamalden[25]	High	High	Low	High	Low	Low
Van Der Meer[26]	Low	High	Low	High	Low	Moderate
Ozer[27]	Low	High	Low	High	Low	Moderate
Auinger[28]	High	High	Low	High	Low	Low
Faizal[29]	High	Low	Low	High	Low	Moderate
Jung[30]	High	High	Low	High	High	Low
Amaro[31]	Low	High	Low	High	Low	Low
Honnurappa[32]	Low	Low	Low	High	Unclear	Moderate
Hutson[33]	High	High	Low	High	Low	Low
Marina[34]	High	High	Low	High	High	Low
Carlton[35]	High	High	Low	High	Low	Low
Hasibi[36]	High	Low	Low	High	Low	Moderate
Bhasker[37]	High	High	Low	High	Unclear	Low
Glikson[38]	High	High	Low	High	High	Low
Bhat[39]	High	High	Low	High	High	Low
Verim[40]	High	High	Low	High	High	Low
Soudry[41]	High	Low	Low	High	High	Low
Franco-Vidal[42]	Low	High	Low	High	Low	Low
Lang[43]	High	High	Low	High	Low	Low
Sade[44]	Low	High	Low	High	Low	Moderate
Kraus[45]	Low	High	Low	High	Low	Moderate
Salit[46]	High	High	Low	High	Unclear	Low
Doroghazi[47]	Low	High	Low	High	Low	Moderate

treatment was solely delivered in the out-patient setting.[22] The latter assessed home-administered intravenous treatment, which was proposed as an alternative to in-patient treatment in resource-poor settings.

Out-patient antibiotic therapy studies for necrotising otitis externa are surprisingly limited, especially since this is a commonplace practice. Out-patient antibiotic therapy has been shown to be highly effective in the management of other infections.[50] Failure of out-patient antibiotic therapy in necrotising otitis externa has been associated with extensive disease on imaging, facial-nerve involvement, and medical co-morbidities.[22] Although the delivery of out-patient antibiotic therapy and home-based treatment could be limited by the need for training and education, they remain cost-effective options for the management of necrotising otitis externa.[50]

Most included studies (50 per cent) initiated treatment on an empirical basis, and amended treatment based on microbiological culture results. Although this is the most popular approach, reporting of outcomes was not sufficiently robust to identify whether this approach was more efficacious or safe than other strategies. Notably, microbiological sampling techniques varied between studies and are discussed in several studies. Culture-negative cases of clinically and radiologically diagnosed necrotising otitis externa are well recognised,[20] and may be explained by prior antibiotic use, fungal necrotising otitis externa or inadequate sampling technique.[51] In culture-negative and non-resolving cases, deep tissue sampling is increasingly being used[52] to optimise antimicrobial therapy choices and strategies.

Mean antimicrobial treatment duration identified in this review was approximately nine weeks. A median could not be calculated due to limited and variable reporting of treatment duration between studies, reflecting the lack of consensus on optimal duration. Although some studies documented treatment duration, they did not provide explanations for treatment durations, or variations between these within their own patient cohort.

It would be ideal to identify optimal treatment duration, or criteria for treatment cessation, because extended courses of antimicrobials such as fluoroquinolones can be associated with complications. For example, prolonged use is associated with side effects such as tendon rupture and *clostridium difficile infection*,[22] and may contribute to increased pseudomonal resistance.[16,22] This is concerning because pseudomonas has

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Table 6. Antibiotic usage by class

Drug class	Number of patients ($n = 896$)	Percentage (%) of patients
Antifolate	1	0.1
Lipopeptide	1	0.1
Monobactam	1	0.1
Macrolide	2	0.2
Polymyxin	2	0.2
Tetracycline	2	0.2
Nitroimidazole	3	0.3
Sulphonamide	3	0.3
Oxazolidinones	6	0.7
Lincomycin	7	0.8
Glycopeptide	17	2
Beta-lactamase inhibitor	72	8
Aminoglycoside	90	10
Penicillin	127	14
Carbapenem	257	29
Cephalosporin	329	37
Fluoroquinolone	610	68

intracellular efflux mechanisms that reduce antibiotic penetration, rendering it a challenge to eradicate.[16] Although challenging to attribute specific antimicrobial regimens due to heterogeneous reporting, it is clear from this review that the side effects of antimicrobial therapy are common and can be serious.[23]

Criteria for cessation of treatment were provided by 10 studies. These included variable combinations of disease resolution based on clinical symptoms and examination, imaging and inflammatory markers. Inflammatory markers must be used with caution in immunocompromised populations because they can be unreliable.[53–55] Due to insufficient and heterogeneous variable reporting, an accepted process for treatment cessation could not be identified.

All-cause mortality was reported by 71 per cent of included studies, with a mean of 19 per cent, although follow-up periods varied. Disease-specific mortality was estimated as being five per cent across studies. These figures may be unreliable for several reasons, including inadequate reporting across studies, variability in patient follow-up duration and disease-specific mortality identification in a frail patient population with multiple co-morbidities.

Outcomes such as disease progression, relapse and readmission were reported variably between studies, rendering it impossible to compare outcomes or to pair outcomes with treatment strategies, either within or between studies. Furthermore, these terms were variably defined between studies, if indeed they were defined at all. One study reported that relapse is not associated with antibiotic treatment duration, but rather, complex disease.[24] Some studies reported that fungal infections and/or antibiotic-resistant organisms can contribute to advanced disease.[9,56] Other studies report no association between pathogens and outcomes.[15,56]

Table 7. Antibiotic combinations

Antibiotic therapy combinations	Number of patients ($n = 791$)	Percentage (%) of patients
First line		
– Monotherapy	336	42
– Dual therapy	453	57
– Triple therapy	2	0.3
Second line		
– Monotherapy	185	23
– Dual therapy	16	2
– Triple therapy	0	0
– Quadruple therapy	1	0.1
Did not require/ unknown	589	74

Table 8. Route of antibiotic delivery

Route of administration	Number of patients ($n = 562$)	Percentage (%) of patients
First line		
– Oral	23	4
– Intravenous	463	82
– Oral and intravenous	76	14
Second line		
– Oral	174	31
– Intravenous	2	0.4
– Oral and intravenous	0	0

Table 9. Setting of antibiotic delivery

Setting of antibiotic delivery	Number of studies	Percentage (%) of studies ($n = 20$)
In-patient	10	50
Out-patient	1	5
In-patient then out-patient	9	45

Table 10. Basis for antibiotic delivery

Basis for antibiotic delivery	Number of studies	Percentage (%) of studies ($n = 14$)
Empirical	2	14
Culture guided	3	21
Empirical then culture guided	7	50
Empirical and culture guided	2	14

Strengths and limitations

This systematic review is the first to assess antimicrobial regimens and associated clinical outcomes in necrotising otitis externa. Date restrictions were not applied, to allow a

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Table 11. Antibiotic treatment duration

Author of study	Duration of antibiotic treatment (mean number of days)
Ijaz[23]	82
Ozer[27]	98
Jung[30]	115
Hutson[33]	122
Marina[34]	21
Bhasker[37]	42
Glikson[38]	38
Bhat[39]	22
Franco-Vidal[42]	66
Sade[44]	44

Table 13. Side effects of antibiotic therapy for necrotising otitis externa

Side effect	Number of patients	Percentage (%) of patients ($n = 196$)
Allergy/intolerance	18	9
Headache	1	0.5
Rash	6	3
Gastrointestinal disturbance	2	1
Decreased hearing	2	1
Cardiovascular (e.g. cardiac failure, cardiac disease) exacerbation	4	2
Fever	2	1
Hepatotoxicity	14	7
Thrombocytopenia	4	2
Pancytopenia	1	0.5
Leukopenia (e.g. neutropenia)	12	6
Clostridioides difficile infection	1	0.5
Renal impairment	17	9

comprehensive review to be completed. The review identified numerous areas requiring attention and research. The low quality of published data on necrotising otitis externa therapies and outcomes is a major limitation. Due to the wide variability and inconsistent data reporting, it was not possible to attribute outcomes to treatment regimens, preventing the identification of optimal therapy choices in terms of efficacy and safety. It is likely that duplicated patient data exists in the literature, with separately published case series arising from the same centre and authors, with overlapping time periods. The role of antifungal therapies could not be analysed due to lack of robust reported data.

Published reviews[14–18] have highlighted a lack of quality research in necrotising otitis externa. Existing literature consists largely of uncontrolled, retrospective case series with high bias and low certainty of assessment results. The limitations of this review highlight a further valuable perspective – that robust and consistent outcome reporting is essential for analysis of the efficacy and safety of treatment regimens. Our team recently have completed a collaborative national Delphi study to reach consensus on the diagnostic criteria and core outcome set for necrotising otitis externa. It is hoped that this will improve outcome reporting in future studies and facilitate optimal management strategies to be identified through consistency in reporting, as well as facilitate future prospective clinical trials focused on comparing and identifying the safest and most effective treatment strategies.

Conclusion

Heterogeneous, inadequate and variable reporting of treatment strategies and clinical outcomes in necrotising otitis externa research mean that the most effective and safe regimens cannot be determined, and an appropriate process for treatment cessation cannot be identified. The lack of primary research on this theme, together with inconsistencies in reporting results from single-centre case series, are barriers to identifying best practice.

Robust, consistent reporting of clinical outcomes is important, and will be facilitated by the publication of a core outcome set for necrotising otitis externa. Whilst consensus processes can be useful in the identification of best practice regarding the initiation, cessation, and modification of treatment, and disease monitoring in the absence of high-level evidence, robust clinical trials are indicated to definitively answer the

Table 12. Criteria for the cessation of antibiotic therapy

Author of study	Criteria for the cessation of treatment
Chaabouni[20]	Gallium scan – resolution of infection
Durojaiye[22]	Disease resolution: clinical examination and radiological imaging
Kamalden[25]	Symptom improvement and radiological imaging
Van der Meer[26]	Complete clinical recovery based on decreased metabolic activity on PET scan or clinical and radiological findings or palliative care/mortality/allergic reaction
Faizal[29]	PET scan normalisation
Jung[30]	Complete remission of disease based on imaging, laboratory markers, clinical examination, patient symptoms
Hutson[33]	Improving laboratory markers, resolving symptoms and normal clinical exam (EAC)
Bhasker[37]	Documented clinical resolution or patient-reported symptom improvement (pain resolution)
Verim[40]	Treatment was stopped when VAS scores had decreased to 0, CRP levels to 0.0–0.8 mg/dl, and ESR to 0–30 mm/h for women and 0–20 mm/h for men
Soudry[41]	Complete clinical resolution of symptoms and negative gallium scans

PET = positron emission tomography; EAC = external auditory canal; VAS = visual analogue scale; CRP = C-reactive protein; ESR = erythrocyte sedimentation rate

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question that repeatedly arises in necrotising otitis externa publications: What is the optimal treatment strategy for necrotising otitis externa?

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