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Retrospective analysis of outcomes of outpatient parenteral antimicrobial therapy (OPAT) for necrotising otitis externa

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SUMMARY

Purpose

Necrotising otitis externa (NOE) is an uncommon but life-threatening infection that requires prolonged systemic antimicrobial therapy. This study aims to identify factors associated with treatment response and outcome in patients with NOE treated through outpatient parenteral antimicrobial therapy (OPAT).

Methods

We performed a retrospective analysis of patients with NOE treated over a four-year period (January 2018 – January 2022) at a tertiary referral hospital in Derbyshire, UK. We defined OPAT failure as unplanned readmission within 30 days of discontinuation of OPAT. Prolonged duration of therapy was defined as length of parenteral antimicrobial treatment of more than 8 weeks.

Results

A total of 46 cases of NOE were reviewed. OPAT failure and prolonged therapy were recorded in 9 (19.6%) and 23 (50.0%) episodes respectively. Facial nerve involvement (odds ratio [OR], 14.54; 95% confidence interval [CI], 2.76-76.60; p = 0.002), dementia (OR, 7.65; 95% CI, 1.23-47.46; p = 0.029), Charlson comorbidity score (OR, 1.41 per unit increase; 95% CI, 1.00-2.00; p = 0.049) and peak CRP level (OR, 1.03 per unit increase; 95% CI, 1.00-1.06; p = 0.027) were associated with increased risk of treatment failure. Facial nerve involvement (OR, 16.30; 95% CI, 2.60-102.31; p = 0.003) and peak CRP level (OR, 1.04; 95% CI, 1.01-1.07; p = 0.016) were also associated with an increased need for prolonged antimicrobial therapy. In addition, extent of disease (based on imaging findings) was linked to prolonged therapy (OR, 22.89; 95% CI, 3.62-144.76; p = 0.001).

Conclusions

NOE could be effectively managed as outpatient via OPAT. However, vigorous antimicrobial treatment and close monitoring of patients with pre-existing comorbidities, facial nerve paralysis, extensive disease and markedly elevated inflammatory markers are essential to optimise clinical outcomes.

Keywords

Malignant otitis externa; Necrotising otitis externa; Outcomes; OPAT; Outpatient parenteral antimicrobial therapy; Treatment failure

Introduction

Necrotising otitis externa (NOE) (also termed malignant otitis externa) is an uncommon and potentially fatal infection of the external auditory canal and surrounding structures, which typically occurs in elderly diabetic and immunocompromised patients. Although there are currently no established treatment guidelines for NOE, it is often treated with prolonged courses of parenteral antimicrobials which may necessitate lengthy inpatient stays. 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 [1-2]. However, studies on OPAT for NOE are very limited.

We aimed to identify factors that might be associated with increased risk of treatment failure and prolonged antimicrobial therapy in patients with NOE treated at an OPAT service based in a large tertiary referral teaching hospital in Derbyshire, UK.

Materials and Methods

Patient population and setting

This study is a single-centre, retrospective cohort study of all episodes of confirmed NOE treated with OPAT at Royal Derby Hospital (Derbyshire, England, UK) between January 2018 and January 2022. Cases of NOE were clinically and radiologically confirmed (with computed tomography (CT) and/or magnetic resonance imaging (MRI) scan) and referred for OPAT by their Ear, Nose and Throat (ENT) specialist following initial inpatient management. The Derby OPAT service, established in 2013, is run by a multidisciplinary team of infection specialists, clinical pharmacists and specialist nurses. The OPAT service maintains an electronic database to prospectively record patient demographics, clinical diagnosis, antimicrobial agents and duration of antimicrobial treatment. The clinical responsibility for patients receiving OPAT and their follow-ups were shared between the referring clinicians and the OPAT team, unless otherwise agreed. Patients were regularly reviewed in person during their OPAT treatment, and their progress was discussed at a weekly multidisciplinary meeting. Patient selection and individualised OPAT treatment plans were the responsibility of the OPAT infection specialists. In summary, patients with confirmed NOE received 6 to 8 weeks course of intravenous (IV) antimicrobial therapy and had repeat imaging (usually gallium scan) to assess for resolution of infection. Patients with active infection after the 6-8 weeks of treatment received extended courses of therapy with modification of the antimicrobial regimens. Follow-up examinations and radiological imaging were repeated as required until disease resolution.

Data collection

We reviewed the OPAT, hospital electronic clinical and laboratory databases. Data extracted included patient demographics, comorbidities, microbiology culture results, peak white cell count (WCC), erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) levels, imaging findings, complications of NOE, antimicrobial regimens, duration of inpatient and OPAT therapy, mode of OPAT delivery, OPAT outcomes, hospital readmission, and reasons for and length of hospitalisation. In patients with diabetes mellitus, mean blood glucose levels and haemoglobin A1c (HbA1c) were also analysed. Poor diabetes/glycaemic control was defined as HbA1c above 53 mmol/mol (7%) and required inpatient diabetes team review [3]. Age (years) was determined at the time of commencing OPAT. Weighted Charlson comorbidity score was calculated for each patient and was determined at the time OPAT was commenced [4]. Clinical cure was defined as complete resolution of clinical symptoms, normalisation of inflammatory markers and negative findings on follow-up imaging. Chronic kidney disease was based upon an estimated glomerular filtration rate of < 60 ml/min/1.73 m^2 [5]. All patient data were anonymised prior to analysis. The study was approved by the local clinical audit/effectiveness unit as part of ongoing commitment to service development and clinical governance.

Outcomes and Definitions

The outcomes were 'OPAT failure' at 30 days and 'prolonged duration' of IV antimicrobial therapy. OPAT failure was defined as unplanned readmission to an acute care hospital for any reason, recrudescence of infection or death within 30 days of discontinuation of OPAT. Prolonged duration of therapy was defined as length of IV antimicrobial treatment of more than 8 weeks.

Statistical analysis

Numerical data were summarised as mean with standard deviation (SD) or median with interquartile range (IQR) depending on the degree of skewness in the distributions. Categorical data were presented as frequency counts and percentages. Risk factors of OPAT failure and prolonged IV antimicrobial therapy were assessed using logistic regression with penalized maximum likelihood estimation (Firth's method) to account for small sample size [6]. A set of 30 potential risk factors were examined, including patient-related, infection-related and treatment-related variables, based on clinical judgment and literature review. None of the candidate risk factors had missing values. Non-linearity in the log (odds) for continuous variables was examined using lowess smoothed logit plots and was modelled with restricted cubic splines [7]. Due to the small effective sample size, multivariable analysis was not possible. Data were processed and analysed using STATA v.17 (StataCorp, College Station, TX, USA).

Results

Cohort characteristics

We identified 46 episodes of NOE treated through OPAT during the study period with a mean age of 81 (range, 56 – 96) years. 33% (15/46) were female. Table 1 shows the demographic and clinical characteristics of the cohort. 67% (31/46) were diabetic; 20 (65%) of them had poor glycaemic control. The mean diabetes duration was 21 (SD, 16; range, 5-76) years. The mean blood glucose and HbA1c levels at presentation were 10 (SD, 4) mmol/L and 64 (SD, 18) mmol/mol respectively. *Pseudomonas aeruginosa* was the most common causative pathogen isolated (74%; 34/46). All but three *P. aeruginosa* isolates were sensitive to ciprofloxacin. Fungi were isolated in four episodes; they were all established to be commensal organisms and antifungal therapy was not required. Details of peak CRP, WCC and ESR levels are shown Table 1. ESR was checked in only 8 (17%) episodes. Elevated inflammatory markers were recorded in 39 (85%) episodes.

CT or MRI findings were categorised according to extent of the disease. All 46 episodes had external auditory canal (EAC) involvement. The petrous apex was also involved in 14 (30%) episodes. Facial nerve palsy was observed in 13 (28%) episodes; other cranial nerves were not affected. 11% (5/46) had skull base osteomyelitis. Other intracranial complications of NOE (brain abscess and thrombus) occurred in 3 (7%) episodes. Piperacillin/tazobactam was the most frequently prescribed parenteral antimicrobial agent (59%; 27/46). Combination antimicrobial therapy was prescribed in 18 (39%) episodes.

The mean duration of inpatient antimicrobial therapy was 10 (SD, 5; range, 2 – 25) days. The total number of days of patient care (bed-days saved) delivered through OPAT was 2802 (median 48 days; IQR, 33-86; range, 12 – 260 days), with an estimated saving of £996,500 (one hospital bed day on an ENT unit is approximately £356).

Clinical outcomes

Follow-up imaging showed complete resolution of infection in 39 (85%) episodes. In six (13%) episodes follow-up scans were not performed. Three of these patients died from other causes (not related to MOE) before the imaging. Two could not tolerate the scans due to chronic back pain and claustrophobia, and treatment discontinuation was based on clinical improvement and normalisation of inflammatory markers. OPAT failure was recorded in 9 (20%) episodes – mostly due to unplanned readmission. The reasons for unplanned readmission are shown in Online Resource 1. Infection persisted beyond the initial 6-8 week treatment period in half (50%) of the episodes which necessitated additional antimicrobial

treatment. Despite prolonged course of antimicrobial therapy, two patients had disease progression. Both were deemed unfit for surgical management by their ENT specialist due to underlying comorbidities. One of them was referred for hyperbaric oxygen therapy (HBOT), and the second succumbed to the disease. The mean follow-up duration was 17 (SD, 15; range 1 - 46) months. During the follow-up period, recurrence of disease was observed in four (7%) cases after a mean of 4 months. The survival rate was 67% (31/46), with 2% disease-specific mortality and 30% mortality from other causes.

Risk factor analysis

Tables 3 and 4 show the results of the logistic regression analyses of the risk factors for OPAT failure and prolonged IV therapy, respectively. Facial nerve involvement (odds ratio [OR], 14.54; 95% confidence interval [CI], 2.76 – 76.60; p = 0.002), dementia (OR, 7.65; 95% CI, 1.23 – 47.46; p = 0.029), Charlson comorbidity score (OR, 1.41 per unit increase; 95% CI, 1.00 – 2.00; p = 0.049) and peak CRP levels (OR, 1.03; 95% CI, 1.00 – 1.06; p = 0.027) were associated with increased risk of 30-day OPAT failure. Extent of disease - based on imaging findings (OR, 22.89; 95% CI, 3.62 – 144.76; p = 0.001), facial nerve involvement (OR, 16.30; 95% CI, 2.60 – 102.31; p = 0.003) and peak CRP level (OR, 1.04; 95% CI, 1.01 – 1.07; p = 0.016) were associated with an increased need for prolonged IV antimicrobial therapy.

Discussion

NOE is a complex and potentially fatal infection with many associated complications. In the UK, its incidence is increasing probably due to ageing population and increasing comorbidities [8]. The diagnosis and management of NOE present several unique challenges. Treatment often involves prolonged courses of parenteral antimicrobials which may necessitate lengthy inpatient stays with associated cost and risk to both the patient and hospital.

In non-OPAT related studies, a number of factors have been purported to affect the clinical outcome of NOE [9]. In the current study, we explore factors associated with treatment failure and prolonged parenteral antimicrobial therapy in patients with NOE treated with OPAT. Our definitions of OPAT failure and prolonged antimicrobial therapy are supported by previous studies [9-11]. We identified pre-existing comorbidities, facial nerve involvement and CRP level, which are readily available at the time of commencing OPAT, to be associated with OPAT failure. We also found that patients with extensive disease (based on imaging findings), facial nerve palsy and high CRP were more likely to require prolonged courses of antimicrobial therapy.

Facial nerve involvement, pre-existing comorbidities, CRP levels and extent of disease have been associated with poor outcomes in several non-OPAT related studies [9,10,12-14]. Hence, these risk factors observed in our study may not be directly related to the OPAT. The rate of unplanned readmission in our cohort was similar to other OPAT studies [15,16]. However, most of the observed readmissions were non-OPAT related. Our relapse rate is also comparable to other studies [17,18]. All four recurrences occurred within a year of completion of OPAT and were treated with extended courses of broad-spectrum antimicrobial agents. Thus, it is essential to follow up patients with NOE for at least one year after therapy [9,19]. We did not explore the risk factors for these disease recurrences due to the relatively small number of events. 15 patients died during the follow-up period; all but one death were unrelated to NOE.

We have previously identified pre-existing comorbidities to be associated with increased risk of unplanned hospital readmission from OPAT [20]. Patients with multimorbidity were likely to be readmitted due to the underlying comorbidities and related complications. For some patients in our cohort, the risk of readmission, and thus, OPAT failure may be a direct consequence of their underlying comorbidities rather than as a consequence of NOE. Although a number of staging systems for NOE have been proposed based on extent of disease or neurologic complications, none has yet been widely adopted [21,22]. Similar to Lee et al., we classified the extent of disease according to the expected course of infection [14]. As reported by Nadol, the disease process typically starts in the EAC and spreads to the middle cranial fossa via the stylomastoid foramen, jugular foramen and petrous apex [23]. In our cohort, all patients had CT and/or MRI imaging prior to treatment to confirm the diagnosis and assess location and extent of disease. Patients who had more extensive disease (i.e. jugular foramen and petrous apex involvement) were more likely to have received longer courses of antimicrobial treatment. We recommend CT and/or MRI scans for all patients with suspected NOE - not only to confirm the diagnosis but also to guide duration of antimicrobial treatment.

Cranial nerve palsy is a sign of disease progression and a controversial prognostic factor in NOE [14,24]. The facial nerve is the most commonly affected cranial nerve due to its proximity to the EAC. Similar to Arsovic et al. and Stern Shavit et al., we found facial nerve paralysis to be associated with treatment failure and prolonged therapy [10,25]. Our findings support the view that facial nerve involvement may affect the prognosis of NOE. We did not identify skull base osteomyelitis and other intracranial complications of NOE as risk factors for OPAT failure and prolonged therapy, probably due to the relatively small number of these complications in our cohort.

We also observed associations between peak CRP and both OPAT failure and prolonged therapy. CRP correlates closely with disease progression and may serve as an indicator of disease severity. Elevated CRP levels have been linked to longer time to disease resolution and poor outcomes [12,14]. We advise regular monitoring of CRP and other inflammatory markers until complete resolution of the disease is achieved.

The optimal duration of treatment for NOE is uncertain. However, treatment depends on prolonged administration of systemic antimicrobial therapy with antipseudomonal activity. Surgical management is reserved for refractory cases that fail to resolve with appropriate antimicrobial therapy. None of the patients in our cohort underwent surgery. Current IV antipseudomonal antibiotics require frequent dosing which may preclude their use in outpatient settings. Similar to other studies, piperacillin/tazobactam was the most frequently prescribed parenteral antimicrobial agent in our cohort [8,26]. We often reserve ceftazidime and meropenem for patients with a definite history of non-urticarial rash allergy to penicillin or evidence of antimicrobial resistance to piperacillin/tazobactam. In our cohort, piperacillin/tazobactam was administered by continuous infusion using elastomeric pumps since it allows for once daily community nurse visits and ease of patient teaching and use. Elastomeric pumps allow for continuous and prolonged antimicrobial infusions in OPAT. This helps to optimise the pharmacokinetic/pharmacodynamic ratio (percentage of the time between two injections during which the antibiotic is superior to the minimum inhibitory concentration of the bacteria under consideration) of time-dependent antibiotics (such as penicillins, carbapenems and cephalosporins) and reduces risk of failure and resistance emergence during treatment [27]. In our cohort, antibiotic dosing was appropriately adjusted according to renal function based on established guidelines. Although we did not explore the effects of antimicrobial concentration on clinical outcomes in patients with impaired renal function, we did not find any association between antimicrobial agents and OPAT failure.

Oral antimicrobial therapy (e.g. oral ciprofloxacin) may be a suitable alternative to OPAT in selected patients with NOE. However, OPAT remains a safe, cost-effective and efficacious alternative to inpatient treatment when oral therapy is not appropriate due to antimicrobial resistance, drug interactions, intolerance, poor adherence or poor oral absorption. Furthermore, patients with advance disease and complications such as intracranial complications may require prolonged parenteral therapy. Fluoroquinolones (FQs) are the only available oral treatment for *P. aeruginosa* infections, but resistance is becoming increasingly prevalent. In our cohort, ciprofloxacin-resistant *P. aeruginosa* strains were isolated in three cases which precluded use of oral therapy. There is increasing concerns regarding prolonged use of FQs due to potential serious adverse effects such as tendon rupture, aortic aneurysm and dissection, cardiac arrhythmia (QTc prolongation), hypoglycaemia and *Clostridium difficile* infection.

Consequently, oral antimicrobial treatment for uncomplicated NOE could potentially be administered within an OPAT setting to allow close monitoring for compliance and side effects, and timely intervention [28].

Evaluating treatment response in NOE can be challenging. Treatment discontinuation is often based on clinical and radiological improvement, and normalisation of inflammatory markers. Gallium citrate Ga-67 scan is the imaging of choice for follow-up in our centre since it can identify areas of residual infection and often returns to normal once inflammation subsides [29]. A small number of patients in our study had normal inflammatory markers (i.e. CRP, ESR and WCC) at diagnosis, and treatment discontinuation was based on clinical and radiological improvement. We did not find an association between presence of elevated inflammatory markers and clinical outcome. However, changes in inflammatory can help to monitor response to antimicrobial therapy.

Although we did not carry out a cost-effectiveness analysis, we observed considerable cost savings by treating our cohort of patients outside the hospital setting. It is worth mentioning that OPAT provides several indirect benefits and cost savings (e.g. reduction in the cost of nosocomial infections, increased productivity and quality of life) for patients and healthcare systems [2].

Our study is limited by its retrospective design, relatively small sample, and restriction to single-centre experience. The data were initially collected prospectively, which reduces the risk of measurement bias or poor data accuracy. Despite extensive analysis of previously reported risk factors for poor outcomes in patients with NOE, we cannot be certain that we have not missed other important risk factors or the influence of unrecorded confounders. Although our epidemiological data are comparable to other cohort studies, the relatively low incidence of NOE suggests that large multicentre studies are required to confirm our findings and comprehensively explore prognostic factors in NOE treated with OPAT. Novel studies such as the IONOE study could provide more insights into the optimal management of NOE [30].

Our study provides an insight into the duration of therapy for NOE and risk of treatment failure. It shows that patients with NOE could be safely and effectively treated in outpatient settings with substantial cost savings. However, some patients may be at risk of treatment failure and prolonged treatment. Careful patient selection for OPAT, vigorous antimicrobial treatment and close monitoring of patients with pre-existing comorbidities, facial nerve paralysis, extensive disease and very high inflammatory markers are recommended to optimise clinical outcomes.

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Statements and Declarations

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Competing Interests

The authors have no relevant financial or non-financial interests to disclose.

Author Contributions

OCD conceived the study, collected and analysed data, and wrote the manuscript. AS collected data and revised the manuscript. EIK analysed data and revised the manuscript.

Ethical approval

This study was approved by the local clinical audit/effectiveness unit as part of ongoing commitment to service development and clinical governance

Consent to participate

Not applicable

Consent to publish

Not applicable

Tables

Table 1. Baseline patient characteristics (*N* = 46)

Characteristic	n (%)
Age (years), mean ± SD (range)	80.7 ± 9.7 (56 - 96)
Male sex	31 (67.4)
Diabetics	31 (67.4)
Diabetic control [based on HbA1c (mmol/mol)]	
Good control (HbA1c < 53.0)	11 (23.9)
Poor control (HbA1c > 53.0)	20 (43.5)
HbA1c (mmol/mol), mean ± SD (range)[a]	64.3 ± 17.6 (33.0 - 106.0)
Random blood glucose (mmol/L), mean ± SD (range)[a]	30.1 ± 26.4 (1.0 - 99.0)
Duration of diabetes (years), mean ± SD (range)	10.5 ± 4.2 (4.8 – 20.3)
Previous NOE	4 (8.7)
Charlson comorbidity index score, mean ± SD (range)	2.9 ± 2.1 (0 - 7)
Comorbidities	
Congestive heart failure / coronary artery disease	15 (32.6)
Peripheral vascular disease	5 (10.9)
Cerebrovascular disease	4 (8.7)
Dementia	5 (10.9)
Chronic obstructive pulmonary disease	5 (10.9)
Diabetes without complication	13 (28.3)
Diabetes with complications	18 (39.1)
Moderate or severe renal disease	18 (39.1)
Tumour without metastasis	4 (8.7)
Moderate or severe liver disease	1 (2.2)
Microbiology result	
No growth/normal skin flora	10 (21.7)
Pseudomonas aeruginosa	34 (73.9)
Other pathogens[b]	2 (4.3)
Polymicrobial culture[c]	10 (21.7)
Extent of Disease	
EAC/SF	31 (67.4)
JF/PA	15 (32.6)
Facial nerve involvement	13 (28.3)
Skull base osteomyelitis	5 (10.9)
Intracranial complications	3 (6.5)
Presence of elevated inflammatory markers (CRP, WCC or ESR)	39 (84.8)
Peak CRP (mg/L), mean ± SD (range)	30.1 ± 26.4 (1.0 - 99.0)
Peak WCC ($x10^9$/L), mean ± SD (range)	9.3 ± 2.9 (4.7- 17.0)
Peak ESR (mm/hr), mean ± SD (range)[d]	30.4 ± 29.1 (1.0 - 73.0)

Data are presented as mean ± SD for continuous measures, and n (%) for categorical measures unless otherwise indicated. CRP = C-reactive protein; EAC = external auditory canal; ESR = erythrocyte sedimentation rate; HbA1c = haemoglobin A1c; JF = jugular foramen; NOE = necrotising otitis externa; PA = petrous apex; SD = standard deviation; SF = stylomastoid foramen; WCC = white cell count.

[a] HbA1c and random blood glucose were only recorded in patients with diabetes mellitus (*n* = 31).

[b] Other pathogens included: *Staphylococcus aureus* and *Klebsiella pneumoniae.*

[c] Polymicrobial culture included: *P. aeruginosa* with one or more other organisms (anaerobes, *Candida* spp., *Cutibacterium acnes, Enterococcus faecalis, Streptococcus agalactiae* and *Streptococcus anginosus*).

[d] ESR was recorded in only 8 patient episodes.

Table 2. Treatment characteristics and outcomes (*N* = 46)

Characteristic	n (%)
Duration of pre-OPAT (inpatient) antimicrobial therapy (days), mean ± SD (range)	9.5 ± 4.8 (2 - 25)
Duration of OPAT (days), median (IQR)	47.5 (33 - 86)
Total length of IV antimicrobial therapy (weeks), median (IQR)	8.9 (7.0 - 15.1)
Mode of antimicrobial (OPAT) delivery	
Self/carer administration	43 (93.5)
Visiting nurse	3 (6.5)
Use of central venous access	23 (50.0)
Antimicrobial regimen	
Antipseudomonal penicillin-based	
IV piperacillin/tazobactam monotherapy	19 (41.3)
IV piperacillin/tazobactam plus oral ciprofloxacin	7 (15.2)
IV piperacillin/tazobactam plus oral metronidazole	1 (2.2)
Cephalosporin-based	
IV ceftazidime monotherapy	6 (13.0)
IV ceftazidime plus oral ciprofloxacin	8 (17.4)
IV ceftazidime plus oral amoxicillin	1 (2.2)
Carbapenem-based	
IV meropenem monotherapy	2 (4.3)
IV meropenem plus IV teicoplanin	1 (2.2)
Cyclic lipopeptide (IV daptomycin)	1 (2.2)
Outcomes	
OPAT Failure	9 (19.6)
Prolonged IV antimicrobial therapy	23 (50.0)
Recurrence within follow-up period	4 (8.7)
Duration of follow-up for recurrence (months), mean ± SD (range)	16.7 ± 15.1 (1 - 46)

Data are presented as mean ± SD and median (IQR) for continuous measures, and n (%) for categorical measures unless otherwise indicated.
IQR = interquartile range; IV = intravenous; OPAT = outpatient parenteral antimicrobial therapy; SD = standard deviation.

Table 3. Association between clinical, infection and therapy-related factors and 30-day outpatient antimicrobial therapy failure (*N* = 46)

Risk factor	No. (%) of patients or mean ± SD			Bivariate association measure		
	Total cohort (n = 46)	OPAT success (n = 37)	OPAT failure (n = 9)	OR	95% CI	*P* value
Age (years), linear RCS term	80.7 ± 9.7	79.3 ± 9.6	86.7 ± 8.2	0.94	0.80 - 1.11	0.054
Age (years), non-linear RCS term				1.17	0.98 - 1.40	
Male sex	31 (67.4)	25 (67.6)	6 (66.7)	0.91	0.21 - 3.94	0.900
Diabetic patient	31 (67.4)	24 (64.9)	7 (77.8)	1.65	0.34 - 8.01	0.532
Diabetes control						
No diabetes	15 (32.6)	13 (35.1)	2 (22.2)	1.00	-	0.694
Well-controlled	11 (23.9)	8 (21.6)	3 (33.3)	2.22	0.35 - 13.94	
Poorly-controlled	20 (43.5)	16 (43.2)	4 (44.4)	1.47	0.27 - 8.10	
Diabetes duration (years), linear RCS term	14.4 ± 16.5	13.6 ± 16.9	17.4 ± 15.5	1.08	0.93 - 1.26	0.529
Diabetes duration (years), non-linear RCS term				0.91	0.74 - 1.12	
Previous NOE	4 (8.7)	3 (8.1)	1 (11.1)	1.74	0.22 - 13.58	0.597
Charlson comorbidity score, per unit	2.9 ± 2.1	2.6 ± 2.0	4.2 ± 2.1	1.41	1.00 - 2.00	0.049
Comorbidities[a]						
Congestive heart failure/coronary artery disease	15 (32.6)	13 (35.1)	2 (22.2)	0.60	0.12 - 2.93	0.532
Peripheral vascular disease	5 (10.9)	3 (8.1)	2 (22.2)	3.29	0.54 - 19.98	0.196
Dementia	5 (10.9)	2 (5.4)	3 (33.3)	7.65	1.23 - 47.46	0.029
Chronic obstructive pulmonary disease	5 (10.9)	4 (10.8)	1 (11.1)	1.31	0.18 - 9.66	0.789
Moderate or severe renal disease	18 (39.1)	12 (32.4)	6 (66.7)	3.79	0.88 - 16.40	0.075
Polymicrobial culture	10 (21.7)	9 (24.3)	1 (11.1)	0.53	0.08 - 3.49	0.508
Extent of disease, EAC/SF vs JF/PA	15 (32.6)	10 (27.0)	5 (55.6)	3.20	0.76 - 13.44	0.112
Facial nerve involvement	13 (28.3)	6 (16.2)	7 (77.8)	14.54	2.76 - 76.60	0.002
Presence of elevated inflammatory markers (CRP, WCC or ESR)	39 (84.8)	31 (83.8)	8 (88.9)	1.17	0.17 - 8.06	0.874
Peak CRP (mg/L)	30.1 ± 26.4	25.5 ± 22.6	49.2 ± 33.3	1.03	1.00 - 1.06	0.027
Peak WCC ($x10^9$/L), linear RCS term	9.3 ± 2.9	9.0 ± 2.8	10.4 ± 3.2	0.92	0.44 - 1.93	0.356
Peak WCC ($x10^9$/L), non-linear RCS term				1.32	0.56 - 3.12	
Use of central venous access	23 (50.0)	20 (54.1)	3 (33.3)	0.46	0.11 - 1.95	0.293
Combination antimicrobial therapy	18 (39.1)	16 (43.2)	2 (22.2)	0.43	0.09 - 2.08	0.297
Antibiotic agent[b]						
IV ceftazidime	15 (32.6)	11 (29.7)	4 (44.4)	1.89	0.45 - 7.84	0.383
IV piperacillin/tazobactam	27 (58.7)	23 (62.2)	4 (44.4)	0.50	0.12 - 2.06	0.341
Oral ciprofloxacin	7 (15.2)	7 (18.9)	0 (0.0)	0.21	0.01 - 4.11	0.306

CI = confidence interval; CRP = C-reactive protein; EAC = external auditory canal; ESR = erythrocyte sedimentation rate; IV = intravenous; JF = jugular foramen; NOE = necrotising otitis externa; OPAT = outpatient parenteral antimicrobial therapy; OR = odds ratio; PA = petrous apex; RCS = restricted cubic splines; SD = standard deviation; SF = stylomastoid foramen; WCC = white cell count.

[a] Comorbid conditions that occurred in at least 5 patients (10%) were examined. [b] The 3 most frequently used antibiotic agents were examined.

Table 4. Association between clinical, infection and therapy-related factors and prolonged intravenous antimicrobial therapy (*N* = 46)

Risk factor	No. (%) of patients or mean ± SD			Bivariate association measure		
	Total cohort (n = 46)	Expected duration (n = 23)	Prolonged duration (n = 23)	OR	95% CI	P value
Age (years)	80.7 ± 9.7	80.0 ± 9.4	81.5 ± 10.2	1.02	0.96 - 1.08	0.598
Male sex	31 (67.4)	14 (60.9)	17 (73.9)	1.76	0.52 - 5.95	0.360
Diabetic patient	31 (67.4)	14 (60.9)	17 (73.9)	1.76	0.52 - 5.95	0.360
Diabetes control						0.661
No diabetes	15 (32.6)	9 (39.1)	6 (26.1)	1.00	-	
Well-controlled	11 (23.9)	5 (21.7)	6 (26.1)	1.73	0.38 - 7.83	
Poorly-controlled	20 (43.5)	9 (39.1)	11 (47.8)	1.77	0.47 - 6.60	
Duration of diabetes (years)	14.4 ± 16.5	9.8 ± 10.2	19.0 ± 20.2	1.04	0.99 - 1.08	0.105
Previous NOE	4 (8.7)	2 (8.7)	2 (8.7)	1.00	0.16 - 6.37	1.000
Charlson comorbidity score, per unit	2.9 ± 2.1	2.3 ± 2.0	3.5 ± 2.0	1.33	0.98 - 1.79	0.064
Comorbidities[a]						
Congestive heart failure/coronary artery disease	15 (32.6)	5 (21.7)	10 (43.5)	2.62	0.75 - 9.11	0.131
Peripheral vascular disease	5 (10.9)	0 (0.0)	5 (21.7)	13.97	0.73 - 269.23	0.081
Dementia	5 (10.9)	1 (4.3)	4 (17.4)	3.46	0.50 - 24.20	0.211
Chronic obstructive pulmonary disease	5 (10.9)	1 (4.3)	4 (17.4)	3.46	0.50 - 24.20	0.211
Moderate or severe renal disease	18 (39.1)	9 (39.1)	9 (39.1)	1.00	0.31 - 3.18	1.000
Polymicrobial culture	10 (21.7)	5 (21.7)	5 (21.7)	1.00	0.26 - 3.84	1.000
Extent of disease, EAC/SF vs JF/PA	15 (32.6)	1 (4.3)	14 (60.9)	22.89	3.62 - 144.76	0.001
Facial nerve involvement	13 (28.3)	1 (4.3)	12 (52.2)	16.30	2.60 - 102.31	0.003
Presence of elevated inflammatory markers (CRP, WCC or ESR)	39 (84.8)	17 (73.9)	22 (95.7)	5.57	0.85 - 36.59	0.074
Peak CRP (mg/L)	30.1 ± 26.4	19.2 ± 16.2	41.0 ± 30.2	1.04	1.01 - 1.07	0.016
Peak WCC ($x10^9$/L)	9.3 ± 2.9	8.5 ± 2.7	10.0 ± 3.0	1.20	0.97 - 1.49	0.089
Use of central venous access	23 (50.0)	10 (43.5)	13 (56.5)	1.65	0.53 - 5.17	0.388
Combination antimicrobial therapy	18 (39.1)	6 (26.1)	12 (52.2)	2.93	0.88 - 9.76	0.081
Antibiotic agent[b]						
IV ceftazidime	15 (32.6)	8 (34.8)	7 (30.4)	0.83	0.25 - 2.76	0.760
IV piperacillin/tazobactam	27 (58.7)	12 (52.2)	15 (65.2)	1.68	0.53 - 5.34	0.381
Oral ciprofloxacin	7 (15.2)	1 (4.3)	6 (26.1)	5.57	0.85 - 36.59	0.074

CI = confidence interval; CRP = C-reactive protein; EAC = external auditory canal; ESR = erythrocyte sedimentation rate; IV = intravenous; JF = jugular foramen; NOE = necrotising otitis externa; OR = odds ratio; PA = petrous apex; SD = standard deviation; SF = stylomastoid foramen; WCC = white cell count.

[a] Comorbid conditions that occurred in at least 5 patients (10%) were examined.

[b] The 3 most frequently used antibiotic agents were examined.

SUPPLEMENTARY DATA

Supplementary Table 1. Reasons for 30-day unplanned readmission (*n* = 9).

Reason for readmission	*n* (%)
Worsening of existing infection/no improvement	2 (22.2)
New infection[a]	2 (22.2)
Adverse drug reaction	1 (11.1)
Non-OPAT related[b]	4 (44.4)

OPAT = outpatient parenteral antimicrobial therapy

[a] New infection included: chest infection and herpes zoster encephalitis.

[b] Non-OPAT related included: strangulated hernia, hyperglycaemia, worsening renal impairment and heart failure

Supplementary Table 2. Duration of pre-OPAT (inpatient) antimicrobial therapy (*N* = 46).

Duration of therapy (days)	*n* (%)
< 1 week	3 (6.5)
1-2 weeks	37 (80.4)
2-3 weeks	5 (10.9)
3-4 weeks	1 (2.2)

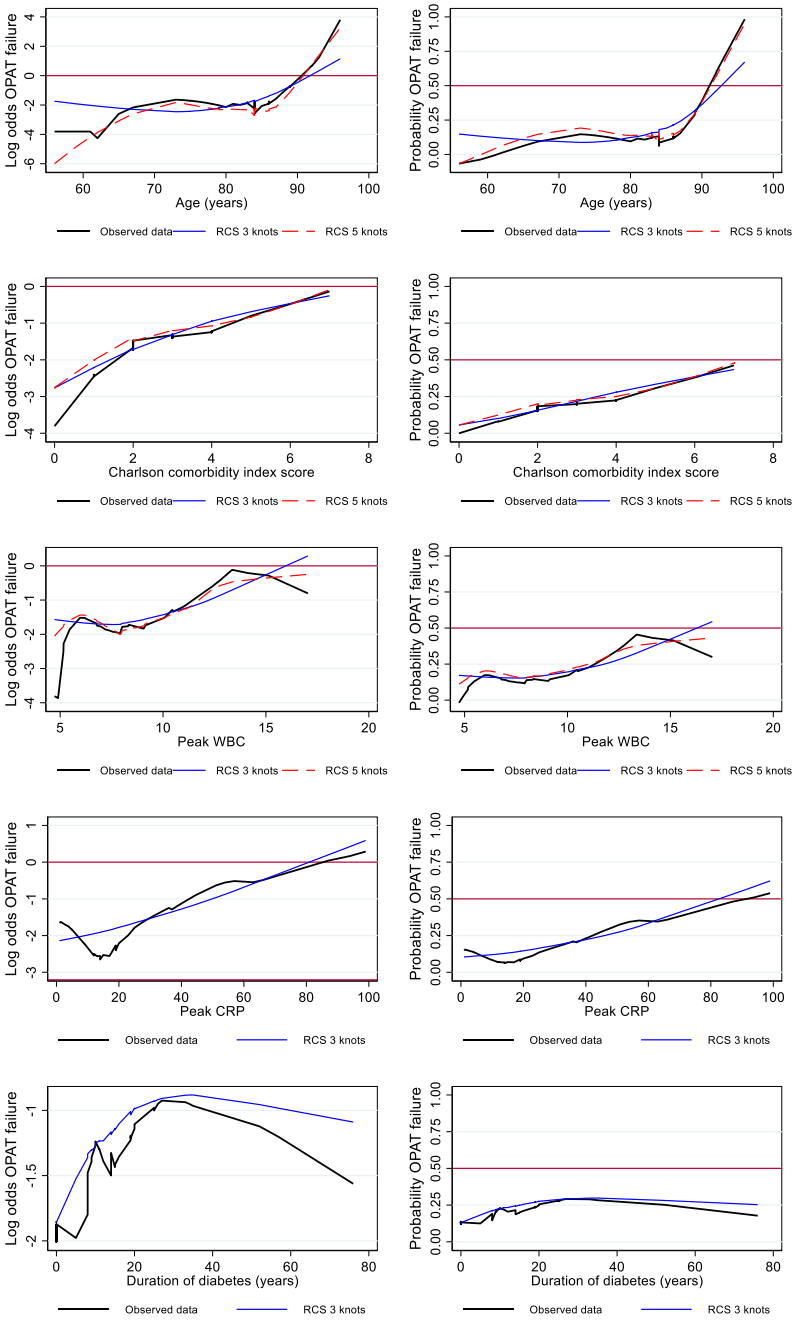
OPAT = outpatient parenteral antimicrobial therapy

Supplementary Table 3. Imaging methods used at the time of diagnosis sites (*N* = 46).

Imaging method	*n* (%)
CT	33 (71.7)
CT+ Gallium scan	3 (6.5)
CT + MRI	9 (19.6)
MRI	1 (2.2)

CT = computed tomography; MRI = magnetic resonance imaging

Supplementary Figure S1. Smoothed locally weighted regression lines (lowess) of the associations of continuous variables with outpatient parenteral antimicrobial therapy (OPAT) failure on the log-odds scale (left) and on the probability scale (right). Entering an untransformed continuous variable into a logistic regression model assumes linearity on the log-odds scale. The graphs show that observed associations (black lines) are approximately linear for Charlson comorbidity score and peak C-reactive protein (CRP) level, whereas age, peak white cell count (WCC) level, and duration of diabetes need to be modelled non-linearly. Restricted cubic splines (RCS) with five knots (red dashed lines) were better fits to the observed data but were not possible to define for all variables due the small sample sizes available. Therefore, RCS with three knots were used (blue lines). The knots were chosen so that the slope of the smoothed curves changes at the 10th, 50th and 90th percentiles.



Supplementary Figure S2. Smoothed locally weighted regression lines (lowess) of the associations of continuous variables with prolonged parenteral antimicrobial therapy on the probability scale. Restricted cubic splines (RCS) with five knots (RCS 5, red dashed lines) or three knots (RCS 3, blue lines) were better fits to the observed data but linear models (black short dash lines) were also good approximations for all variables.