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Case Reports and Series

Nocardiosis at a London teaching hospital: Be aware and beware of what is rare

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ABSTRACT

Aims: To review all laboratory-confirmed cases of nocardiosis at a tertiary referral hospital over an extended period (2000–2018; 216 months) with regard to microbiological and epidemiological characteristics, risk factors, clinical management, morbidity and mortality.
Methods: The medical records and microbiological data of all laboratory-confirmed cases of nocardiosis, identified by culture (with reference laboratory confirmation) or identified in a reference laboratory only, were included and analysed retrospectively.
Results: 18 cases of nocardiosis were identified; 72% (n = 13) were male; all were UK resident. Median age at presentation was 56 years (range 6–83 years). Most had underlying pathology or risk factors including cancer in 39% (n = 7) and immunosuppression in 33% (n = 6). Alcohol and acid fast bacilli (AAFB) microscopy performed in 8/18 cases was negative. Routine 48-hour bacterial culture of 18 isolates was positive in 15; 3 culture-negative specimens were subsequently confirmed positive in a reference laboratory. Four patterns of clinical presentation were observed: cerebral 39% (n = 7), disseminated 28% (n = 5), pulmonary 17% (n = 3), and isolated cutaneous/articular (both n = 1). In addition one case of bacteraemia was noted. *Nocardia farcinica* accounted for half (n = 9) of all nocardia species identified. 55% (n = 10) required surgical intervention. One co-trimoxazole resistant isolate was identified. Morbidity and mortality were high: 78% (n = 14) required critical care. More than half of patients (55%; n = 10) died from refractory infection, including all of those with disseminated disease (n = 5).
Conclusions: Nocardia spp should never be regarded as a contaminant or commensal organism in clinical specimens. Correlation of clinical and radiology findings plus risk factors are imperative for nocardiosis to be considered in the differential diagnosis in order to guide appropriate laboratory processing of specimens. Although rare, recognition of nocardiosis is important because of its high mortality. Routine 48-hour bacterial culture does not always identify *Nocardia* spp and isolates should also be sent to a reference laboratory.

Introduction

Nocardia spp are globally-distributed, ubiquitous, saprophytic bacteria found in fresh and salt water, dust, soil, decomposing environmental vegetation and organic matter (including animal faecal matter); human acquisition is usually exogenous.[18,22] The genus was named after Dr. Edmond Nocard, a 19th-century French veterinarian and microbiologist (1850–1903), who described the identification of a pathogenic aerobic actinomycete in cattle with bovine farcy in 1888.[14] The genus *Nocardia* currently contains more than 80 species, of which approximately 30 have been associated with human disease to date, but this number is increasing due to improved access to molecular diagnostics.[6] Healthcare-associated transmission or acquisition of *Nocardia* spp has been documented, but is relatively rare, and therefore *Nocardia* spp are not considered to be readily communicable.[8,10]

Nocardiosis is an indolent subacute process and only one third of all nocardiosis clinical cases occur in immunocompetent patients.[3,4] The presence of *Nocardia* spp should never be regarded as a contaminant or commensal organism in clinical specimens.[24] Primary cutaneous and soft tissue nocardiosis usually occurs in immunocompetent hosts with the development of cellulitis or a superficial abscess, which can occasionally be complicated by lymphatic spread, known as lymphocutaneous nocardiosis or sporotrichoid nocardiosis.[13] Pulmonary nocardiosis is the most common clinical presentation as inhalation is the primary route of bacterial exposure.[16] Cerebral nocardiosis commonly accompanies pulmonary disease, but isolated cerebral disease may also occur.[5] Conditions associated with an increased risk of nocardiosis include solid-organ transplantation, haematological malignancies, HIV, long-term steroid treatment,

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including treatment for chronic obstructive pulmonary disease (COPD) and other medications that suppress cell-mediated immunity.[7,21,25] Bacteraemia with *Nocardia* spp is rarely reported, even in the context of disseminated disease.[11]

This 18-year retrospective single-centre review of nocardiosis is one of the largest published to date in the United Kingdom (UK). It details the breadth of presentations of nocardiosis to a tertiary referral hospital and provides insights into risk factors, antimicrobial treatments, morbidity, mortality and diagnostic challenges for this rarely-encountered pathogen.

Materials and methods

Study design

This was a retrospective case-notes review of all laboratory-confirmed cases of nocardiosis, either identified on culture, and confirmed in a reference laboratory, or identified in a reference laboratory only, during the 216 month study period (January 1st 2000-December 31st 2018). Samples with discordant results, such as a local positive culture but a different result from a reference laboratory, were excluded.

Study setting

St George's Hospital (SGH) is a 1300-bed tertiary referral university teaching hospital in south west London, UK, which provides neonatal, paediatric, obstetric and adult medical/surgical care. It is a specialist centre for trauma, stroke, neurosurgery, cardiothoracic surgery, haematology/oncology and renal transplantation.

Study data acquisition

A line list was generated from the microbiology laboratory results system (APEX) of all in-house culture-positive *Nocardia* spp clinical specimens during the study period. For each culture-positive *Nocardia* spp result, a manual check of reference laboratory results was performed to ensure that results correlated. A search was also conducted of reference laboratory reports from culture-negative specimens from which a positive result for *Nocardia* spp was subsequently confirmed. For each clinical case identified, a manual review of medical records (either paper or electronic) was performed and data was extracted regarding demographics, age at diagnosis of nocardiosis, presenting symptoms of nocardiosis, background medical/surgical history, immunosuppressive risk factors, management of nocardiosis (outpatient, inpatient, critical care admissions), antimicrobial therapy employed/duration of treatment, complications of treatment, outpatient follow-up and outcome. A review of all radiographic results was conducted where relevant.

Results

Cases meeting inclusion and exclusion criteria

In total, 19 *Nocardia* spp positive specimens were identified. After exclusion of one culture-positive case in which *Streptomyces* spp were confirmed on partial sequencing of 16S rDNA, 18 cases were included in this study.

Epidemiology and case demographics

Of the 18 cases, 13 (72%) were male. The median age was 56 years (range 6–83 years). 22% of cases (n = 4) were transferred from another centre, although a prior diagnosis of nocardiosis had not been made in any of these cases. All cases were permanent UK residents although two (cases 2 and 12) had travelled to India in the weeks prior to presentation.

Past medical and surgical history/immunosuppressive risk factors

Of patients included in the study, almost all — 83% (n = 15) had background medical or surgical diagnoses (Table 1). A third (cases 2, 6, 7, 8, 14, and 15) were on immunosuppressive medications as maintenance therapy for a variety of respiratory, vasculitic, haematological and rheumatological conditions or as post-transplant immunosuppression including long-term prednisolone (cases 6, 7, 14, and 15), azathioprine (case 2), mycophenolate mofetil (cases 6, 7, and 8), hydroxychloroquine (cases 8 and 15), methotrexate (case 8), and cyclosporine (case 7). Over a third — 39% (n = 7) had a history of cancer although none were on active treatment with either chemotherapy or radiotherapy at the time of nocardiosis diagnosis. None were taking co-trimoxazole prophylaxis at diagnosis. Only 17% (cases 5, 15, and 18) of patients were tested for human immunodeficiency virus (HIV) as part of their initial investigation for nocardiosis; all were negative.

Microbiological characteristics

Diagnostic methodologies used for detection of *Nocardia* are outlined in Table 2. Eight samples assessed by alcohol and acid fast bacilli (AAFB) microscopy were negative. Various clinical specimens were either culture positive, or identified predominantly from partial sequencing of 16S rDNA, including cerebral pus, cerebrospinal fluid (CSF), blood cultures, sputum, tissue samples (empyema, sternal tissue), lymph nodes and wound swabs. 83% (n = 15) of cases had in-house samples that were culture positive for *Nocardia* spp. Three culture-negative samples were positive for *Nocardia* spp at an external reference laboratory. 28% (n = 5) of samples were not sent to a reference laboratory. *N. farcinica* accounted for 50% (n = 9) of all nocardia specimens identified. 28% (n = 5) of specimens were identified as *Nocardia* spp without further identification. Other *Nocardia* species identified included *N. asteroides* (n = 1), *N. transvalensis* (n = 1), *N. ignorata* (n = 1), and *N. puris* (n = 1). Matrix-assisted laser desorption/ionisation time-of-flight mass spectrometry (MALDI TOF-MS) (Bruker) was introduced in our centre in 2012. Results from MALDI TOF-MS identification were available for four isolates; case 14 (*N. farcinica* score 2.1), case 15 (*N. farcinica* score 1.9), case 17 (*N. farcinica* score 2.0), case 18 (*N. farcinica* score 1.8).

Antimicrobial susceptibility testing results

Antimicrobial susceptibility testing results are shown in Table 3. Only one co-trimoxazole resistant isolate was detected from 12 tested; case 5. Seven isolates out of eight tested were moxifloxacin susceptibility. Of ten clinical specimens tested, all were susceptible to imipenem and meropenem and carbapenems were used in the antimicrobial treatment of six patients. Nine isolates were tested for linezolid susceptibility; all were susceptible.

Clinical presentation of nocardiosis and clinical management

Details of clinical management and outcome are summarised in Table 4. Four clinical patterns of nocardiosis were identified during this study.

Cerebral nocardiosis

Isolated cerebral nocardiosis accounted for the highest proportion of cases in this study- seven cases (39%; cases 3, 5, 7, 8, 13, 15, and 18). The median age at presentation was 61 years (range 35–83 years; males n = 5). *N. farcinica* accounted for the largest number of cerebral isolates (n = 4). Three cases (7, 17, and 18) had multiple brain abscesses noted on initial computerised tomography (CT) brain scan; the remainder of cases presented with solitary brain abscess. All seven cases were treated with surgical drainage plus antimicrobials; 57% (n = 4) patients died.

Table 1
Epidemiological and microbiological characteristics.

Case	Age (years)	Sex F = Female M = Male	Clinical presentation	Radiographic findings	Background medical conditions	Clinical form of nocardiosis	*Nocardia* spp identified
1	42	F	Dry cough	Symmetrical mediastinal lymphadenopathy	None	Pulmonary	*Nocardia asteroides*
2	59	M	Reduced Glasgow coma scale, left arm weakness, multiple skin lesions	Empyema Frontal lobe ring enhancing lesion	Pulmonary fibrosis, granulomatous polymyositis	Disseminated (cerebral, cutaneous, pulmonary)	*Nocardia farcinica*
3	35	F	Seizures	Multiple cerebral abscesses	Common variable immunodeficiency syndrome, non-Hodgkins lymphoma, bronchiectasis, idiopathic thrombocytopenic purpura (ITP), splenectomy	Cerebral	*Nocardia farcinica*
4	36	F	Headaches, night sweats, weight loss	None	Previous pulmonary tuberculosis, Grave's Disease	Pulmonary	*Nocardia* spp (*unspeciated*)
5	57	M	Recent dental abscess drainage, headache	Temporal lobe ring enhancing lesion	None	Cerebral	*Nocardia* spp (*unspeciated*)
6	75	M	Weight loss, cough	New cavitatory lung lesion	*Mycobacterium avium* intracellulare (MAI) — on treatment at presentation (rifampicin, ethambutol, clarithromycin), previous aspergilloma, childhood polio, ITP, splenectomy	Pulmonary	*Nocardia transvalensis*
7	73	M	Headache, pyrexia	Multiple cerebral abscesses	Prostate cancer, renal transplant, type 2 diabetes mellitus (T2DM)	Cerebral	*Nocardia farcinica*
8	70	F	Headache, nausea, photophobia, dysarthria, vertigo, 3-stone weight loss in previous 12 months	Cerebellar ring enhancing lesion	Bronchiectasis, rheumatoid arthritis	Cerebral	*Nocardia ignorata*
9	6	F	Community-acquired pneumonia	Bronchopneumonia	Asthma	Bacteraemia	*Nocardia* spp (*unspeciated*)
10	47	M	Surgical site infection (aortic valve replacement)	Sternal osteomyelitis	Inherited connective tissue disorder	Sternal osteomyelitis	*Nocardia farcinica*
11	61	M	Community-acquired pneumonia, upper gastrointestinal bleed	Lobar pneumonia	Meningioma	Disseminated (pulmonary, bacteraemia)	*Nocardia puris*
12	79	M	Recent blunt injury sole of left foot — stepped on a nail, multiple skin abscesses with enlarged lymph nodes left leg	Pulmonary nodules Enlarged cervical lymph nodes	Chronic kidney disease, emphysema, giant cell arteritis, chronic inflammatory demyelinating polyneuropathy, T2DM, recurrent non-typhoidal *Salmonella* spp bacteraemia	Disseminated (cutaneous, pulmonary, epicardial)	*Nocardia farcinica*
13	83	M	Dysphasia, dysgraphia, right-sided facial weakness	Temporal lobe ring enhancing lesion	Bladder cancer	Cerebral	*Nocardia* spp (*unspeciated*)
14	57	M	Headache, dysphagia	Frontal lobe ring enhancing lesion	Metastatic lung cancer	Disseminated (bacteraemia, cerebral)	*Nocardia farcinica*
15	61	M	Nausea, vomiting, tremor, abnormal gait, headache	Cerebellar ring enhancing lesion	Antisynthetase syndrome (Anti Jo-1), tongue & oropharyngeal cancer, interstitial lung disease	Cerebral	*Nocardia farcinica*
16	59	M	Nasal bridge abscess post-outdoor trauma	No imaging	None	Cutaneous	*Nocardia* spp (*unspeciated*)
17	67	M	Skin abscesses	Multiple cerebral abscesses	Prostate cancer	Disseminated (cutaneous, cerebral)	*Nocardia farcinica*
18	49	M	Headache, vertigo, slurred speech, ataxia	Cerebellar ring enhancing lesions	Obesity, gastric bypass surgery, renal stones	Cerebral	*Nocardia farcinica*

Disseminated nocardiosis

There were five cases of disseminated nocardiosis (28%): case 2 — cerebral, cutaneous, pulmonary; case 11 — pulmonary, bacteraemia; case 12 — cutaneous, pulmonary, epicardial; case 14 — cerebral, bacteraemia; case 17 — cutaneous, cerebral. The median age at presentation was 65 years (range 57–79 years); males n = 5. Case 14 did not receive antimicrobial treatment as care was palliative. As outlined in Table 1, all cases were immunosuppressed at presentation. All cases of disseminated nocardiosis died.

Pulmonary nocardiosis

Three cases of pulmonary nocardiosis were identified (17%; cases 1, 4, and 6). Case 1 was referred with suspected sarcoidosis and case 4 with suspected recurrence of pulmonary tuberculosis; both diagnoses were subsequently ruled out. Case 1 and case 4 did not receive antimicrobial therapy for nocardiosis and both were discharged. Neither case presented again to this hospital. Case 6 had a significant respiratory past medical history (aspergilloma, *Mycobacterium avium* intracellulare infection) and received prolonged inpatient and outpatient treatment for a cavitatory lung lesion from which samples cultured positive for *N. transvalensis.*

Cutaneous and articular nocardiosis

Only one case of isolated cutaneous nocardiosis (case 16) was identified, a nasal bridge abscess, secondary to mild trauma sustained outdoors. He received empiric therapy for skin/soft tissue infection. There was no documentation in his medical records of the positive culture result for *Nocardia* spp and no record of a change in antimicrobial therapy on the basis of laboratory results but the patient never presented to this hospital again. One case of radiographically confirmed sternal osteomyelitis due to *N. farcinica*, related to a postoperative aortic valve replacement surgical site infection was identified (case 10). The case required prolonged antimicrobial therapy plus multiple sternal wound debridements in theatre.

Table 2
Diagnostic methodologies for *Nocardia* diagnosis and results.

Case	Year	Local microscopy/culture results				Reference laboratory result	Reference laboratory method
		Clinical sample(s)	AAFB[a] microscopy	AAFB culture[b]	Routine bacterial 48 h culture		
1	2000	Mediastinal lymph node	Negative	Positive	Negative	Positive	Unknown
2	2001	Cerebral pus *Skin swabs also culture positive at referring hospital*	Negative	Negative	Positive	Positive	Unknown
3	2001	Cerebral pus	ND[d]	ND	Positive	Positive	Unknown
4	2014	Sputum	Negative	Positive	Negative	Positive	Unknown
5	2005	Cerebral pus	ND	ND	Positive	Positive	Unknown
6	2005	Fine needle aspirate of lung abscess	Negative	Positive	Positive	Not sent	NA[c]
7	2006	Cerebral pus	ND	ND	Positive	Not sent	NA
		Cerebrospinal fluid	ND	ND	Positive	Not sent	NA
8	2006	Cerebral pus	ND	ND	Positive	Positive	Partial sequencing of 16S rDNA
9	2006	Blood culture	ND	ND	Positive	Positive	Partial sequencing of 16S rDNA
10	2007	Tissue sternum	ND	ND	Positive	Positive	Partial sequencing of 16S rDNA
11	2009	Sputum	ND	ND	Positive	Positive	Partial sequencing of 16S rDNA
		Blood culture	ND	ND	Positive	Positive	Partial sequencing of 16S rDNA
		Wound swab chest	ND	ND	Positive	Positive	Partial sequencing of 16S rDNA
12	2011	Neck lymph node	Negative	Negative	Positive	Positive	Partial sequencing of 16S rDNA
13	2015	Cerebral pus	Negative	Negative	Negative	Positive	Partial sequencing of 16S rDNA
14	2015	Blood culture	ND	ND	Positive	Not sent	NA
15	2017	Cerebral pus	Negative	Negative	Positive	Positive	Partial sequencing of 16S rDNA
16	2017	Wound swab nose	ND	ND	Positive	Not sent	NA
17	2018	Wound swab skin	ND	ND	Positive	Positive	Partial sequencing of 16S rDNA
18	2018	Cerebral pus	Negative	Positive	Positive	Positive	Partial sequencing of 16S rDNA

[a] Alcohol and acid fast bacilli.
[b] AAFB culture positive for *Nocardia* spp only.
[c] Not applicable.
[d] Not done.

Nocardia *spp bacteraemia*

Isolated bacteraemia with no clinical or microbiological evidence of dissemination was only observed in one case, the only paediatric case in this series, a 6-year old asthmatic presenting with community-acquired pneumonia requiring respiratory support. A blood culture taken on admission flagged positive with *Nocardia* spp after the child had been discharged. No respiratory specimen was received for processing in the laboratory and she was treated successfully with azithromycin. No nocardia specific treatment was given. The child did represent again to this hospital, between 2006 and 2018, but never with clinical signs or symptoms related to sequelae of untreated nocardiosis.

Complications arising from antimicrobial treatment of nocardiosis

Case 15 developed a reversible pancytopenia related to use of intravenous co-trimoxazole necessitating a change of antimicrobial treatment. Case 18 developed a severe transaminitis secondary to co-trimoxazole, which improved on drug cessation. Case 17 experienced unilateral hearing loss related to amikacin administration, which partially improved, and also encephalopathy secondary to imipenem, which resolved on cessation of imipenem. Case 18 developed anaemia secondary to linezolid and reduced from twice-daily to once-daily dosing on day 45.

Nocardiosis morbidity and mortality

Case 2 developed a bilateral flaccid paralysis of his lower limbs following the drainage of his cerebral abscess. Case 6 developed *Clostridium difficile* colitis. Case 8 became colonised with methicillin-resistant *Staphylococcus aureus* (MRSA), developed an MRSA pneumonia and died following a respiratory arrest. Case 10 also became colonised with (MRSA) and his sternal wound subsequently became infected with MRSA necessitating treatment. Case 11 developed bilateral pneumothoraces and died shortly after. Case 12 was the only patient who experienced a recurrence of local disease in his left foot while on suppressive therapy in 2013. Most patients (78%; n = 14), required admission to critical care at some stage. Overall, 55% (n = 10) died secondary to refractory infection, including all 5 disseminated cases, 4/7 cerebral cases, and 1/3 pulmonary cases.

Discussion

Nocardiosis is a rare disease with a high mortality that can have a myriad of clinical presentations as described in this 18-year retrospective study — the largest nocardiosis case series to date published in the UK. From reviewing the medical notes of all 18 cases, it is striking that nocardiosis was not an expected result in any case, emphasising the need for microbiologists and infectious diseases clinicians to keep nocardiosis in the differential diagnosis if the clinical presentation arouses suspicion and to consider empiric cover. This study also identified four cases where there was no acknowledgement of the *Nocardia* spp result in the medical notes, which represents an area for clinical improvement. As far as we can tell, none of these cases presented again with progressive disease.

Table 3
Nocardia antimicrobial susceptibility testing results.

Case	Year	*Nocardia* spp	Amikacin	Doxycycline	Co-amoxiclav	Ciprofloxacin	Co-trimoxazole	Cefotaxime	Ceftriaxone	Gentamicin	Linezolid	Imipenem	Meropenem	Moxifloxacin
1	2000	*Nocardia asteroides*	Data missing											
2	2001	*Nocardia farcinica*	Data missing											
3	2001	*Nocardia farcinica*	NT[a]	NT	NT	NT	S[b]	S	NT	NT	NT	NT	NT	NT
4	2004	*Nocardia* spp	Data missing											
5	2005	*Nocardia* spp	S	R[c]	S	S	R	S	S	R	NT	S	S	S
6	2005	*Nocardia transvalensis*	R	R	S	R	S	S	S	R	S	S	S	NT
7	2006	*Nocardia farcinica*	S	R	S	S	S	S	S	R	S	S	S	NT
8	2006	*Nocardia ignorata*	NT	R	S	R	S	S	S	S	S	S	S	S
9	2006	*Nocardia* spp	Data missing											
10	2007	*Nocardia farcinica*	S	R	S	S	S	S	S	S	NT	S	S	NT
11	2009	*Nocardia puris*	S	R	S	R	S	S	S	S	S	S	S	S
12	2011	*Nocardia farcinica*	S	I	S	S	S	S	S	R	S	S	S	S
13	2015	*Nocardia* spp	Data missing											
14	2015	*Nocardia farcinica*	S	NT	S	S	S	S	NT	R	S	NT	NT	S
15	2017	*Nocardia farcinica*	S	I	S	S	S	S	S	R	S	S	S	S
16	2017	*Nocardia* spp	Data missing											
17	2018	*Nocardia farcinica*	S	R	S	S	S	S	S	R	S	S	S	S
18	2018	*Nocardia farcinica*	NT	NT	S	R	S	I[d]	R	NT	S	S	S	R

[a] NT = not tested.
[b] S = sensitive.
[c] R = resistant.
[d] I = intermediate.

In terms of comparable case series, a study of 34 cases over a 10-year period[9] in the south of France, showed some similarities to our study; their median age was similar (55.4 years; range 7–94 years), and the male-preponderance was replicated (70.6%). Malignancy predominated as a risk factor for immunosuppression and *N. farcinica* was the most frequently identified *Nocardia* spp.[9] However, only 38% of French patients underwent surgery in comparison to 53% in our study. Mortality was also lower at 11.7%, but deaths occurred in disseminated, pulmonary and cerebral nocardiosis, as seen in London. A recently published epidemiological study of *Nocardia* isolates from human samples (53.8% pulmonary) from a French laboratory dedicated to *Nocardia* (Observatoire Français des Nocardioses) also showed a predominance of *Nocardia farcinica* (20.2% of 793 isolates; 2010–2015) with the proportion of *N. farcinica* increasing significantly over time from 13% in 2010 to 27.6% in 2014.[12] In comparison, a large study from Thailand reviewed 70 cases[20] with a reported mortality of 20%.[20] This study differed though from both this and the French study in that pulmonary nocardiosis was the most common clinical presentation and one third of cases were HIV positive — whereas no cases reviewed in London or France were HIV positive.

There is no international consensus with regard to the optimum antimicrobial agents or duration of treatment for nocardiosis. As shown in Table 4 there was variation in our study with regard to duration of treatment and antimicrobial agents employed. Existing recommendations are largely based on observational studies and expert opinion; three months for cutaneous disease, at least six months for pulmonary or disseminated infections and at least 12 months if there is central nervous system involvement, but there is no agreement on duration of IV therapy or for how long total treatment should be prolonged in the immunosuppressed.[1] The antimicrobial management of nocardiosis is challenging as antimicrobial susceptibility patterns can vary widely amongst *Nocardia* spp and combination therapy is recommended. Current Australian guidelines recommend co-trimoxazole plus at least one other agent.[2] Recent studies have found that 75%–89% of *Nocardia* spp were sensitive to co-trimoxazole.[2,17,19] In our study, only one co-trimoxazole resistant isolate was detected from 12 available but antimicrobial data was missing for six cases, which is a limitation of our study. Combination therapy with co-trimoxazole and a carbapenem, if susceptible, is recommended if invasive infection is suspected as *in vitro* synergism has been demonstrated.[9] The French epidemiological study by Lebeaux et al.[12] reviewed antimicrobial susceptibility testing (AST) and their results were broadly similar to ours. Linezolid, amikacin, trimethoprim-sulfamethoxazole, minocycline and imipenem were the most frequently identified active antibiotics with, 0% (0/734), 2.9% (21/730), 5.4% (40/734), 9.4% (69/734) and 19.5% (143/732), respectively of isolates not susceptible. Interestingly, 79.7% (118/148) of *N. farcinica* isolates were not susceptible to cefotaxime which differs to our AST result where 91% (11/12 isolates) were susceptible.[20] Regardless of what antimicrobial agents are used, as demonstrated in this study, serious complications from therapy can arise and patients on prolonged nocardiosis treatment need diligent monitoring for physical and biochemical adverse events.

The diagnosis of nocardiosis can be challenging as the bacteria is difficult to culture and grows slowly but molecular diagnostics have made identification quicker and more precise. Partial sequencing of 16S rDNA is the most commonly used method as the gene is highly conserved and contains regions present in all species as well as variable regions that are species specific.[14,23] We recommend that all isolates are sent to a reference laboratory for PCR confirmation. The use of MALDI TOF-MS to aid the identification of *Nocardia* spp is not completely robust but is evolving. A recent paper reported that the use of the commercial database alone and in combination with an in-house library afforded 94.5% and 95.9% of correct species-level identifications, respectively; no isolate was misidentified at the genus level with either database.[15] Our experience of using MALDI TOF-MS for identification demonstrated a variance in scores, some below 2.0, but reassuringly all results correlated with confirmatory reference laboratory results.

Table 4
Clinical management and outcome.

Case	Clinical form of nocardiosis	*Nocardia* spp identified	Nocardiosis management			
			Surgery	Antimicrobial therapy [duration — days]		Outcome [days between nocardiosis diagnosis and death]
				Intravenous therapy	Oral therapy	
1	Pulmonary	*Nocardia asteroides*	N/A	None	None	Discharged
2	Disseminated	*Nocardia farcinica*	Yes	Co-trimoxazole [68 days], cefotaxime [68 days], metronidazole [68 days]	None	Died [66 days]
3	Cerebral	*Nocardia farcinica*	Yes	Co-trimoxazole [25 days], ceftriaxone [25 days], clindamycin [25 days]	Co-trimoxazole [497 days]	Died [522 days]
4	Pulmonary	*Nocardia* spp	No	None	None	Discharged
5	Cerebral	*Nocardia* spp	Yes	Meropenem [21 days], co-trimoxazole [21 days]	Moxifloxacin [365 days]	Discharged
6	Pulmonary	*Nocardia transvalensis*	No	None	Co-trimoxazole [356 days]	Died [356 days]
7	Cerebral	*Nocardia farcinica*	Yes	Co-trimoxazole [58 days], metronidazole [61 days], amoxicillin [61 days], cefotaxime [61 days]	None	Died [58 days]
8	Cerebral	*Nocardia ignorata*	Yes	Cefotaxime [17 days], metronidazole [17 days]	Moxifloxacin [2 days]	Died [16 days]
9	Bacteraemia	*Nocardia* spp	No	None	None	Discharged
10	Sternal osteomyelitis	*Nocardia farcinica*	Yes	None	Co-trimoxazole [14 days], co-amoxiclav [63 days], ciprofloxacin [185 days]	Discharged
11	Disseminated	*Nocardia puris*	Yes	Co-amoxiclav [8 days], clarithromycin [8 days], piperacillin-tazobactam [9 days], gentamicin [9 days] *Treatment withdrawn	None	Died [30 days]
12	Disseminated	*Nocardia farcinica*	No	Meropenem [228 days], co-trimoxazole [228 days]	Co-amoxiclav [2026 days]	Died [2646 days]
13	Cerebral	*Nocardia* spp	Yes	Meropenem [12 days while in St George's]	None	Discharged, interhospital transfer — lost to follow-up
14	Disseminated	*Nocardia farcinica*	No	None *Palliative at diagnosis	None	Died [5 days]
15	Cerebral	*Nocardia farcinica*	Yes	Meropenem [4 days], imipenem [68 days], co-trimoxazole [7 days]	Moxifloxacin [73 days], co-trimoxazole [145 days]	Died [226 days]
16	Cutaneous	*Nocardia* spp	No	None	None	Discharged
17	Disseminated	*Nocardia farcinica*	No	Imipenem [6 days], amikacin [22 days], meropenem [42 days], co-trimoxazole [42 days]	Moxifloxacin [48 days], co-trimoxazole [48 days]	Died [90 days]
18	Cerebral	*Nocardia farcinica*	Yes	Imipenem [28 days], co-trimoxazole [5 days], meropenem [day 33 to date; on-going]	Moxifloxacin [day 43 to date; on-going], linezolid [day 58 to date; on-going]	Discharged on outpatient antimicrobial therapy (OPAT) January 2019

In conclusion, nocardiosis is uncommon in the UK and even large specialist centres will see cases very infrequently. Patients with nocardiosis usually have a predisposing risk factor for immunosuppression but nocardiosis can also present in immunocompetent patients. Multidisciplinary management is essential, antimicrobial treatment is generally prolonged and mortality is high depending on the anatomical site (s) of infection. The clinical complexity of nocardiosis cannot be overstated and the significance of clinical isolates should not be overlooked.

Ethics approval

The study proposal was reviewed by the St George's, University of London Research Ethics Coordinator; ethical approval was deemed not necessary.

Declaration of competing interest

The authors have no competing interests to declare.

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