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ORIGINAL ARTICLE

A multi-centre retrospective study of *Nocardia* speciation and antimicrobial susceptibility in Queensland, Australia

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Abstract

The study aims to characterise the species identification and antimicrobial susceptibility testing (AST) results of Nocardial isolates from adult patients across major public hospitals in Queensland, Australia, over a 15-year period. A multi-centre retrospective observational study of *Nocardia* sp. isolates was conducted from 7 major public hospitals in Queensland, Australia, over a 15-year period. Clinical samples from patients aged ≥ 18 years that isolated *Nocardia* sp. were included. Demographic and clinical data were collected, along with species identification and AST results. Overall, 484 *Nocardia* sp. were isolated. Most patients were male (297, 61%) with a mean (IQR) age of 60 (51–75) and a median (IQR) Charlson Comorbidity Index of 4 (2–6). Of these, 239 (49%) patients were immunosuppressed. Organisms were most frequently isolated from sputum (174, 36%), and superficial swabs (102, 21%). Patients presented with pulmonary infections (165, 35%) and superficial skin and soft tissue infections (87, 18%) most commonly. One hundred (21%) isolates were deemed pulmonary colonisation and were not treated. Of the speciated organisms, *N. nova* complex was the most common (93, 19%), followed by *N. farcinica* complex (79, 16%). Organisms were reliably susceptible to linezolid (240/245, 98%), amikacin (455/470, 97%), and trimethoprim/sulfamethoxazole (459/476, 96%), but less so to imipenem (243/472, 51%) and ceftriaxone (261/448, 58%). This is the largest Australian description of *Nocardia* sp. to date. Given antimicrobials are often commenced prior to AST results and sometimes even speciation, characterisation of local species and antibiogram data is important to guide empiric choices and local guidelines.

Keywords Nocardia · Nocardiosis · Epidemiology · Microbiology · Antibiotic resistance

Introduction

Nocardia, a ubiquitous environmental Gram-positive actinomycete, is a rare cause of human disease, but infections are frequently associated with high morbidity and mortality [1]. The worldwide incidence of *Nocardia* sp. infections has been increasing, largely due to an improvement in detection and identification methods, but also due to the increasing number of immunocompromised patients [2]. A move from biochemical to molecular identification methods has

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improved species discrimination but resulted in significant taxonomic change and revision of our understanding of this important pathogen [3]. Species previously grouped together were recognised to be distinct with correspondingly dissimilar drug susceptibility patterns [3].

Nocardiosis typically presents as one of three clinical syndromes: cutaneous infection, which often occurs in immunocompetent individuals after direct inoculation and may present as either skin and soft tissue infection (SSTI), deeper bone and joint infections such as osteomyelitis and septic arthritis, pulmonary infection, and disseminated disease which can include bloodstream infection and central nervous system (CNS) involvement [4]. Disseminated disease is usually seen in immunocompromised patients — typically in those with impaired cellular immunity — and is associated with a mortality rate of up to 40% [5].

Treatment is made more difficult by the frequent delays in diagnosis and, even when the diagnosis is established, limited treatment options for the isolated *Nocardia* species [6]. While intraspecies antimicrobial susceptibility is predictable for individual species, there is significant variability between species, and marked differences in their geographical distribution [7]. It is therefore essential to define locally prevailing *Nocardia* species precisely to inform optimal empiric antibiotic selection.

In the last decade, there have been 3 reviews of nocardiosis in the different states of Australia, but given the varying geography and climates across the country, these are not necessarily generalisable. Two studies — one in New South Wales and a single-site study in Victoria — examined 270 and 68 isolates respectively; these were published in 2020 and 2018 respectively [8, 9]. A 2016 study conducted in the Northern Territory, which is more similar to Queensland in its climate, examined 61 isolates [10]. However, the last reported study of nocardiosis in Queensland was published in 1992 and examined only 102 patients [11]. This study represents the largest Australian series of *Nocardia* sp. isolates to date.

Hence, this study aimed to describe the species and antimicrobial susceptibility testing (AST) results of *Nocardia* isolates identified in adults treated at major public hospitals in Queensland, Australia, over a 15-year period. It was hoped that this data might be used to inform the optimal selection of empirical therapies of patients diagnosed with Nocardiosis in the region.

Methods

Ethics approval

Research was conducted in accordance with the Declaration of Helsinki and national and institutional standards. Ethical approval was provided by the Metro South Health Human Research Ethics Committee (LNR/2019/QMS/48872). As the data was retrospective and de-identified, the Committee waived the requirement for informed consent. Site-specific approval was obtained for each participating hospital.

Data collection

This retrospective multi-centre study was conducted at 7 large public hospitals in Queensland, Australia, a state of 4.7 million people spread across 1.9 million km^2 (supp Fig. 1). Climate is variable across the state with arid regions in west, tropical in the north, and subtropical in the south.

Clinical samples from patients aged ≥ 18 years collected between 1st January 2004 and 31st December 2018 that isolated *Nocardia* sp. in culture were included in the analysis. All isolates were initially identified in these hospitals' microbiology laboratories and were then referred to a state-wide tertiary reference laboratory (Queensland Mycobacterium Reference Laboratory) for genus confirmation, speciation, and antimicrobial susceptibility testing. Episodes where the same organism was isolated from the same patient within 12 months were excluded, as were specimens in which the site of collection was not documented. Demographic, clinical, and laboratory data were collected to determine the site of infection, the *Nocardia* species and AST.

SSTI was defined as cellulitis or cutaneous abscess. Bone and joint infection included osteomyelitis and septic arthritis. Disseminated disease was bloodstream infection or ≥ 2 discontiguous sites of involvement (not including multiple SSTI sites). Central nervous system (CNS) infection included meningitis and cerebral abscesses. Pulmonary disease included abscesses, nodular disease, and pneumonia. Pulmonary colonisation was defined as any *Nocardia* spp. isolated from pulmonary samples where patients recovered without treatment. Patients were classified as immunosuppressed if they had a current history of malignancy, chemotherapy, transplantation, human immunodeficiency virus, or were taking any systemic immunosuppressive medications (oral corticosteroids at any dose, calcineurin inhibitors, mammalian target of rapamycin inhibitors, or antimetabolites). Comorbidity was quantified using the Charlson Comorbidity Index.

Isolates and antimicrobial susceptibility testing

Primary isolation of putative *Nocardia* sp. was conducted by local microbiology laboratories using standard media applicable to the specimen type. In some cases, prolonged incubation was used to enhance detection. Isolates were referred to the reference laboratory where identification and antimicrobial susceptibility testing was performed. The oldest isolates in this study were confirmed

phenotypically as *Nocardia* sp. and speciated using patterns of susceptibility. AST was performed using disc susceptibility testing as advocated by Wallace et al. and recorded as susceptible, intermediate, or resistant [12]. MIC data was not available for these isolates. Identification of newer isolates was first attempted by mass spectrometry. Where possible, species were grouped into complexes as defined by Conville et al. [3].

Evolution of methods saw the introduction of 16S rDNA, Sanger sequencing for species identification (2007), and broth microdilution (BMD) for AST using the commercial Sensititre assay (Trek Diagnostics/ThermoFisher) (2011). Despite 16S rDNA sequencing, with reference matching to NCI BLAST, some isolates failed to meet criteria for species reporting (≥ 99.6%) match as per Clinical and Laboratory Standards Institute (CLSI) recommendations [13] and were reported to genus level only. Methodology and interpretation of BMD minimum inhibitory concentrations were determined using CLSI standards [13]. Due to differences in AST methodology and reporting over the time period and laboratories, the numbers of isolates tested for each antibiotic varied.

Data management and analysis

Data were entered into an electronic database (REDCAP) and analysed using statistical software (Rstudio). Descriptive statistics were performed and are presented as the absolute number (%), mean ± standard deviation or median (interquartile range) as appropriate. Analysis for trend was conducted using an extension of the Wilcoxon rank-sum test [14].

Results

Demographics

Over the 15-year period, 484 *Nocardia* sp. isolates were identified in clinical samples at the study hospitals (supp Fig. 1). Most patients were male (297, 61%), with a median age of 66 (IQR 51–75), and a median (IQR) Charlson Comorbidity Index of 4 (2–6). Almost half (239, 49%) of patients were immunosuppressed, most commonly due to steroid use (supp Fig. 2). There was no trend towards increasing number of *Nocardia* cases over time ($p = 0.21$) (supp Fig. 5).

Site of infection

Organisms were isolated from a variety of samples, most commonly sputum (174, 36%), and superficial swabs (102, 21%) (Table 1). This corresponded to 165 (34%) pulmonary infections and 87 (18%) skin and soft tissue infections (Table 2; supp Fig. 3): the two leading clinical syndromes observed. 100 (21%) sputum isolates were thought to represent colonisation.

Speciation

Of the isolates that were able to be identified to species level, *N. nova* complex was the most common (93, 19%), followed by *N. farcinica* complex (79, 16%) (supp Fig. 4). Among patients with pulmonary infection, *N. cyriacigeorgica* complex was the most common isolate (39, 24%) followed by *N. nova* complex (34, 21%). Of those deemed to be colonised, *N nova* complex was most common (32, 32%), followed by *N. farcinica* complex (21, 21%) (Table 2). In bronchial

Table 1 Distribution of sample types that the Nocardia species were isolated from. Presented as *n* (%). One *N. brasiliensis* isolate did not have a sample site recorded. Majority of organisms were isolated from sputum ($n = 174$), followed by superficial swab ($n = 102$). *Cerebrospinal fluid

Site Complex	Blood culture $n = 17$	Bone or joint $n = 5$	Bronchial wash $n = 90$	CSF* $n = 2$	Deep abscess or tissue $n = 81$	Eye $n = 12$	Sputum $n = 174$	Swab $n = 102$
N. abscessus	0 (0)	0 (0)	2 (2.2)	0 (0)	11 (14)	0 (0)	9 (5.2)	3 (2.0)
N. brasiliensis	1 (5.9)	1 (20)	3 (3.3)	1 (50)	5 (6.2)	1 (8.3)	2 (1.1)	47 (46)
N. brevicatena/N. paucivorans	1 (5.9)	0 (0)	3 (3.3)	1 (50)	10 (12)	0 (0)	0 (0)	4 (3.9)
N. cerradoensis	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (8.3)	0 (0)	0 (0)
N. cyriacigeorgica	0 (0)	0 (0)	20 (22)	0 (0)	3 (3.7)	0 (0)	36 (21)	7 (6.9)
N. farcinica	7 (41)	1 (20)	11 (12)	0 (0)	17 (21)	4 (33)	31 (18)	8 (7.8)
N. nova	3 (18)	0 (0)	16 (18)	0 (0)	12 (15)	2 (17)	47 (27)	13 (13)
N. otitidiscavarium	2 (12)	0 (0)	1 (1.1)	0 (0)	2 (2.5)	0 (0)	5 (2.9)	4 (3.9)
N. pseudobrasiliensis	2 (12)	1 (20)	1 (1.1)	0 (0)	1 (1.2)	1 (8.3)	4 (2.3)	2 (2.0)
N. transvalensis	0 (0)	0 (0)	9 (10)	0 (0)	2 (2.5)	2 (17)	20 (11)	0 (0)
Nocardia sp.	1 (5.9)	2 (40)	24 (27)	0 (0)	18 (22)	1 (8.3)	20 (11)	14 (14)

Table 2 Infection site and their causative Nocardia sp., presented as *n* (%). Disseminated disease was most commonly caused by N. farcinica (*n* = 15, 27%), pulmonary infection by N. nova (32, 32%), and superficial skin and soft tissue infection (SSTI) was most commonly caused by N. brasiliensis (*n* = 51, 59%)

Infection site Complex	Bone and joint *n* = 14	CNS *n* = 15	Disseminated *n* = 55	Pulmonary colonisation *n* = 100	Pulmonary infection *n* = 165	SSTI *n* = 87	Other and unspecified *n* = 48
N. abscessus	2 (14)	2 (13)	2 (4)	3 (3)	11 (7)	3 (3)	2 (4)
N. brasiliensis	0 (0)	1 (7)	3 (5)	0 (0)	3 (2)	51 (59)	4 (8)
N. brevicatena/N. paucivorans	0 (0)	4 (27)	8 (15)	1 (1)	4 (2)	1 (1)	1 (2)
N. cerradoensis	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)
N. cyriacigeorgica	1 (7)	1 (7)	0 (0)	16 (16)	39 (24)	3 (3)	6 (13)
N. farcinica	0 (0)	4 (27)	15 (27)	21 (21)	19 (12)	8 (9)	12 (25)
N. nova	5 (36)	0 (0)	5 (9)	32 (32)	34 (21)	9 (10)	8 (17)
N. otitidiscavarium	0 (0)	1 (7)	3 (5)	3 (3)	4 (2)	2 (2)	1 (2)
N. pseudobrasiliensis	1 (7)	0 (0)	2 (4)	1 (1)	4 (2)	2 (2)	2 (4)
N. transvalensis	0 (0)	0 (0)	3 (5)	14 (14)	14 (8)	0 (0)	2 (4)
Nocardia sp.	5 (36)	2 (13)	14 (25)	9 (9)	33 (20)	8 (9)	9 (19)

washings, *N. cyriacigeorgica* complex was most frequently isolated (20, 22%), and in sputum, this was *N. nova* complex (47, 27%) (Table 1).

N. brasiliensis was the predominant organism (51, 59%) isolated from those with skin and soft tissue infections (SSTI) followed by *N. nova* (9, 10%) (Table 2). This corresponded to the predominant isolation of *N. brasiliensis* from superficial swabs (47, 46%) (Table 1). Identified species causing disseminated disease were mostly *N. farcinica* complex (15, 27%) (Table 2).

Significant numbers of isolates were not able to be identified to the species level (Tables 1–2). There was no trend towards improved speciation of isolates over time ($p = 0.06$) (supp Fig. 4). Despite the 12 month limit imposed between each episode, 29 samples from 11 patients grew the same organism more than 12 months apart. These were largely deemed pulmonary colonisation (21, 72%).

Antimicrobial susceptibility testing results

Pooled sensitivities of all *Nocardia* sp. isolated demonstrated that the isolates were most frequently susceptible to linezolid (240/245, 98%), followed by amikacin (455/470, 97%), then trimethoprim/sulfamethoxazole (TMP/SXT; 459/476, 96%). Conversely, only 51% of the isolates were susceptible to imipenem (243/472), and ceftriaxone (261/448, 58%) (Table 3). Linezolid susceptibility was only available for 50% of the isolates due to changes in AST reporting over the study period.

N. nova complex, the predominant isolate in this dataset, was reliably susceptible to TMP/SXT (93/93, 100%), amikacin (93/93, 100%), linezolid (40/40, 100%), and imipenem (90/93, 97%), but less so to ceftriaxone (60/88, 68%) (supp Fig. 6). *N. farcinica* complex, the second most commonly speciated isolate, was similarly susceptible to TMP/SXT

Table 3 Antimicrobial susceptibility data (AST) for all Nocardia sp. isolates (total *n* = 484). Available data points for each antimicrobial are presented here. Shaded MIC values indicate intermediate or resistant susceptibility as per CLSI M62 guidelines.

Antimicrobial	*Nocardia* sp. isolates with MIC value (mg/L)										MIC		Susceptibility data			
	<1	1	2	4	8	16	32	64	>64	Total	MIC50	MIC90	%S	%I	%R	Total
Amikacin	119	94	11	6	7	5	1		1	244	1	2	97	1	2	470
Amox/clav[!]		2[*]					39	46		87	64/32	64/32	23	23	54	474
TMP/SXT[$]		204[*]			4	3[&]				211	<2/1	<2/1	96	0	4	476
Ciprofloxacin	26	14	8	31	91	73	1[**]			244	8	16	22	5	73	475
Clarithromycin	73	19	9	4	13	18	103	1[^]		240	32	32	43	5	53	472
Ceftriaxone		1	14	59	37	43	26	20	42	242	16	>64	58	17	25	448
Doxycycline	3	2	11	12	9	2				39	4	8	15	59	26	39
Imipenem	9	8	51	17	27	46	27	24	34	243	16	>64	51	10	39	472
Linezolid	23	59	84	66	9	2[&]				243	2	4	98	0.4	1.2	245
Minocycline	16	19	59	117	14	3				228	4	4	24	67	9	455
Moxifloxacin	6	3	11	13	6	1	2[**]			42	4	8	22	27	51	42

[!]Amoxicillin/clavulanate, based on the amoxicillin component, [$]Trimethoprim/sulfamethoxazole, based on the trimethoprim component,*MIC < 2/1 mg/L, **MIC > 16 mg/L, [^]MIC > 32 mg/L, [&]MIC > 8 mg/L

(72/77, 94%), amikacin (74/76, 95%), and linezolid (30/31, 97%), but less so to ceftriaxone (10/73, 14%) and imipenem (31/76, 41%) (supp Fig. 7). Furthermore, species-specific AST breakdowns are presented in supplementary Figs. 8–11.

Of the isolates unable to be identified to species level, the majority were once again susceptible to linezolid (51/51, 100%), TMP/SXT (74/77, 96%), and amikacin (74/76, 99%), whereas susceptibility to ceftriaxone (39/75, 52%) and imipenem (47/77, 61%) was more variable.

Discussion

Since the advent of molecular techniques, taxonomy of *Nocardia* sp. has expanded rapidly and many new species have been identified [3]. These have been grouped into complexes based on genotypic and phenotypic similarity, but clinical correlation based on these complexes is still nebulous [3]. Despite the use of 16S rDNA sequencing, a large proportion of the isolates were still only able to be identified down to the genus level (80, 17%) and the percentage of isolates identified only to species level did not decrease over time. This is likely in part due to lack of research in the field and limited availability of sequencing data in the NCBI database. Thus, species identification remains difficult despite progression in molecular techniques. This has the potential to delay de-escalation or optimal antimicrobial prescribing, given the variation in susceptibility patterns over the different species.

Species distribution of our isolates differed from previous international studies highlighting the geographical variation and environmental requirements for different *Nocardia* sp. Of the isolates identified to species level in our study, *N. nova* complex was the most commonly isolated, followed by *N. farcinica* complex, *N. cyriacigeorgica* complex, then *N. brasiliensis*. The high proportion of *N. farcinica* complex isolates in our study is of concern given this species is known to be particularly resistant and is increasingly recognised as a nosocomial pathogen [15]. Hence, awareness of *Nocardia* sp. as a pathogen remains important, especially given increases in comorbidity amongst patients, and degree of immunosuppression with the advent of more immunologically challenging donor-recipient matches and expansion of novel treatment of malignancies. Our study did also contain a large proportion of *N. brasiliensis* species (62, 13%) which is in keeping with its role as major SSTI pathogen as well as previous observations that this species is more frequently found in tropical or subtropical climates [16].

In contrast, a Japanese study found a predominance of *N. farcinica* complex, followed by *N. cyriacigeorgica* complex and *N. brasiliensis* [17]. Studies conducted in Spain and USA found *N. cyriacigeorgica* complex followed by *N. nova* complex were the most prevalent species [18, 19]. A French study of 793 isolates found a clear predominance of *N. farcinica* and *abscessus* complex [20]. While climate is likely to play a large role, part of the difference could be due to the over-representation of pulmonary isolates in our study which could reflect persistent colonisation despite treatment.

Other studies have described a change in the species distribution in keeping with changing patient and environmental factors: in particular, Lebeaux et al. documented an increase in the prevalence of *N. farcinica* complex over time, which they postulated was secondary to an increase in infections amongst solid organ transplant recipients [15, 20]. A similar time trend was not observed in our study.

Australian therapeutic guidelines recommend trimethoprim/sulfamethoxazole (TMP/SXT) for cutaneous disease, TMP/SXT with either ceftriaxone or linezolid for pulmonary disease, and TMP/SXT and linezolid, with amikacin, imipenem, or meropenem for severe or disseminated disease [21]. Most of our isolates were susceptible to most of these antimicrobials with the notable exceptions of ceftriaxone and imipenem. The high rate of resistance to ceftriaxone is likely contributed by the proportion of *N. farcinica* complex in our dataset, which has high rates of resistance to beta-lactam antibiotics [22]. This is of concern given that ceftriaxone is the recommended backbone of therapy for pulmonary disease according to our local guidelines [16, 21]. One study previously reported increasing TMP/SXT resistance which was suggested to be plasmid mediated, but our isolates had low rates of resistance (< 5%), as consistent with other recent studies [17, 20, 23–25].

In Australian guidelines, meropenem is recommended in the initial treatment of severe or disseminated disease, but our local laboratories are unable to test specifically for it. Clinicians sometimes use imipenem results to extrapolate meropenem susceptibility, but this is not recommended by our reference laboratory as the validity of this is questionable [26]. In addition, the high rates of resistance to imipenem found here suggest that amikacin, which is recommended as an alternative, may be more effective, and should be considered as first-line in disseminated disease over meropenem [21]. However, the use of amikacin may be limited by its significant side-effect profile. For example, pre-existing renal impairment may be a contraindication in vulnerable transplant patients, as would vestibular and ototoxicity in patients with CNS disease.

Our study is limited by its retrospective nature, the high proportion of isolates not able to speciated, and the absence of MIC data with the older isolates, where susceptibilities were recorded categorically (i.e. susceptible, intermediate, and resistant, without specific MIC data due to the use of disc diffusion AST). In addition, changes in speciation and AST methods over the timeframe could

reduce reliability of identification and AST. Due to the retrospective nature of this data, it was not possible to discern the different methods of testing, nor was it possible to retest the isolates. Our study also had a predominance of pulmonary isolates, which could also reflect persistent colonisation and ease of sampling. Definitions of immunosuppression included steroid use at any dose, which could overestimate the number of patients who were deemed immunosuppressed. However, acknowledging these limitations, this is still the largest Australian study of *Nocardia* sp. to date and provides understanding of the local milieu and antimicrobial susceptibility profiles. Given the wide geographical variation in species, this is important to understand in order to guide empiric treatment recommendations, especially given ongoing difficulty in identifying isolates to species level despite advances in molecular technology.

In light of the antimicrobial susceptibility profiles, review of local guidelines should be considered, especially with regards to empiric ceftriaxone and meropenem. Investigation into clinical treatment and outcomes in these settings is necessary to help guide this. Further work should also be undertaken to enable accurate identification and susceptibility testing, for example, through expansion of sequencing databases. It is likely that evolution of mass spectrometry techniques as well as the application of Next Generation Sequencing techniques will allow greater accuracy of species identification as well as potential resistance prediction.

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Author contribution All authors contributed to the study conception, design, and data collection. Material preparation was performed by Evan Bursle and Andrew Henderson. Analysis was performed by Beatrice Sim, Luke Aaron, Evan Bursle, and Andrew Henderson. The first draft of the manuscript was written by Beatrice Sim, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Data availability The datasets generated during and/or analysed during the current study are not publicly available due to patient confidentiality and privacy reasons, but may be available from the corresponding author on reasonable request.

Declarations

Consent to participate Not applicable.

Consent for publication Not applicable.

Conflict of interest The authors declare no competing interests.

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