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MAJOR ARTICLE

# Nocardiosis in the Tropical Northern Territory of Australia, 1997–2014

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***Background.*** *Nocardia* is an opportunistic pathogen that can cause life-threatening disease. We aimed to characterize the epidemiological, microbiological, and clinical features of nocardiosis in the tropical north of Australia.

***Methods.*** We conducted a retrospective cohort study of nocardiosis diagnosed between 1997 and 2014. Population-based incidences were calculated using district population data.

***Results.*** Clinically significant nocardiosis was identified in 61 patients. The unadjusted population-based annual incidence of nocardiosis was 2.02 (95% confidence interval [CI], 1.55–2.60) per 100 000 people and was 1.7 (95% CI, .96–2.90) fold higher in Indigenous compared with non-Indigenous persons ($P$ = .027). Of 61 patients, 47 (77%) had chronic lung disease, diabetes, and/or hazardous alcohol consumption; 22 (36%) were immunocompromised; and 8 (13%) had no identified comorbidities. Disease presentations included pulmonary (69%; 42 of 61), cutaneous (13%; 8 of 61), and disseminated nocardiosis (15%; 9 of 61). The most commonly identified species were *Nocardia asteroides* and *Nocardia cyriacigeorgica* (each 11%). Linezolid was the only antimicrobial to which isolates were universally susceptible; 89% (48 of 54), 60% (32 of 53), and 48% (26 of 54) of isolates were susceptible to trimethoprim-sulfamethoxazole, ceftriaxone, and imipenem, respectively. Eighteen patients (30%) required intensive care unit (ICU) admission, and 1-year mortality was 31%.

***Conclusions.*** The incidence of nocardiosis in tropical Australia is amongst the highest reported globally. Nocardiosis occurs in both immunocompromised and immunocompetent hosts, and it is associated with high rates of ICU admission, 1-year mortality, and resistance to commonly recommended antimicrobials. Diagnosis should be considered in patients with consistent clinical features, particularly if they are Indigenous or have chronic lung disease.

**Keywords.** epidemiology; immunocompromised host; *Nocardia*; nocardiosis; treatment.

*Nocardia* is a ubiquitous environmental saprophyte that can cause life-threatening disease in humans [1, 2]. Molecular analyses have identified approximately 86 *Nocardia* species, of which half are implicated in human infections [3]. Inhalation is the primary route of entry, but infection can also occur after direct cutaneous inoculation. Subsequent haematogenous dissemination may lead to infection of almost any organ, most commonly the central nervous system (CNS) and cutaneous tissues [4]. Nocardiosis typically affects immunocompromised hosts, particularly those with defects in cell-mediated immunity [1, 4].

*Nocardia* case series are frequently restricted to specific groups, such as solid organ transplant recipients [5, 6] or cancer patients [7], or specific clinical presentations such as pulmonary nocardiosis [8, 9]. There are limited data on the demographics, clinical manifestations, treatment, and long-term outcomes in cohorts that include both immunocompromised and immunocompetent individuals, and very few studies report the population-based incidence of nocardiosis [10].

There are few reported series of clinical nocardiosis in Australia and none from the tropical north; the incidence of nocardiosis is unknown because the disease is not notifiable. We aimed to review the epidemiology, demographics, comorbidities, clinical presentation, microbiology, treatment, and outcomes of all *Nocardia* infections presenting to Royal Darwin Hospital (RDH) in the tropical north of Australia, over an 18-year period from 1997 to 2014.

## METHODS

### Design and Setting

We conducted a retrospective cohort study of nocardiosis managed at RDH, a 350-bed tertiary referral center that serves a well defined population of 170 000 over an area of approximately 500 000 km$^2$ [11]. Ethics approval was provided by the Human Research Ethics Committee of the Northern Territory (NT) Department of Health (HREC 10–1354).

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### Study Population

All patients with clinically significant culture-positive *Nocardia* infection identified between January 1997 and December 2014 were eligible for inclusion. Potential cases were identified through the following: (1) the RDH microbiology isolate database; (2) hospital discharge summary coding data; and (3) the infectious diseases consultation database. All cases were reviewed by at least 2 investigators, and a consensus was reached to classify the patient as "colonized" or "infected". Cases were classified as clinically significant (infected) when culture of *Nocardia* species was associated with clinical disease judged by an infectious diseases specialist as requiring treatment.

Infections were divided into 3 categories: primary pulmonary (infection confined to the lungs and pleural space), primary cutaneous (infection localized to the skin and soft tissues with no other organ involvement), and disseminated disease (involvement of ≥2 noncontiguous organs, disease of the CNS, or the presence of *Nocardia* species in blood samples). Hazardous alcohol consumption was defined according to the definition of "harmful drinking" in Australian Guidelines [12]. Individual patient consent was not required because only data collected in the course of routine clinical care were extracted.

### Data Collection

Demographic, clinical, treatment, and outcome data were collected from medical records. Microbiological data (specimen type, *Nocardia* species, and antimicrobial susceptibility) were obtained from the laboratory database. Data were entered into a purpose-built database (Epidata 3.1, Odense, Denmark).

### Microbiology Methods

Presumptive diagnosis of *Nocardia* species was made in the RDH microbiology laboratory based on Gram and/or modified acid-fast staining findings and colony morphology. Isolates were referred to a reference laboratory for species identification by sequencing of 16S ribosomal ribonucleic acid and *secA1* housekeeping genes [3, 13, 14]. Antimicrobial susceptibility testing was performed by Clinical and Laboratory Standards Institute standardized broth microdilution methods [15].

### Statistical Analysis

Data were analyzed using STATA (version 10; StataCorp, College Station, TX). Descriptive statistics are presented as means, medians, and proportions, and between group differences were assessed with the Fisher's exact test and Wilcoxon rank-sum test, as appropriate for the data. Population-based incidence was calculated using health district population data from 1997 to 2014, collated from Australian Bureau of Statistics data by the Health Protection Division of the NT Department of Health [11].

## RESULTS

### Epidemiology and Demographics

Between January 1997 and December 2014, *Nocardia* was isolated from the clinical specimens of 75 patients. Sixty-one patients had isolates that were considered clinically significant and were included in the analysis. Fourteen patients were thought to be colonized with *Nocardia* and were excluded: all had *Nocardia* isolated from respiratory specimens, none met criteria for clinical nocardiosis, and none received specific treatment for nocardiosis. Follow-up data were available for 7 (50%) patients: patients were observed for a median of 12 months (range, 8–55 months) with 2 reported deaths: one attributed to metastatic cancer and the other to end-stage chronic lung disease.

The overall population-based incidence of *Nocardia* infections was 2.02 (95% confidence interval [CI], 1.55–2.60) per 100 000 people per year and was 1.7 (95% CI, .96–2.90; $P = .027$) fold higher in Indigenous people (2.8 [95% CI, 1.83–4.32] per 100 000/year) compared with non-Indigenous people (1.71 [95% CI, 1.21–2.35] per 100 000/year). The most common place of residence was urban Darwin (46%; 28 of 61) (Supplemental Figure 1). The mean number of *Nocardia* cases per year was 3.4 (range, 0–9), and the yearly number of cases between 1997 and 2014 demonstrated an upward trend (1, 3, 1, 1, 3, 2, 0, 1, 3, 5, 4, 6, 5, 3, 2, 6, 6, 9).

Demographic features are described in Table 1. The median age was 57 years (range, 1–80); 34 (56%) were male and 23 (38%) were Indigenous. Indigenous patients were more likely to be female (65%; 15 of 23) compared with non-Indigenous patients (32%; 12); odds ratio = 2.07, 95% CI = 1.19–3.60, $P = .016$. The most frequently identified predisposing factor was chronic lung disease, which was present in 32 patients (52%), primarily related to chronic obstructive pulmonary disease. Other common predisposing factors were hazardous alcohol consumption (18 patients; 30%) and diabetes mellitus (13 patients; 21%). Fifty-three patients (87%) had at least 1 predisposing factor, and 22 patients (36%) were recognized to be immunocompromised. The most common immunocompromising factors identified were immunosuppressive drug therapy (15 patients; 25%) and active malignancy (12 patients; 20%). Other immunocompromising factors included solid organ transplant (3 patients; 5%) and human immunodeficiency virus (HIV) infection (2 patients; 3%). It is noteworthy that 39 (64%) patients were considered to be immunocompetent, and 8 patients (13%) had no documented predisposing or immunocompromising factors.

### Clinical Characteristics

Sites of infection for all patients are shown in Figure 1. Forty-two patients (69%) had primary pulmonary, 8 (13%) had primary cutaneous, and 9 (15%) had disseminated disease. Six patients (67%) with disseminated disease had evidence of CNS disease. Two patients had localized infections at other sites: one was a peritoneal dialysis patient with *Nocardia* peritonitis, the other was a patient with metastatic colorectal cancer complicated by an ilio-vaginal fistula who had *Nocardia* isolated from a recurrent pelvic collection.

**Table 1. Demographic Features of 61 Patients**

| Patient Characteristics | Number (%) |
|---|---|
| Age, median years (range) | 57 (range 1–80) |
| Male | 34 (56%) |
| Indigenous | 23 (38%) |
| Male | 8 (35%) |
| Female | 15 (65%) |
| Nonindigenous | 38 (62%) |
| Male | 26 (68%) |
| Female | 12 (32%) |
| Predisposing and immunocompromising factors | |
| Chronic lung disease | 32 (52%) |
| Diabetes mellitus | 13 (21%) |
| Hazardous alcohol consumption | 18 (30%) |
| Immunosuppressive medication[a] | 15 (25%) |
| High-dose corticosteroid-based therapy in preceding 3 months[b] | 13 (21%) |
| Other immunosuppressive therapy[c] | 2 (3%) |
| Active malignancy | 12 (20%) |
| Cytotoxic chemotherapy in past 6 months | 5 (8%) |
| Solid organ transplantation[d] | 3 (5%) |
| HIV infection | 2 (3%) |
| Number of predisposing/immunocompromising factors (from above list) | |
| 0 | 8 (13%) |
| 1 | 26 (43%) |
| 2 or more | 27 (44%) |
| Immunocompromised[e] | 22 (36%) |

Abbreviations: HIV, human immunodeficiency virus.

[a]Immunosuppressive medications included corticosteroids, calcineurin inhibitors, mycophenolate mofetil, azathioprine, and methotrexate.

[b]Defined as ≥20 mg/day prednisolone or >2 mg/day dexamethasone for 1 month or >2 pulses of 1 gram intravenous methylprednisolone with or without other immunosuppressive agents.

[c]Patients receiving low-dose prednisolone (<20 mg/day) and at least 1 other immunosuppressive agent.

[d]Renal transplantation in all 3 patients.

[e]Defined as presence of any of the following: immunosuppressive medication, history of transplantation, HIV infection, active malignancy.

There was no clear association between clinical disease pattern and immune status (Figure 2). Of the 8 patients with primary cutaneous disease, only 1 was immunocompromised (history of active malignancy and autoimmune hepatitis on prednisolone and azathioprine). Nineteen of the 42 patients with pulmonary disease were immunocompromised, including the 3 solid organ transplant recipients and 2 HIV-infected patients. Of the 9 patients with disseminated disease, only 1 was immunocompromised (history of active malignancy and recent iatrogenic corticosteroids). Other predisposing factors for disseminated disease included hazardous alcohol (4 patients), chronic lung disease (4 patients), and diabetes (2 patients).

### Microbiology and Susceptibility Profiles

*Nocardia* was isolated from 71 sites from the 61 patients. Most cases were diagnosed from noninvasive samples, including sputum (58%) and wound swabs (14%). Only 1 patient had *Nocardia* isolated from blood cultures.

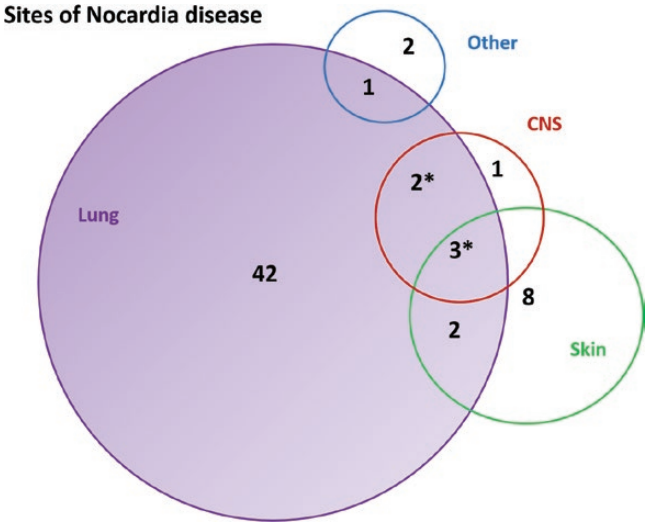


**Figure 1.** Sites of infection for 61 patients with *Nocardia*. *These patients also had disease at an "other" site. Sites of *Nocardia* in patients with disseminated disease included lung (8 patients, 89%), skin (5 patients, 44%), central nervous system (CNS) (6 patients, 67%), bones or joints (3 patients, 33%), kidney (1 patient, 11%), and adrenal (1 patient, 11%). Venn diagram drawn and calculated using eulerAPE software (Micallef L, Rodgers P. eulerAPE: Drawing Area-Proportional 3-Venn Diagrams Using Ellipses. PLoS ONE, 2014; 9(7):e101717. http://www.eulerdiagrams.org/eulerAPE).

Sixty-three *Nocardia* isolates were submitted for molecular identification. The 41 isolates identified to the species level represented 15 different species (Table 2). An additioinal 9 isolates were identified as belonging to the *Nocardia asteroides* complex, and 13 isolates were identified as *Nocardia* but species could not be further determined. No association between *Nocardia* species and clinical disease pattern was noted. Antimicrobial susceptibility testing results were available for 55 isolates, and significant variability in susceptibility was seen across different species. The only antimicrobial to which isolates were universally susceptible was linezolid (Table 2). Eighty-nine percent of tested isolates were susceptible to trimethoprim-sulfamethoxazole (TMP-SMX) and amikacin, respectively, 60% were

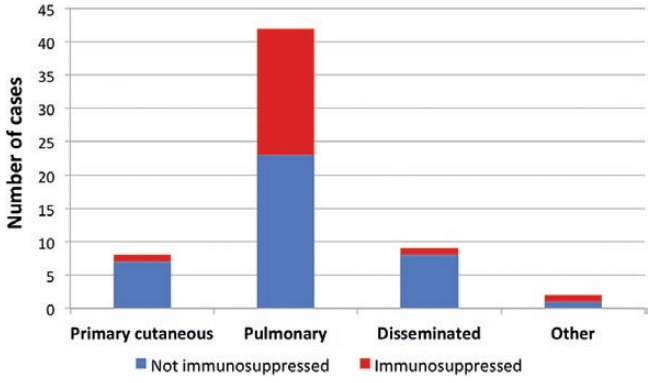


**Figure 2.** Immune status and disease site. Immunosuppressive factors included are immunosuppressive medications, active malignancy, solid organ transplantation, and human immunodeficiency virus.

**Table 2. Species Distribution and Susceptibility Profile of *Nocardia* Isolates**

| Species | No. of Isolates (%Total) | No. of Isolates With AST | Percentage (Proportion) of Isolates Susceptible | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | LZD | TMP-SMX | AMK | CEF | CLA | IMI | CIP | AUG |
| *Nocardia asteroides* sensu stricto | 7 (11%) | 7 | NP | 100% (7/7) | 100% (5/5)* | 100% (7/7) | 33% (1/3)* | 86% (6/7) | 29% (2/7) | 0% (0/7) |
| *N asteroides* complex[†] | 9 (14%) | 9 | 100% (3/3)* | 89% (8/9) | 89% (8/9) | 67% (6/9) | 78% (7/9) | 67% (6/9) | 33% (3/9) | 33% (3/9) |
| *Nocardia beijingensis* | 4 (6%) | 4 | 100% (3/3)* | 100% (4/4) | 100% (4/4) | 100% (4/4) | 100% (3/3)* | 50% (2/4) | 25% (1/4) | 0% (0/4) |
| *Nocardia blacklockiae* | 1 (2%) | 1 | 100% (1/1) | 100% (1/1) | 0% (0/1) | 100% (1/1) | 100% (1/1) | 0% (0/1) | 0% (0/1) | 0% (0/1) |
| *Nocardia brevicatena* | 1 (2%) | 1 | 100% (1/1) | 100% (1/1) | 100% (1/1) | 100% (1/1) | 100% (1/1) | 0% (0/1) | 100% (1/1) | 0% (0/1) |
| *Nocardia caviae* | 3 (5%) | 1 | NP | 100% (1/1) | 100% (1/1) | 0% (0/1) | 0% (0/1) | 100% (1/1) | 0% (0/1) | 0% (0/1) |
| *Nocardia cyriacigeorgica* | 7 (11%) | 6 | 100% (4/4)* | 67% (4/6) | 100% (6/6) | 67% (4/6) | 0% (0/6) | 33% (2/6) | 0% (0/6) | 0% (0/6) |
| *Nocardia cerradoensis* | 1 (2%) | 0 | NP | NP | NP | NP | NP | NP | NP | NP |
| *Nocardia elegans* | 1 (2%) | 1 | 100% (1/1) | 100% (1/1) | 100% (1/1) | 0% (0/1) | NP | 0% (0/1) | NP | NP |
| *Nocardia farcinica* | 3 (5%) | 2 | 100% (1/1)* | 100% (1/1)* | 100% (2/2) | 0% (1/1)* | 0% (1/1)* | 0% (0/1)* | 100% (2/2) | 0% (0/1)* |
| *Nocardia nova* | 2 (3%) | 1 | NP | 100% (1/1) | 100% (1/1) | NP | 100% (1/1) | 100% (1/1) | 0% (0/1) | 0% (0/1) |
| *Nocardia otidiscaviarum* | 3 (5%) | 3 | NP | 100% (3/3) | 100% (2/2)* | 0% (0/3) | 0% (0/2)* | 33% (1/3) | 33% (1/3) | 0% (0/3) |
| *Nocardia pseudobrasiliensis* | 2 (3%) | 2 | NP | 100% (2/2) | 50% (1/2) | 100% (2/2) | 100% (2/2) | 0% (0/2) | 100% (2/2) | 0% (0/2) |
| *Nocardia seriolae* | 1 (2%) | 1 | NP | 100% (1/1) | 100% (1/1) | 0% (0/1) | 100% (1/1) | 0% (0/1) | 0% (0/1) | 0% (0/1) |
| *Nocardia transvalensis* | 2 (3%) | 2 | 100% (1/1)* | 50% (1/2) | 0% (0/2) | 100% (2/2) | 0% (0/2) | 0% (0/2) | 50% (1/2) | 0% (0/2) |
| *Nocardia veterana* | 3 (5%) | 3 | NP | 100% (3/3) | 100% (3/3) | 67% (2/3) | 67% (2/3) | 67% (2/3) | 0% (0/2)* | 0% (0/3) |
| *Nocardia* sp (unspeciated) | 13 (21%) | 11 | 100% (7/7)* | 82% (9/11) | 91% (10/11) | 27% (3/11) | 60% (6/10)* | 45% (5/11) | 27% (3/11) | 10% (1/10)* |
| Total (all *Nocardia* isolates) | 63 | 55 | 22/22 (100%) | 48/54 (89%) | 46/52 (89%) | 32/53 (60%) | 25/46 (55%) | 26/54 (48%) | 16/53 (30%) | 4/52 (8%) |

Abbreviations: AMK, amikacin; AST, antimicrobial susceptibility testing; AUG, amoxicillin-clavulanate; CEF, ceftriaxone/cefotaxime; CIP, ciprofloxacin; CLA, clarithromycin; IMI, imipenem/meropenem; LZD, linezolid; NP, testing not performed; TMP-SMX, trimethoprim-sulfamethoxazole.

*Indicates that 1 or more isolates were not tested.

[†]The "*N asteroides* complex" is an old taxonomic classification referring to a group of *Nocardia* isolates that have now been separated into different species (including *N nova*, *N transvalensis*, and *N farcinica*).

susceptible to ceftriaxone, and only 48% were susceptible to imipenem.

#### Treatment

Information on treatment prescribed was available for 58 patients (95%). The remaining 3 patients did not receive treatment for nocardiosis; 1 was palliated, and the other 2 died before the diagnosis being made. Four patients did not commence treatment until after susceptibility results were available. The remaining 54 patients (89%) received empirical combination therapy. Empiric TMP-SMX was almost universal (52 patients; 96%), usually in combination with ceftriaxone (32 patients; 59%) and/or meropenem (26 patients; 48%). Amikacin (6 patients) and linezolid (3 patients) were uncommon in empiric regimens.

Drug susceptibility results were available for 46 of 54 patients who received empiric therapy. Of these, 93% (43 of 46) received empirical treatment with at least 1 antibiotic active against the corresponding isolate, and 57% (26 of 46) received 2 or more active antibiotics. Three patients (7%) did not receive effective empiric treatment: all 3 had isolates resistant to TMP-SMX, ceftriaxone, and imipenem. One of the 3 had disseminated nocardiosis and died before susceptibilities became available: he was treated with ceftriaxone, meropenem, and TMP-SMX but his *Nocardia* sp isolate only tested susceptible to amikacin and linezolid.

Among the 43 patients who completed treatment and whose susceptibility results were known, oral TMP-SMX was the most commonly prescribed antibiotic (37 patients; 86%), administered either alone (10 of 37) or in combination with other agents. Definitive regimens included ceftriaxone (17 patients), meropenem (8 patients), amikacin (6 patients), linezolid (6 patients), ciprofloxacin (5 patients), clarithromycin (3 patients), minocycline (3 patients), and amoxicillin-clavulanate (1 patient). Sixteen patients (28%) developed a drug-related adverse event requiring treatment modification; 13 (81%) were related to TMP-SMX and included the development of cytopenia, rash, and/or gastrointestinal upset. Two adverse events were related to amikacin: 1 case each of reversible acute kidney injury and reversible hearing loss. One patient receiving linezolid developed anemia after 2 weeks of therapy, but the drug was successfully reintroduced 2 weeks later without further complications.

In those who completed treatment, the mean duration of therapy was 7 months (range, 2–15 months; interquartile range [IQR], 5–9 months). The mean duration of intravenous (IV) therapy was 28 days (range, 0–5 months), and mean duration of oral therapy was 6 months (range, 1–14 months). Patients with primary cutaneous disease received shorter treatment courses, with a mean duration of 4.5 days IV (range, 0–14 days) and 3 months oral therapy (range, 2–6 months). In contrast, those with disseminated disease who survived beyond 30 days received a mean duration of 2 months IV (range, 1–4 months) and 9 months oral therapy (range, 3–15 months).

#### Outcome

Fifty-eight patients were hospitalized. Median length of stay was 20 days (IQR, 10–44 days). Patients were observed for a median of 461 days. Four patients were lost to follow up at 30 days, and 8 patients were lost to follow up at 1 year. No deaths or ICU admissions occurred in the primary cutaneous nocardiosis group. Of the 39 immunocompetent patients, 12 (31%) were admitted to ICU and 9 (27%) died within 1 year of diagnosis. Amongst the immunocompromised patients, 6 (27%) were admitted to ICU and 10 (45%) died within 1 year of diagnosis. Of the 42 patients with pulmonary disease, 12 (29%) were admitted to ICU, 30-day mortality was 13%, and 1-year mortality was 40%. Of the 9 patients with disseminated disease, 56% (5 of 9) were admitted to ICU and 30-day mortality was 33% (3 of 9); no additional deaths were recorded at 1 year. No statistically significant association ($P < .05$) was identified between any clinical risk factors and mortality or ICU admission (Table 3). High rates of ICU admission (34%) and 1-year mortality (31%) were seen in the chronic lung disease group.

## DISCUSSION

This large case series provides the first detailed account of the spectrum of nocardiosis in Australia's tropical north. The annual incidence of nocardiosis was 2.02 per 100 000 people, substantially higher than previously reported rates in Quebec, Canada [16], Madrid, Spain [10], and South Australia (ranging from 0.47 to 0.87 per 100 000 people) [17].

We observed similar clinical presentations to those seen in other unrestricted case series. Pulmonary nocardiosis is described as the most common clinical presentation of *Nocardia* infection [4], and 82% of our cohort had pulmonary involvement. Fifteen percent of patients in our series had disseminated disease, slightly higher than the 6%–13% seen in other unrestricted case series [7, 18, 19] but lower than the 20%–21% reported in highly immunosuppressed populations such as solid organ transplant patients [5, 20]. The overall proportion of immunocompromised hosts in our population (36%) was lower than that reported in a previous review of the *Nocardia* literature [2].

Our findings highlight the importance of hazardous alcohol as a predisposing factor for nocardiosis. Hazardous alcohol use was reported in 30% of cases, including 44% of the patients with disseminated disease. In 13% of cases (8 of 61), hazardous alcohol use was the only reported predisposing factor for nocardiosis. These findings support previous studies that have suggested (1) an association between hazardous alcohol use and nocardiosis [19, 21–23], (2) that alcohol abuse may be a predisposing factor for dissemination of *Nocardia* to the CNS [21, 22, 24], and (3) that alcohol may be an important cofactor in predisposition to *Nocardia* infection due to its effect on macrophage function [25].

**Table 3. Univariate Analysis of Death and ICU Admission***

| Variable | ICU Admission (N = 61) | | Death 30 d (N = 57)† | | Death 1 y (N = 53)† | |
|---|---|---|---|---|---|---|
| | Y (N = 18) Number (%) | N (N = 43) Number (%) | Y (N = 8) Number (%) | N (N = 49) Number (%) | Y (N = 19) Number (%) | N (N = 34) Number (%) |
| Age >60 | 5 (28%) | 17 (40%) | 4 (50%) | 17 (35%) | 8 (42%) | 12 (35%) |
| Female gender | 7 (39%) | 20 (47%) | 2 (25%) | 25 (51%) | 6 (32%) | 20 (59%) |
| Diabetes | 4 (22%) | 9 (21%) | 2 (25%) | 11 (22%) | 4 (21%) | 9 (26%) |
| Hazardous alcohol | 7 (39%) | 11 (26%) | 3 (38%) | 15 (31%) | 4 (21%) | 12 (35%) |
| Malignancy | 3 (17%) | 9 (21%) | 2 (25%) | 8 (16%) | 6 (32%) | 4 (12%) |
| Chronic lung disease | 10 (56%) | 22 (51%) | 5 (65%) | 24 (49%) | 10 (53%) | 19 (56%) |
| Transplant | 1 (6%) | 2 (5%) | 0 (0%) | 3 (6%) | 0 (0%) | 3 (9%) |
| HIV | 0 (0%) | 2 (5%) | 0 (0%) | 2 (4%) | 0 (0%) | 2 (6%) |
| Immunosuppressive medication | 6 (33%) | 9 (21%) | 3 (38%) | 11 (22%) | 7 (37%) | 7 (21%) |
| Indigenous | 8 (44%) | 15 (35%) | 2 (25%) | 21 (43%) | 7 (37%) | 15 (44%) |
| Cutaneous disease | 0 (0%) | 8 (19%) | 0 (0%) | 8 (16%) | 0 (0%) | 3 (9%) |
| Pulmonary disease | 12 (67%) | 30 (70%) | 5 (65%) | 35 (71%) | 16 (84%) | 24 (71%) |
| Disseminated disease | 5 (28%) | 4 (9%) | 3 (38%) | 5 (10%) | 3 (16%) | 5 (15%) |
| Remote | 8 (44%) | 10 (23%) | 2 (25%) | 16 (33%) | 7 (37%) | 10 (29%) |
| Immunocompromised | 6 (33%) | 16 (37%) | 3 (38%) | 17 (35%) | 10 (53%) | 10 (29%) |
| *Nocardia* isolate resistant to TMP-SMX | 2 (11%) | 4 (9%) | 1 (13%) | 5 (10%) | 2 (11%) | 3 (9%) |

Abbreviations: CNS, central nervous system; HIV; human immunodeficiency virus; ICU, intensive care unit; TMP-SMX, trimethoprim-sulfamethoxazole.

*Associations between categorical variables measured using Fisher's exact test.

†Numbers in these columns relate to cases where data was available. Four patients were lost to follow up by 30 days, and 8 patients were lost to follow up by 1 year. Note: $P > .05$ in each instance.

Chronic lung disease is well recognized as a predisposing factor for pulmonary nocardiosis, both in the presence and absence of immunosuppressive factors [9, 17, 24, 26]. Chronic lung disease was an important predisposing factor for nocardiosis in our population; approximately two fifths of these patients also had coexistent immunosuppressive factors. Furthermore, chronic lung disease was associated with high rates of ICU admission and 1-year mortality. The presence of clinical nocardiosis in this population may reflect very severe lung disease and heralds a poor prognosis.

Our study accords with previous reports of high mortality (31%–40%) and high rates of ICU admission in unrestricted studies of pulmonary and disseminated nocardiosis [10, 19, 26–28]. Severe disease was common, and fulminant presentations were seen in both immunocompetent and immunocompromised individuals. One third of those with pulmonary and disseminated nocardiosis were admitted to ICU, and 1-year mortality was 38%. It is worth noting that there was a wide range of clinical presentations among immunocompetent hosts, including disseminated disease, as has also been reported previously in Australia [19, 21, 22].

Previous case series of nocardiosis have reported a higher proportion of men compared with women [7–9]. This was not the case in our series, largely due to the overrepresentation of women amongst Indigenous patients with nocardiosis, a phenomenon seen with other infections in this population [29, 30]. A higher incidence of nocardiosis was seen in Indigenous people versus nonindigenous people (2.88 versus 1.71 incident cases per 100 000 people per year); similar findings have also been observed in the setting of other infections in the NT [29]. Possible explanations for the disproportionate burden of nocardiosis in the Indigenous population include a higher rate of predisposing factors such as diabetes, chronic lung disease [31], and hazardous alcohol use, as well as increased environmental exposure.

Randomized controlled trials investigating the treatment of *Nocardia* infection are extremely challenging given the low numbers of patients presenting at a single institution. Hence, existing recommendations are largely based on observational studies and expert opinion. Because susceptibility profiles vary widely among *Nocardia* species, combination therapy is frequently used. Current Australian guidelines [32] recommend the use of TMP-SMX plus at least 1 other agent. In our cohort, the most common empirical regimen was TMP-SMX plus ceftriaxone and/or meropenem, and the majority of cases (93%) received an empiric regimen containing at least 1 antibiotic that was active against the corresponding isolate. Rates of TMP-SMX resistance amongst isolates in our study were relatively low (11%), but ceftriaxone (40%) and imipenem (52%) resistance was common, and 4 *Nocardia* isolates included in our study were resistant to TMP-SMX, ceftriaxone, and imipenem, including 2 *Nocardia cyriacigeorgica* isolates. All 4 of these isolates were susceptible to linezolid.

Large antimicrobial susceptibility studies of *Nocardia* isolates have been performed in the United States, Canada, Spain, and Taiwan. Reported resistance rates to imipenem (25%–51%) and ceftriaxone (32%–86%) are high; whereas resistance to amikacin (0%–5%) and linezolid (0%–1%) is uncommon [16, 33–37]. There is considerable variability in reporting of TMP-SMX

resistance, ranging from 2% to–43% across these studies. Although geographic variation in *Nocardia* isolates may account for some of the variability between studies, Brown-Elliott et al [36] (who report a 2% TMP-SMX resistance rate amongst their *Nocardia* isolates) hypothesize that the discrepancy may be associated with difficulty in the laboratory interpretation of in vitro minimum inhibitory concentrations and the lack of quality controls for *Nocardia* for TMP-SMX. Although reports of in vitro resistance TMP-SMX have increased, there have only been rare clinical reports describing treatment failure with TMP-SMX [36, 38]. It is notable that 1 patient in our series with TMP-SMX resistance had a fatal outcome.

All of the isolates presented here demonstrated in vitro susceptibility to linezolid. In vitro activity of linezolid against all clinically relevant species of *Nocardia* has previously been demonstrated [33, 37], and clinical success has been reported in case reports and series [38, 39]. Although linezolid has excellent bioavailability and crosses the blood-brain barrier, the barriers to its use are high cost and serious toxicities associated with prolonged administration, which include myelosuppression, lactic acidosis, peripheral neuropathy, and optic neuritis [40]. However, in light of its excellent in vitro profile against *Nocardia*, it is attractive as an option for empiric treatment of nocardiosis in patients with extensive or disseminated disease. Based on our experience, we would recommend an empiric regimen that includes TMP-SMX and linezolid in unwell patients pending susceptibilities.

There are some limitations to our study. Data were collected retrospectively and did not include potentially relevant comorbidities such as chronic liver disease and nondialysis-dependent chronic kidney disease. Species identification of *Nocardia* isolates occurred at the time of collection, and taxonomic changes have occurred over time. In addition, this is a single-center study from a geographically restricted area, and findings regarding species type and susceptibilities are not necessarily applicable to other settings.

## CONCLUSIONS

The annual incidence rate of *Nocardia* infections in our setting is the highest reported globally to date. Chronic lung disease was the most common underlying condition. Most of the patients in our series did not have classic immunosuppressive risk factors, but hazardous alcohol use and diabetes were common. Severe disease was seen in both immunocompromised and immunocompetent hosts, and there were high rates of ICU admission and 1-year mortality. Linezolid and TMP-SMX demonstrated the best in vitro activity against the isolates studied and should be considered for inclusion in an empiric regimen for unwell patients with nocardiosis pending susceptibilities. The diagnosis of nocardiosis should be considered in patients presenting with consistent clinical features regardless of immunosuppression status, particularly if they have underlying chronic lung disease.

## Supplementary Data

Supplementary material is available at *Open Forum Infectious Diseases* online.

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