Journal of Microbiology, Immunology and Infection 56 (2023) 382–391

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.e-jmii.com

Original Article

Clinical manifestations and outcome of nocardiosis and antimicrobial susceptibility of *Nocardia* species in southern Taiwan, 2011–2021

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Received 15 May 2022; received in revised form 15 October 2022; accepted 12 November 2022
Available online 17 November 2022

KEYWORDS
Nocardiosis;
Antimicrobial susceptibility;
Microbroth dilution method;
Carbapenem;
Trimethoprim-sulfamethoxazole

Abstract *Background/Purpose:* Nocardiosis is an uncommon infectious disease. This study aimed to assess the clinical outcome of patients with nocardiosis and examine the antimicrobial susceptibility profiles of *Nocardia* spp. isolated.
Methods: We retrospectively reviewed the medical records of all inpatients diagnosed with nocardiosis between 2011 and 2021. The identification of *Nocardia* spp. at the species level was performed with the use of MALDI-TOF and 16S rRNA assays. The antimicrobial susceptibility of *Nocardia* spp. was performed using the microbroth dilution method. Factors associated with 90-day all-cause mortality were identified in multivariate logistic regression analysis.
Results: Of 60 patients with nocardiosis in the 11-year study period, the lungs (55.0%) were the most common site of involvement, followed by the skin and soft tissue (45.0%). Twenty-two patients (36.7%) died within 90 days following the diagnosis. All of the *Nocardia* isolates were susceptible to trimethoprim-sulfamethoxazole, linezolid, and amikacin, whereas more than 70% of the isolates were not susceptible to ciprofloxacin, imipenem-cilastatin, moxifloxacin, cefepime, and clarithromycin. Nocardiosis involving the lungs (relative risk [RR], 9.99; 95% confidence

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https://doi.org/10.1016/j.jmii.2022.11.002

interval [CI], 1.52–65.50; $p = 0.02$), nocardiosis involving the skin and soft tissue (RR, 0.15; 95% CI, 0.02–0.92; $p = 0.04$), and treatment with trimethoprim-sulfamethoxazole (RR, 0.14; 95% CI, 0.03–0.67; $p = 0.01$) were independently associated with 90-day all-cause mortality.
Conclusions: Nocardia spp. identified between 2011 and 2021 remained fully susceptible to trimethoprim-sulfamethoxazole, linezolid, and amikacin. Nocardiosis of the lungs, skin and soft tissue infection, and treatment with trimethoprim-sulfamethoxazole were independently associated with 90-day all-cause mortality.

Introduction

As an aerobic filamentous Gram-positive rod with beaded, right-angled branching hyphae resembling *Actinomyces* and *Mycobacterium*, *Nocardia* spp. can cause infections at various body sites, most of which are caused by *N. asteroides complex* (*N. abscessus, N. brevicatena/paucivorans complex, N. cyriacigeorgica, N. farcinica,* and *N. nova complex*).[1] In immunocompromised patients, pulmonary nocardiosis is more common than extrapulmonary nocardiosis that is characterized by a pyogenic bacterial process that evolves into a chronic granulomatous mass, usually presenting as a brain abscess. Either localized infection or disseminated infection may occur, and in rare cases, *Nocardia* spp. cause bacteremia. In immunocompetent patients, nocardiosis involving the skin and soft tissue is more common, which usually manifests as cellulitis, mycetoma, and sporotrichosis-like lympho-cutaneous lesions.[2] The mortality rate of nocardiosis may vary widely among different patient groups. In one study, the overall 1-year all-cause mortality rate of nocardiosis was 19% [3]; the mortality rates were 27% and 7% for immunocompromised and immunocompetent patients, respectively.[3] In another study of invasive nocardiosis, the mortality rates were 41% for patients with pneumonia, and 64% for those with disseminated infection; and the mortality was as high as 100% for those with nocardiosis involving the central nervous system (CNS).[4] Invasive nocardiosis involving the lung or CNS may mimic other indolent infections such as tuberculosis and fungal disease, sarcoidosis, and neoplasia,[5] for which clinical imaging may not be sensitive or specific. The diagnosis of nocardiosis might not be made timely due to time-consuming confirmation by culture, and concerns about the risk of obtaining tissue for microbiologic or histopathologic investigations, or due to partial treatment with broad-spectrum antimicrobials.[5] Rapid molecular diagnosis and appropriate antibiotic treatment according to antimicrobial susceptibility profiles is imperative to achieve treatment success and improve survival.

Sulfa drugs such as trimethoprim-sulfamethoxazole (TMP-SMX) are the drugs of choice for treating nocardiosis.[6] However, TMP-SMX can cause toxicities, including nausea, vomiting, renal tubular injury with hyperkalemia, Stevens-Johnson syndrome, and agranulocytosis.[7] Moreover, immunocompromised patients, such as people living with HIV, are at higher risk of acquiring nocardiosis caused by TMP-SMX-resistant strains.[8] While the alternative regimens may include several beta-lactam antibiotics, such as cefotaxime, ceftriaxone (CRO), imipenem-cilastatin (IMP), and meropenem, as well as aminoglycosides, macrolides, quinolones, tetracycline, and linezolid (LZD),[2,9] the antimicrobial susceptibility of *Nocardia* spp. to these antimicrobials is highly variable, with some species having higher levels of multi-drug resistance, such as *N. farcinica*.[10] Among these antimicrobials for nocardiosis, IMP is one of the recommended antibiotics for combination or alternative treatment of nocardiosis[9] and treatment with IMP-containing regimens was reported to be effective in cases that were refractory to TMP-SMX.[11] However, more data are needed to better define the susceptibility of clinical *Nocardia* strains to IMP and other antimicrobials.

A previous multicenter study in Taiwan between 1998 and 2009 revealed that *N. brasiliensis* was the most common species, less than 10% of the *Nocardia* isolates were resistant to amikacin, TMP-SMX, and LZD, and 30% of the isolates were non-susceptible to IMP.[12] A recent study of nocardiosis conducted in northern Taiwan between 2011 and 2020 showed that, with *N. brasiliensis* being the common isolate, the rate of resistance to IMP had increased over time, while 98.9% of the isolates remained susceptible to TMP-SMX and LZD.[13] In contrast, Chen et al. found that *N. cyriacigeorgica* was the predominant species in patients with pulmonary nocardiosis in southern Taiwan between 2004 and 2010,[14] suggesting that geographic and temporal variations in terms of species distribution and antimicrobial susceptibility may occur for nocardiosis. This study aimed to identify the associated factors with mortality of patients with nocardiosis and to examine the susceptibility profiles of *Nocardia* spp. collected at a tertiary hospital in southern Taiwan between 2011 and 2021.

Methods

Study design

This retrospective cohort study was conducted at Kaohsiung Chang Gung Memorial Hospital (KCGMH). The study included inpatients aged >18 years who received a diagnosis of nocardiosis between 2011 and 2021. Electronic medical records were reviewed to collect clinical information on disease severity using the Charlson Comorbidity Index,[15] diagnosis of septic shock, immunocompromising conditions including hematological malignancy, solid tumor, autoimmune diseases, AIDS, and use of immunosuppressives, and intensive care unit stay 6 months prior to the diagnosis of nocardiosis being made.

Microbiological investigations

Identification of *Nocardia* spp. at the species level was conducted with the use of matrix-assisted laser desorption ionization-time of flight mass spectrometry (MALDI-TOF MS)[16] and 16S rRNA assays.[17,18] The microbroth dilution method was used for antimicrobial susceptibility testing (Sensititre RAPMYCOI; TREK Diagnostic Systems Ltd., Cleveland, OH, USA).[19] *Staphylococcus aureus* ATCC 29213 and *Escherichia coli* ATCC 25922 were used as quality control strains. The antibiotics tested included amikacin (AN), amoxicillin/clavulanic acid (AMC), cefepime (FEP), CRO, ciprofloxacin (CIP), clarithromycin (CLA), doxycycline (DOX), IMP, LZD, moxifloxacin (MXF), tigecycline (TGC), and TMP-SMX. The Clinical and Laboratory Standards Institute (CLSI) of M24 and M62 charts were the minimum inhibitory concentration (MIC) references for aerobic actinomycetes.[19] Antimicrobial susceptibility of the included antibiotics against *Nocardia* spp. were presented as MIC range (minimum to maximum), MIC_{50}, MIC_{90}, MIC-geometric mean, and rate of antimicrobial non-susceptibility. The rate of antimicrobial non-susceptibility was defined as the proportion of isolates not classified as susceptible, according to the CLSI reference.19 An analysis of the trends of *Nocardia* spp. with IMP non-susceptibility was performed. Only the first isolate of *Nocardia* spp. cultured from each patient with nocardiosis was included for antimicrobial susceptibility testing if more than one isolate was collected from the same patient during the hospital stay.

Definitions

The sites of infection were defined according to the culture site, clinical manifestations, and imaging findings. Nocardiosis was defined as a positive culture for Nocardia species and the presence of clinical signs and/or radiological evidence of organ involvement (lung, skin, brain, cerebrospinal fluid, joint, peritoneum, eye, and salivary gland).[20] Disseminated nocardiosis was defined as nocardiosis involving two or more non-contiguous sites; and bacteremia was regarded as a form of disseminated infection.[6] Appropriate antimicrobial therapy included appropriate empiric treatment, defined as receiving antimicrobials shown to be active in vitro against Nocardia isolates before the diagnosis of nocardiosis was made, and appropriate definite treatment, defined as receiving antimicrobials with in-vitro activity against Nocardia isolates after diagnosis.

Outcomes and covariates

The primary outcome was the 90-day all-cause mortality. The factors investigated to be associated with 90-day all-cause mortality included demographics, underlying diseases such as diabetes, chronic liver disease, chronic obstructive pulmonary disease (COPD), interstitial lung diseases, hemodialysis, and neurological disease, Charlson comorbidity index, septic shock at presentation, surgical intervention, antimicrobial susceptibility, appropriate empiric antimicrobial use, time to appropriate definite antimicrobial treatment, immunosuppressive conditions, sites of infection, and species of *Nocardia* strains.

Statistical analysis

Descriptive statistics were presented as means and standard deviations for continuous variables, and absolute numbers and proportions (%) were used for categorical variables. Continuous variables were compared using the Mann—Whitney U test, while categorical variables were compared using the chi square test. Factors with p value < 0.1 in univariate analysis were entered into a multivariate logistic regression model to determine the independent factors for mortality. Kaplan—Meier analysis with log-rank test was also used to estimate the 90-day all-cause mortality following the symptom onset of nocardiosis. All statistical analyses were performed using the SPSS version 25 software (Chicago, Armonk, NY, USA). Statistical significance was set at $p < 0.05$, and all tests were two-tailed.

Results

Patient characteristics

During the 11-year study period, 60 patients diagnosed with nocardiosis were identified (Table 1). The mean age of the patients was 66 $\pm$ 15 years, and 39 (65.0%) were men. The most common comorbid diseases were diabetes mellitus and

Table 1 Clinical characteristics of the 60 patients with nocardiosis.

Variables	
Age, means (SD), years	66.1 (15.0)
Age > 65 years, n (%)	39 (65.0)
Male, n (%)	35 (58.3)
Comorbid condition, n (%)	
Diabetes	20 (33.3)
Chronic liver disease	7 (11.7)
COPD	16 (26.7)
ILD	1 (1.7)
Bronchiectasis	4 (6.7)
Hemodialysis	4 (6.7)
Neurological diseases	11 (18.3)
Immunocompromising condition, n (%)	
Hematological malignancy	4 (6.7)
Solid tumor	13 (21.7)
Autoimmune disease	11 (18.3)
AIDS	2 (3.3)
Receipt of immunosuppressants	4 (6.7)
Site of involvement, n (%)	
Lung	33 (55.0)
Central nervous system	6 (10.0)
Skin and soft tissue	27 (45.0)
Blood stream	6 (10.0)
Disseminated (including blood stream)	15 (25.0)
Charlson Comorbidity Index, means (SD)	5.68 (2.55)
Septic shock at presentation, n (%)	25 (41.7)
90-day mortality, n (%)	22 (36.7)

Abbreviations: AIDS, acquired immunodeficiency syndrome; COPD, chronic obstructive pulmonary disease; ICU, intensive care unit; ILD, interstitial lung disease; SD, standard deviation.

COPD, which were present in 20 (33.3%) and 16 (26.7%) patients, respectively. Among the 33 (55.0%) patients presenting with pulmonary nocardiosis, 17 (51.5%) had underlying chronic lung diseases, including COPD, bronchiectasis, and interstitial lung disease. Of the 6 patients with nocardiosis of the central nervous system (CNS), only 2 (33.3%) had underlying neurological diseases. A total of 31 (51.7%) patients had other immunocompromising conditions, with solid tumor (41.9%) being the most common. The most common sites of infection were the lungs (55.0%), followed by skin and soft tissue (45.0%). Six patients (10.0%) had CNS infection and another six (10.0%) had *Nocardia* bacteremia. Overall, 15 (25.0%) were diagnosed with disseminated nocardiosis.

Clinical outcomes

A total of 22 (36.7%) patients died within 90 days following the diagnosis of invasive nocardiosis and the median (interquartile range) interval between hospital arrival and death was 22 (11–38) days. In univariate analysis (Table 2), 90-day all-cause mortality was associated with underlying

Table 2 Comparisons of the clinical characteristics between the patients with nocardiosis who survived and those who died at 90 days of nocardiosis.

	Survived (n = 38)	Died (n = 22)	*p*
Age > 65 years, n (%)	23 (60.5)	16 (72.7)	0.34
Male, n (%)	25 (65.8)	14 (63.6)	0.87
Comorbid condition, n (%)			
Diabetes	13 (34.2)	7 (31.8)	0.85
Chronic liver disease	5 (13.2)	2 (9.1)	0.64
COPD	8 (21.1)	8 (36.4)	0.20
ILD	1 (2.6)	0	0.44
Bronchiectasis	1 (2.6)	3 (13.6)	0.10
Hemodialysis	1 (2.6)	3 (13.6)	0.10
Neurological diseases	5 (13.2)	6 (27.3)	0.17
Immunosuppressive condition, n (%)			
Hematological malignancy	3 (7.9)	1 (4.5)	0.62
Solid tumor	5 (13.2)	8 (36.4)	0.04
Autoimmune disease	7 (18.4)	4 (18.2)	0.98
AIDS	1 (2.6)	1 (4.5)	0.69
Receipt of immunosuppressants	3 (7.9)	1 (4.5)	0.62
Site of involvement, n (%)			
Lung	13 (34.2)	20 (90.0)	<0.01
Central nervous system	6 (15.8)	0	0.05
Skin and soft tissue	25 (65.8)	2 (9.1)	<0.01
Blood stream	2 (5.3)	4 (18.2)	0.11
Disseminated (includes blood stream)	9 (23.7)	6 (27.3)	0.76
Nocardia species, n (%)			
N. cyriacigeorgica	7 (18.4)	13 (59.1)	<0.01
N. brasiliensis	12 (31.6)	0	<0.01
N. farcinica	9 (23.7)	4 (18.2)	0.62
N. beijingensis	6 (15.8)	2 (9.1)	0.46
Charlson Comorbidity Index, means (SD)	4.71 (2.29)	7.36 (2.08)	0.01
Septic shock at presentation, n (%)	3 (7.9)	22 (100)	<0.01
Adequate surgical intervention, n/N (%)	15/17 (88.2)	0/0	>0.99
Antimicrobial treatment, n (%)			
A carbapenem	15 (39.5)	11 (50.0)	0.43
Trimethoprim-sulfamethoxazole	30 (78.9)	7 (31.8)	<0.01
Trimethoprim-sulfamethoxazole alone	16 (42.1)	1 (4.5)	<0.01
Trimethoprim-sulfamethoxazole with a carbapenem	14 (36.8)	6 (27.3)	0.45
An aminoglycoside	1 (2.6)	1 (4.5)	0.69
Appropriate empirical antimicrobial therapy	10 (26.3)	0	<0.01
Appropriate definite antimicrobial therapy	32 (84.2)	10 (45.5)	<0.01
Appropriate treatment days, mean (SD), days	93.62 (81.04)	10.54 (17.72)	<0.01
Time to appropriate definite antimicrobials initiated, mean (SD), days	14.44 (18.55)	12.20 (7.39)	0.81

Abbreviations: AIDS, acquired immunodeficiency syndrome; COPD, chronic obstructive pulmonary disease; ICU, intensive care unit; ILD, interstitial lung disease; SD, standard deviation.
n: number of data being positive, N: number of data being needed.

solid tumor (36.4% vs. 13.2%, $p = 0.04$), higher Charlson comorbidity index (7.36 versus 4.71, $p = 0.01$), septic shock (100% vs. 7.9%, $p < 0.01$), lung involvement (90.0% vs. 34.2%, $p < 0.01$), and infection by *N. cyriageorgica* (59.1% vs. 18.4%, p = 0.01). In contrast, patients with nocardiosis involving the CNS (0 vs. 15.8%, $p = 0.05$) or skin and soft tissue (9.1% vs. 63.2%, $p < 0.01$), those with infections due to *N. brasiliensis* (0 vs. 31.6%, $p < 0.01$), and those who received treatments containing TMP-SMX (31.8% vs. 78.9%, $p < 0.01$) had a lower mortality rate. Treatment with carbapenems ($p = 0.43$) or aminoglycosides ($p = 0.69$) was not found to be statistically significantly associated with the 90-day all-cause mortality.

The empiric antibiotic treatment used before the diagnosis of nocardiosis was made were mostly beta-lactams (n = 50), followed by quinolones (n = 8), glycopeptides (n = 6), and TMP-SMX (n = 3). Only 10 (16.7%) patients received appropriate empiric antimicrobials, and all these 10 patients continued to receive appropriate definite antimicrobials, including AMC (n = 3), TMP-SMX (n = 6), and IMP (n = 1). The appropriate empiric and definite antimicrobial treatments were significantly associated with a lower 90-day all-cause mortality rate in univariate analysis (26.3% vs. 0, $p < 0.01$; and 84.2% vs. 45.5%, $p < 0.01$, respectively), whereas the time intervals between presentation to the hospital and initiation of appropriate definite antimicrobials, predominantly TMP-SMX, was not ($p = 0.81$).

The mean observation duration between the diagnosis of nocardiosis made and the last hospital visit available in the medical records (12 months after diagnosis) for those who survived nocardiosis at 90 days of diagnosis was 9.9 months (range 1—12; SD, 3.5 months). The mean treatment duration for all patients with nocardiosis was 63.2 days (range 0—285; SD, 9.9 days), which was 93.6 days for patients who survived and 10.5 days for those who died (Table 2). A total of 7 patients received treatments for nocardiosis for more than 6 months. All the 38 patients who survived at day 90 had no relapse of nocardiosis during the observation duration, and 3 patients died from other causes of bacterial sepsis than nocardiosis beyond 90 days of nocardiosis diagnosis. The 90-day all-cause mortality was 36.7%, and the overall all-cause mortality at the end of observation was 41.7%. None of the 3 deaths were related to progression or relapse of nocardiosis.

Overall, 37 patients received TMP-SMX as definite antimicrobial therapy, including 17 TMP-SMX monotherapy and 20 combination therapy with TMP-SMX plus IMP (Table 2). The 90-day all-cause mortality was higher with combination therapy with TMP-SMX plus IMP (6 patients) than with TMP-SMX monotherapy (1 patient), but the difference did not reach statistical significance due to small sample sizes (30.0% vs.5.9%, $p = 0.08$) in univariate analysis. The numerically higher mortality rate in patients receiving combination antimicrobial therapy could be related to the fact that, in patients who had more comorbidities and presented with symptoms and signs of higher severity, treating physicians tended to prescribe combination antimicrobial therapy. Moreover, we did not find significant differences in terms of adverse effects or shortened durations of hospitalization in patients receiving TMP-SMX monotherapy and those receiving combination therapy with TMP-SMX plus IMP.

Table 3 Multivariate logistic regression analysis of factors associated with 90-day mortality in patients with nocardiosis.

Variables	Relative risk	95% confidence interval	*p*
Nocardiosis involving the lungs	9.99	1.52—65.50	0.02
Nocardiosis involving the skin and soft tissue	0.15	0.02—0.92	0.04
Treatment with trimethoprim-sulfamethoxazole	0.14	0.03—0.67	0.01

Of these 60 patients, 17 had indications for surgical intervention: 5 with brain abscess, 3 osteomyelitis, 4 necrotizing fasciitis, 4 deep abscess, and 1 pyomyositis. Only two patients (one with pyomyositis and the other one, deep abscess) did not undergo surgical intervention. All these 17 patients survived, regardless of surgical intervention (Table 2).

In multivariate logistic regression analysis, nocardiosis involving the lungs (relative risk [RR], 9.99; 95% confidence interval [CI], 1.52—65.50; $p = 0.02$), nocardiosis involving the skin and soft tissue (RR, 0.15; 95% CI, 0.02—0.92; $p = 0.04$), and treatment with TMP-SMX (RR, 0.14; 95% CI, 0.03—0.67; $p = 0.01$) were independently associated with 90-day all-cause mortality (Table 3). Kaplan—Meier curves of overall mortality within 90 days after the symptom onset of nocardiosis were further stratified by receipt of TMP-SMX. Patients receiving TMP-SMX for nocardiosis had a better survival at 90 days than those who received antimicrobial therapies not containing TMP-SMX (log-rank $p < 0.01$) (Fig. 1).

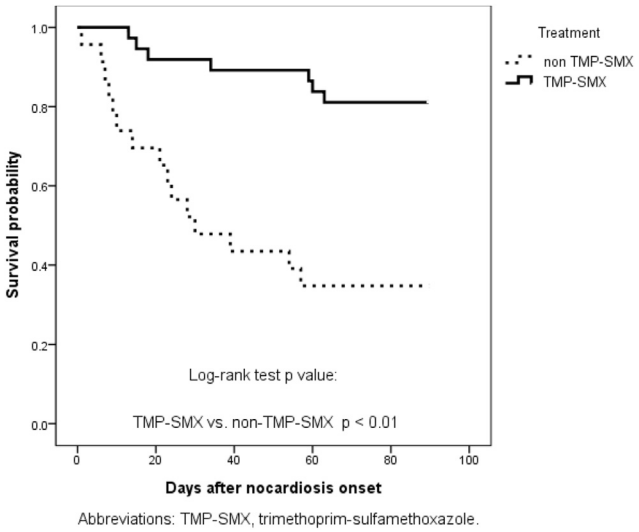

Figure 1. Kaplan—Meier plots of 90-day mortality in the patients with nocardiosis who received treatments containing trimethoprim-sulfamethoxazole (TMP-SMX) and those who received treatments not containing trimethoprim-sulfamethoxazole (non TMP-SMX).

Microbiology and antimicrobial susceptibility profiles

Sixty strains of *Nocardia* spp. identified were *N. cyriacigeorgica* (n = 20), *N. brasiliensis* (n = 12), *N. farcinica* (n = 13), *N. beijingensis* (n = 8), and the remaining seven species each containing one isolate (*N. concava*, *N. otitidiscaviarum*, *N. crassostreae*, *N. amikacinitolerans*, *N. asteroids*, *N. asciatica*, and *N. cerradonensis*) (Table 4). All of the 60 strains of *Nocardia* spp. were demonstrated to be susceptible to TMP-SMX, LZD, and AN by microbroth dilution method. Among the three antibiotics, TMP-SMX had lower MICs (0.25—2 μg/mL). However, more than 70% of the *Nocardia* isolates were shown to be non-susceptible to CIP, IMP, MXF, FEP, and CLR. The MICs for IMP were 2—64 μg/mL, with 87% of the isolates shown to be non-susceptible to IMP; and those for FEP were 1—32 μg/mL, with 92% non-susceptible to FEP (Table 4). During the study period, the prevalence of non-susceptibility to IMP of *Nocardia* spp. was persistently greater than 60% (Fig. 2).

Table 4 Antimicrobial susceptibility test of *Nocardia* spp. isolated from 60 patients with nocardiosis.

Species (Number of isolates)	MICs	TMP-SMX	LZD	CIP	IMP	MXF	FEP	AMC	AN	CRO	DOX	TGC	CLR
N. cyriacigeorgica (20)	Non-susceptible %	0%	0%	100%	85%	100%	100%	100%	0%	35%	70%	10%	95%
	MIC range MIN	0.25	1.00	4.00	2.00	2.00	16.00	16.00	1.00	4.00	0.50	0.25	2.00
	MIC range MAX	2.00	2.00	4.00	16.00	8.00	32.00	64.00	2.00	64.00	4.00	2.00	16.00
	MIC_{50}	0.25	2.00	4.00	12.00	4.00	32.00	48.00	1.00	8.00	2.00	1.00	16.00
	MIC_{90}	2.00	2.00	13.60	16.60	15.20	32.00	64.00	1.60	27.20	10.00	2.00	17.80
	GM	0.32	1.46	4.00	9.85	4.92	25.11	43.71	1.04	8.57	1.93	0.87	13.00
N. brasiliensis (12)	Non- susceptible %	0%	0%	100%	100%	83%	100%	17%	0%	92%	100%	0%	92%
	MIC range MIN	0.25	1.00	4.00	8.00	1.00	16.00	4.00	1.00	4.00	2.00	0.25	2.00
	MIC range MAX	1.00	4.00	4.00	64.00	2.00	32.00	64.00	2.00	64.00	8.00	0.50	16.00
	MIC_{50}	0.50	2.00	4.00	48.00	2.00	32.00	8.00	1.00	64.00	4.00	0.25	8.00
	MIC_{90}	3.20	5.60	12.00	64.00	10.40	32.00	64.00	4.00	64.00	12.00	2.80	16.00
	GM	0.47	2.12	4.00	40.32	1.78	30.20	9.51	1.06	40.32	4.00	0.33	8.00
N. farcinica (13)	Non- susceptible %	0%	0%	38%	100%	23%	100%	85%	0%	92%	100%	62%	100%
	MIC range MIN	0.25	1.00	0.25	8.00	0.25	16.00	8.00	1.00	8.00	2.00	1.00	16.00
	MIC range MAX	2.00	4.00	4.00	64.00	8.00	32.00	32.00	1.00	64.00	8.00	4.00	16.00
	MIC_{50}	2.00	2.00	1.00	32.00	0.25	32.00	16.00	1.00	64.00	4.00	2.00	16.00
	MIC_{90}	3.10	4.90	5.80	64.00	8.50	32.00	32.00	2.20	64.00	13.00	8.50	16.00
	GM	1.24	2.11	1.05	25.85	0.62	30.34	16.00	1.00	49.02	4.00	2.00	16.00
N. beijingensis (8)	Non- susceptible %	0%	0%	75%	63%	63%	63%	50%	0%	38%	63%	0%	38%
	MIC range MIN	0.25	1.00	1.00	2.00	0.25	4.00	8.00	1.00	4.00	0.12	0.12	0.25
	MIC range MAX	1.00	2.00	4.00	64.00	8.00	32.00	64.00	1.00	32.00	4.00	1.00	16.00
	MIC_{50}	0.25	1.00	4.00	36.00	2.00	16.00	36.00	1.00	4.00	2.00	0.25	1.00
	MIC_{90}	5.20	5.60	7.20	64.00	8.00	32.00	64.00	5.20	32.00	6.80	5.20	16.00
	GM	0.32	1.19	2.59	14.67	1.68	14.67	22.63	1.00	8.00	1.08	0.32	1.41
Others[a] (7)	Non- susceptible %	0%	0%	86%	71%	71%	71%	71%	0%	57%	71%	43%	57%
	MIC range MIN	0.25	1.00	0.50	2.00	0.25	1.00	4.00	1.00	4.00	0.12	0.12	0.06
	MIC range MAX	1.00	4.00	4.00	64.00	8.00	32.00	64.00	4.00	64.00	8.00	2.00	16.00
	MIC_{50}	0.50	2.00	4.00	16.00	2.00	32.00	64.00	1.00	64.00	2.00	1.00	16.00
	MIC_{90}	5.20	6.10	6.70	64.00	8.00	32.00	64.00	6.10	64.00	8.00	5.80	16.00
	GM	0.50	1.64	2.69	14.49	1.81	16.00	32.00	1.64	21.53	1.48	0.74	2.18
Total (60)	Non- susceptible %	0%	0%	82%	87%	72%	92%	70%	0%	62%	82%	22%	83%
	MIC range MIN	0.25	1.00	0.25	2.00	0.25	1.00	4.00	1.00	4.00	0.12	0.12	0.06
	MIC range MAX	2.00	4.00	4.00	64.00	8.00	32.00	64.00	4.00	64.00	8.00	4.00	16.00
	MIC_{50}	0.50	2.00	4.00	16.00	2.00	32.00	32.00	1.00	16.00	4.00	1.00	16.00
	MIC_{90}	2.00	4.00	4.00	64.00	8.00	32.00	64.00	2.00	64.00	6.00	4.00	16.00
	GM	0.49	1.68	2.70	17.75	1.98	23.97	22.89	1.08	18.81	2.35	0.74	7.45
CLSI susceptible	MIC	≤2	≤8	≤1	≤4	≤1	≤8	≤8	≤8	≤8	≤1	≤1	≤2
CLSI resistant	MIC	≥4	None	≥4	≥16	≥4	≥32	≥32	≥16	≥64	≥8	None	≥8

[a] Footnote: Other species include *N. concava* (n = 1), *N. asteroides* (n = 1), *N. otitidiscaviarum* (n = 1), *N. crassostreae* (n = 1), *N. asiatica* (n = 1), *N. amikacinitolerans* (n = 1), *N. cerradoensis* (n = 1).

AMC, amoxicillin/clavulanic acid; AN, amikacin; CIP, ciprofloxacin; CLR, clarithromycin; CLSI, Clinical and Laboratory Standards Institutes; CRO, ceftriaxone; DOX, doxycycline; FEP, cefepime; GM, geometric mean; IMP, imipenem; LZD, linezolid; MAX, maximum; MIC, minimum inhibitory concentration; MIN, minimum; MXF, moxifloxacin; TGC, tigecycline; TMP-SMX, trimethoprim-sulfamethoxazole.

Discussion

In this 11-year retrospective study of 60 patients with multiple comorbidities or immunosuppressive conditions, we found that nocardiosis was associated with a high 90-day all-cause mortality rate (36.7%). While all of the 60 *Nocardia* isolates were susceptible to TMP-SMX, LZD, and AN, more than 70% of the isolates were non-susceptible to IMP, a recommended antimicrobial agent for nocardiosis. After adjustment of confounding factors for 90-day all-cause mortality, pulmonary nocardiosis was associated with poor outcome, while skin and soft tissue infection and treatment with TMP-SMX were inversely associated with mortality.

Nationwide data on the epidemiology and clinical manifestations of nocardiosis published from Taiwan have been limited after 2010. To update the epidemiologic and clinical data on nocardiosis in Taiwan, we summarize all published studies of nocardiosis from Taiwan, including ours, in the past 2 decades (Supplementary table).[12–14,21–25] In contrast to the findings in other studies that skin and soft tissue infection were mainly caused by *N. brasiliensis*, we found that *N. cyriacigeorgica* has emerged as the leading cause and more lung infection were noted than skin and soft tissue infection in our study conducted in southern Taiwan.

In this study, our patients with nocardiosis involving the skin and soft tissue were found to have mild disease severity reflected by lower Charlson comorbidity index (means (SD) 4.30 (2.11)). Cutaneous nocardiosis were predominantly caused by *N. brasiliensis* and was most often acquired through traumatic inoculation among immunocompetent patients, which often demonstrates good clinical response to treatment with TMP-SMX.[22,26] The initial presentation of cutaneous nocardiosis usually begins with localized pyogenic abscess that gradually evolves into cellulitis, sporotrichosis- or mycetoma-like appearance. Therefore, patients with cutaneous nocardiosis will be more likely to be treated with anti-staphylococcal antimicrobials, including TMP-SMX,[22,27] and to undergo biopsy and surgical debridement. Although sporadic case reports suggested that nocardiosis involving the skin and soft tissue

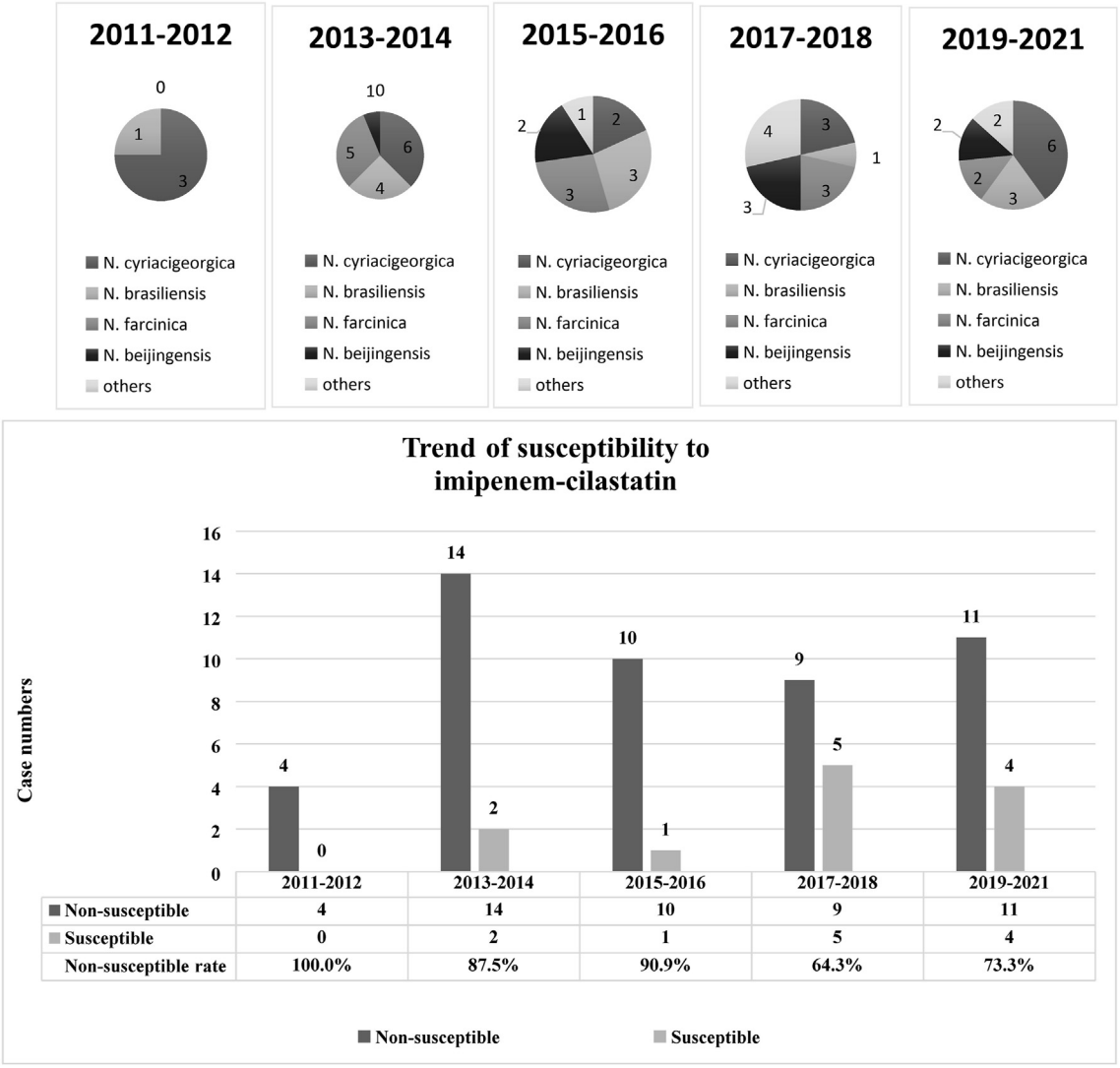

Figure 2. Distribution of *Nocardia* species and susceptibility to imipenem-cilastatin in patients with nocardiosis between 2011 and 2021.

could evolve into necrotizing fasciitis, these patients were cured after fasciotomy and antimicrobial treatment.[28]

Our finding of a higher mortality rate (60.6%) in patients presenting with pulmonary nocardiosis is in line with the finding of a study of 81 patients with nocardiosis in an earlier study of northern Taiwan from 1988 to 2006, in which *N. brasiliensis* was the leading etiology and the mortality rate among patients with pulmonary nocardiosis was 33%.[21] The reasons for the higher mortality rate observed could be multifactorial. The clinical presentations of nocardiosis involving the lungs may be similar to those of other community-acquired pneumonia. Etiologic diagnosis and antimicrobial susceptibility testing based on conventional cultures are time-consuming; in this study, it took about 2 weeks before definite antimicrobial treatments were administered (data not shown). As shown in this study, *Nocardia* spp. are often resistant to the empiric antimicrobials commonly used for community-acquired pneumonia, such as cephalosporins, macrolides and fluoroquinolones. Moreover, patients with pulmonary nocardiosis often had comorbid chronic lung diseases, such as COPD receiving long-term corticosteroids.[29]

TMP-SMX remains the drug of choice for the treatment of nocardiosis. In a recent study of nocardiosis in patients undergoing solid-organ transplantation, 19 of 24 patients (79.2%) who completed at least 30 days of TMP-SMX monotherapy were cured. Clinical outcomes were favorable in these 19 patients, of whom eight (42.1%) had disseminated infection and two (10.5%) had brain nocardiosis.[30] In some case reports, patients infected with *Nocardia* strains susceptible to TMP-SMX had poor clinical response to IMP treatment.[31,32] Our study of patients with multiple comorbidities also found that treatment with TMP-SMX was correlated with a lower mortality. In the presence of adverse effects to TMP-SMX, other alternatives could include TGC, LZD, and AN, based on the antimicrobial susceptibility testing results, although more clinical investigations are warranted to further examine the roles of these antimicrobials in the treatment of nocardiosis[33,34] because of concerns about poor penetration of aminoglycosides into neutrophils and macrophages,[35] low efficacy with TGC for severe infections such as bacteremia and septic shock, and myelosuppressive effects with long-term exposure to LZD.

Our study revealed that all isolates of *Nocardia* spp. collected during the 11 study years were susceptible to TMP-SMX, which is consistent with the findings of most other studies.[12,13,33,34,36] A recent retrospective analysis in northern Taiwan between 2011 and 2020 showed that only 1.1% of *Nocardia* isolates were non-susceptible to TMP-SMX.[13] In contrast, 42% of the *Nocardia* isolates submitted by State Health Departments to the US Centers for Disease Control and Prevention were shown to be resistant to TMP-SMX between 1995 and 2004.[37] The high rate of TMP-SMX resistance observed in the study conducted in the US could be a selection bias because of the tendency of submitting resistant strains to central reference laboratory; moreover, the different laboratory preparation and testing methods may yield discrepant MIC results.[38]

The susceptibility of *Nocardia* spp. to IMP may vary with the regions where the studies were conducted. A high rate of *Nocardia* spp. with IMP resistance was noted in Sydney and the tropical northern territory of Australia,[34,39] but not in Madrid, Spain,[40] and Ontario, Canada.[33] In our study from southern Taiwan between 2011 and 2021, the prevalence of *Nocardia* isolates that were non-susceptible to IMP was as high as 87%, which is consistent with the findings in the latest study from northern Taiwan, in which 68.5% of the isolates were non-susceptible to IMP between 2011 to 2020.[13] The higher rate of IMP non-susceptibility observed in these two studies might be due either to the unique regional resistance profile of *Nocardia* spp. in Taiwan or to the selection pressure from carbapenem overuse worldwide.[41,42]

Our study has several limitations. First, the case number of nocardiosis included in this study was small, which might have precluded us from identifying more factors associated with clinical outcome. Second, this retrospective study assessed 90-day all-cause mortality in a heterogenous patient population over 11 study years. The outcome analyses could be confounded by the diagnoses made, empiric antimicrobial therapy administered, and supportive care provided at the presentation to the hospital and during the hospital stay. Third, we did not investigate the molecular mechanism of antimicrobial resistance of *Nocardia* strains collected to explain the regional variation of antimicrobial susceptibility profiles.

We conclude that a higher mortality was observed in patients with invasive nocardiosis involving the lungs, while nocardiosis involving the skin and soft tissue and treatment with TMP-SMX were associated with a better outcome. *Nocardia* spp. identified between 2011 and 2021 remained fully susceptible to TMP-SMX in our study, which supports the recommendation of TMP-SMX as drug of choice for treating nocardiosis.

Funding

This work was supported by the Research Foundation of the Kaohsiung Chang Gung Memorial Hospital (CMRPG8L0931 & CMRPG 8M0441).

Institutional review board statement

The study was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Review Board of the Chang Gung Medical Foundation (202001763B0C502, date of approval: 2020/10/26).

Informed consent statement

Patient consent was waived for this study because only anonymous data were retrospectively analyzed and published.

Declaration of competing interest

The authors declare no conflicts of interest.

Acknowledgments

The authors would like to thank Dr. Chien-Ching Hung at the Department of Internal Medicine, National Taiwan

University Hospital Yunlin Branch, Yunlin, Taiwan, for his critical review of this manuscript. The authors would also like to thank the Biostatistics Center, Kaohsiung Chang Gung Memorial Hospital, for her assistance with data management and statistical analyses.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jmii.2022.11.002.