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ARTICLE

Clinical and microbiological characteristics of infections caused by various *Nocardia* species in Taiwan: a multicenter study from 1998 to 2010

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Abstract This multicenter study in Taiwan investigated the clinical presentations of various *Nocardia* species infections based on 16S rRNA sequence analysis. Patients with nocardiosis in four large medical centers from 1998 to 2010 were included. A total of 100 preserved nonduplicate isolates causing human infection were identified as *Nocardia* species. Sequencing analysis of 16S rRNA confirmed that 35 of 36 *N. asteroides* isolates identified by conventional tests were non-*asteroides Nocardia* species, and that two of 50 *N. brasiliensis* isolates had also been initially misidentified. *N. brasiliensis* (50%) was the most common pathogen, followed by *N. cyriacigeorgica* (18%). In addition, several rare pathogens were identified, including *N. asiatica*, *N. rhamnosiphila*, *N. abscessus*, *N. transvalensis*, *N. elegans*, and *N. carnea*. Primary cutaneous infection was the most common presentation, noted in 55 (55%) patients, while pulmonary infection presented in 26 (26%) patients. The crude mortality rate was 6.7% (6/89), and was lowest for primary cutaneous infection (2.2%) and highest for disseminated disease and pulmonary infection (16.7%). In conclusion, *N. brasiliensis* and *N. cyriacigeorgica* were the most common pathogens causing nocardiosis in Taiwan. Molecular methods for identifying *Nocardia* to the species level are mandatory for better understanding the epidemiology and clinical characteristics of patients with nocardiosis.

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Introduction

Nocardia species are aerobic actinomycetes, which are ubiquitous in soil and can cause local and disseminated infection, especially in immunocompromised patients [1, 2]. This group of organisms can be found extensively worldwide and their genus is rapidly expanding, with at least 80 species described do date (http://www.bacterio.cict.fr/n/nocardia.html). However, only about 30 members of the *Nocardia* species have been reported to cause human disease [3]. Furthermore, the geographical prevalence of each species may vary greatly throughout the world, and some species are more prevalent in geographical locations with a specific climate [3]. Thus, epidemiologic study is

needed in order to establish the species distribution of *Nocardia* infections in each region.

Traditionally, *Nocardia* was identified to the species level based on microscopic morphology and phenotypic characterization; however, the task is laborious and time-consuming. Moreover, interpretation of the results is difficult and considerable expertise is needed to accurately identify new species [3–5]. Recently, the introduction of molecular methods, such as 16S rRNA and hsp65 gene sequence analysis, have led to more accurate and easier identification and better classification of the taxonomy of *Nocardia* [3, 6]. However, few studies have applied advanced molecular methods for diagnosing *Nocardia* infection in clinical microbiology laboratories [7–12]. This nationwide study in Taiwan investigated the clinical presentations of various *Nocardia* species infection based on 16S rRNA gene sequence analysis of the isolates.

Materials and methods

Patients and setting

Patients with an initial diagnosis of nocardial infection admitted to four large medical centers in Taiwan between 1998 and 2010 were included in this study. These hospitals and their capacities were as follows: National Taiwan University Hospital (NTUH, 2,500 beds), National Cheng Kung University Hospital (NCKU, 1,200 beds), Chi Mei Medical Center (CMMC, 1,500 beds), and Kaohsiung Medical University Chung-Ho Memorial Hospital (KMUH, 1,700 beds). Patients with nocardiosis were identified from the records of the clinical microbiology laboratories of the participating medical centers. The clinical charts of all patients included in this study were retrospectively reviewed. Information was analyzed on age, gender, underlying immunocompromised conditions, including history of immunosuppressant drug use, corticosteroid therapy, diabetes mellitus, chronic obstructive pulmonary disease (COPD), chronic liver disease, chronic kidney disease, malignancy, organ transplantation, human immunodeficiency virus (HIV) infection, types of clinical specimen positive for *Nocardia* spp., and outcome.

Definitions

A diagnosis of pulmonary nocardiosis required at least one positive culture from respiratory samples, and the presence of clinical symptoms and a new lesion on chest film at admission. The respiratory samples included expectorated sputum, endotracheal aspirate, pleural effusion, bronchoalveolar lavage, or lung tissue obtained from biopsy. Disseminated nocardiosis was defined as the isolation of *Nocardia* species from specimens from two or more non-contiguous organs, such as pulmonary, lymph node, cutaneous, and brain, or from blood. Mortality was defined as death from all causes during the study episode of hospitalization.

Bacterial isolates

The identification of *Nocardia* species was based on positive gram-stain (gram-positive branching, beaded, and filamentous bacilli) and positive modified acid-fast stain results, colonial morphotypes, and conventional biochemical reactions, including hydrolysis of casein, xanthine, hypoxanthine, and tyrosine. A total of 100 nonduplicate isolates of *N. brasiliensis* (n=50), *N. asteroides* (n=36), *N. farcinica* (n=2), and unidentified *Nocardia* species (n=12) based on these conventional methods were further identified or confirmed by 16S rRNA gene analysis [2]. Partial sequencing analysis of the 16S rRNA gene of the isolates was performed

Table 1 Identification of *Nocardia* species by conventional biochemical testing and molecular diagnosis using 16S rRNA gene sequencing

Initial identification	Species confirmed by 16S rRNA gene sequencing
N. brasiliensis (n=50)	*N. brasiliensis* (n =48)
	N. cyriacigeorgica (n=1)
	N. nova (n=1)
N. asteroides (n=36)	*N. cyriacigeorgica* (n=15)
	N. farcinica (n=5)
	N. asiatica (n=4)
	N. beijingensis (n=3)
	N. nova (n=2)
	N. otitidiscaviarum (n=1)
	N. abscessus (n=1)
	N. puris (n=1)
	N. asteroides (n=1)
	N. brasiliensis (n=1)
	N. elegans (n=1)
	N. rhamnosiphila (n=1)
Nocardia spp. (n=12)	*N. cyriacigeorgica* (n=2)
	N. asiatica (n=2)
	N. nova (n=2)
	N. beijingensis (n=1)
	N. otitidiscaviarum (n=1)
	N. transvalensis (n=1)
	N. carnea (n=1)
	N. brasiliensis (n=1)
	N. farcinica (n=1)
N. farcinica (n=2)	*N. farcinica* (n=2)

using the primers Noc1 (5′-GCTTAACACATGCAAGTCG-3′) (positions 46 to 64, *Escherichia coli* numbering system) and Noc2 (5′-GAATTCCAGTCTCCCCTG-3′) (positions 663 to 680, *E. coli* numbering system) [2]. The sequences were compared with published sequences in the 16S rRNA database. The closest matches and GenBank accession numbers were obtained. Isolates causing disseminated nocardiosis as well as unusual *Nocardia* species were subjected to susceptibility testing by the broth microdilution method in accordance with the guidelines recommended by the National Committee for Clinical Laboratory Standards (NCCLS) [13, 14]. For the isolates causing disseminated nocardiosis and unusual *Nocardia* species, the agents tested included those used in treating the patients with these infections.

Results

Microbiologic investigation

A total of 100 nonduplicate isolates were available for study, including 90 from NTUH (1998–2010), four from KMUH (2009–2010), and three each from NCKU (2008–2010) and CMMC (2009–2010). The results obtained with molecular methods for species identification by 16S rRNA sequencing among these isolates revealed that 35 of 36 *N. asteroides* isolates identified by conventional methods were actually non-*asteroides Nocardia* species and, also, that two of 50 *N. brasiliensis* isolates had been initially misidentified (Table 1). Finally, based on the findings of molecular diagnosis, *N. brasiliensis* remained the most common

Table 2 Clinical manifestations, microbiological characteristics, and outcomes of 100 patients with nocardiosis

Variable	No. (%) of all patients (n=100)	No. (%) of all patients with pulmonary infection (n=26)	No. (%) of all patients with cutaneous infection (n=55)	No. (%) of all patients with disseminated infection (n=6)
Age, years (mean±SD)	55.0±19.4	54.4±16.2	53.4±21.4	53.4±21.4
Male: female (no. of patients)	69:31	19:7	35:20	4:2
Underlying disease condition				
Diabetes mellitus	10 (10.0)	3 (11.5)	3 (5.5)	1 (16.7)
Chronic kidney disease	12 (12.0)	5 (19.2)	4 (7.3)	3 (50.0)
Autoimmune disease	6 (6.0)	3 (11.5)	2 (3.6)	1 (16.7)
Solid cancer	11 (11.0)	3 (11.5)	4 (7.3)	2 (33.3)
Chronic lung disease	10 (10.0)	6 (23.1)	3 (5.5)	1 (16.7)
Chronic liver disease	11 (11.0)	3 (11.5)	8 (14.5)	0 (0.0)
Transplant recipient	8 (8.0)	3 (11.5)	3 (5.5)	2 (33.3)
Hematological cancer	7 (7.0)	3 (11.5)	3 (5.5)	0 (0.0)
Thyroid dysfunction	4 (4.0)	0 (0.0)	3 (5.5)	0 (0.0)
HIV infection	6 (6.0)	1 (3.8)	5 (9.1)	0 (0.0)
Receiving immunosuppressants	10 (10.0)	2 (7.7)	5 (9.1)	2 (33.3)
Receiving steroids	17 (17.0)	9 (34.6)	6 (10.9)	1 (16.7)
Mortality	6/89 (6.7)	4/24 (16.7)	1/46 (2.2)	1/6 (16.7)
Nocardia spp.				
N. brasiliensis	50 (50.0)	1 (3.8)	42 (76.4)	0 (0.0)
N. cyriacigeorgica	18 (18.0)	10 (38.5)	5 (9.1)	2 (33.3)
N. farcinica	8 (8.0)	4 (15.4)	1 (1.8)	2 (33.3)
N. asiatica	6 (6.0)	2 (7.7)	3 (5.5)	0 (0.0)
N. nova	5 (5.0)	2 (7.7)	3 (5.5)	0 (0.0)
N. beijingensis	4 (4.0)	2 (7.7)	0 (0.0)	1 (16.7)
N. otitidiscaviarum	2 (2.0)	1 (3.8)	0 (0.0)	1 (16.7)
N. abscessus	1 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)
N. puris	1 (1.0)	1 (3.8)	0 (0.0)	0 (0.0)
N. asteroides	1 (1.0)	1 (3.8)	0 (0.0)	0 (0.0)
N. carnea	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)
N. elegans	1 (1.0)	1 (3.8)	0 (0.0)	0 (0.0)
N. rhamnosiphila	1 (1.0)	1 (3.8)	0 (0.0)	0 (0.0)
N. transvalensis	1 (1.0)	0 (0.0)	1 (1.8)	0 (0.0)

pathogen and *N. cyriacigeorgica* was the second most common pathogen, compromising 18 isolates. In addition, several rare pathogens, including *N. asiatica*, *N. rhamnosiphila*, *N. abscessus*, *N. transvalensis*, *N. elegans*, and *N. carnea*, were identified in this study.

Clinical features

The demographic and clinical characteristics of the patients and the annual number of cases of nocardiosis are summarized in Table 2 and Fig. 1, respectively. Primary cutaneous *Nocardia* infection was the most common presentation, occurring in 55 (55%) patients. Most of these infections were caused by *N. brasiliensis* (n=42, 76.4%), followed by *N. cyriacigeorgica* (n=5, 9.1%). Chronic liver disease and steroid use were the most common underlying conditions. *Nocardia* caused pulmonary infection in 26 (26%) patients and *N. cyriacigeorgica* was the most common pathogen (n=10, 38.5%), followed by *N. farcinica* (n=4, 15.4%),. Disseminated *Nocardia* infection developed in 6 (6%) patients, and half of them had chronic kidney disease. All of these six patients had pulmonary infection and four of them had brain abscess.

Medical records adequate to determine outcome were available for 89 of the 100 patients. Nearly all patients received treatment with trimethoprim–sulfamethoxazole-containing regimens and all of the isolates were in vitro-susceptible to this agent. The in-hospital mortality rate was 6.7% (6/89) and was lowest for patients with primary cutaneous infection (2.2%) and highest for patients with disseminated disease and pulmonary infection (16.7%).

The clinical and microbiological features of 11 patients of nocardiosis caused by unusual *Nocardia* species are summarized in Table 3. All of the 11 pathogens from these

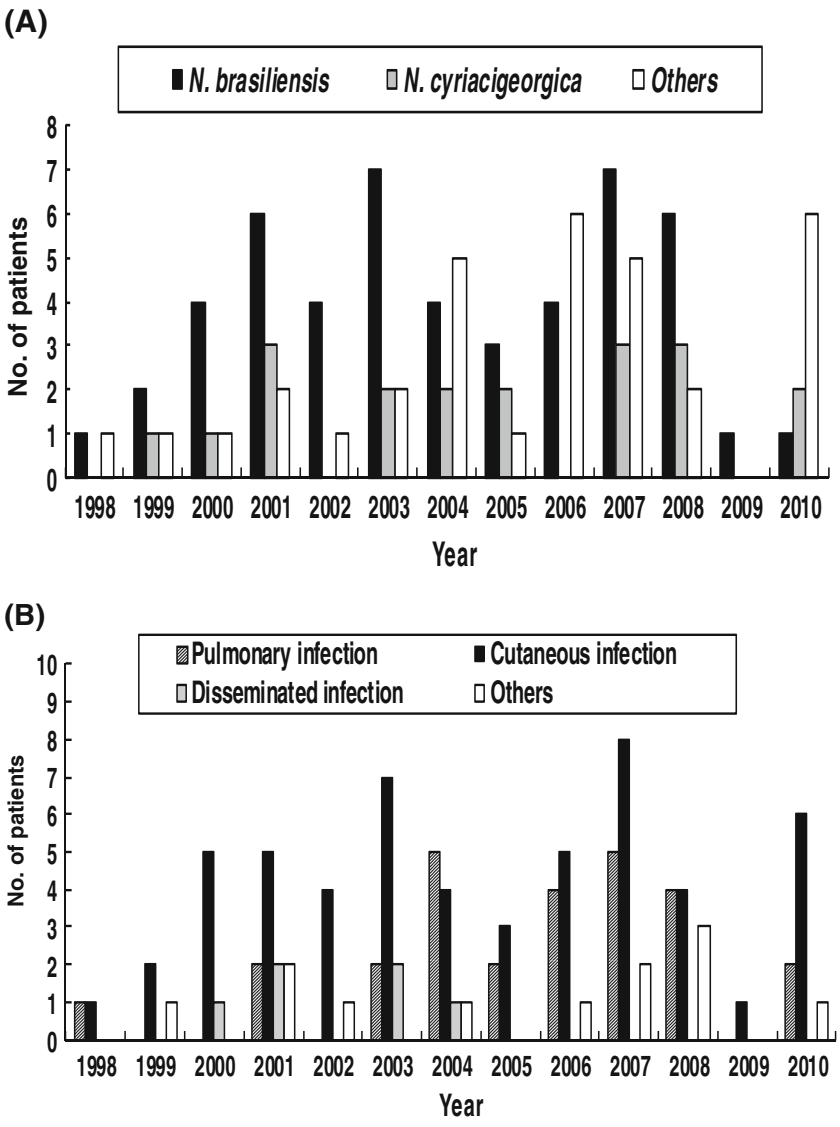

Fig. 1 Annual number of nocardiosis cases from 1998 to 2010 according to species of *Nocardia* (**a**) and types of infection (**b**)

Table 3 Summary of the clinical characteristics and outcomes of 11 patients with nocardiosis caused by unusual *Nocardia* species

No. of patient (year)	Age (years)/sex	Underlying disease or condition	*Nocardia* species	GenBank (accession no.)	Clinical diagnosis	Site of isolate	Antimicrobial therapy (MIC, μg/mL)	Outcome
1 (2000)	31/F	AIDS	*N. asiatica*	GQ217495.1	Cutaneous infection	Skin pus	SXT (8)[a]	Improved
2 (2001)	75/M	Nil	*N. asiatica*	GQ217495.1	Pneumonia	Lung biopsy	SXT (2)	Improved
3 (2004)	70/F	Nil	*N. asiatica*	GQ217495.1	Pneumonia	Skin pus	SXT (4)	Improved
4 (2004)	53/F	Nil	*N. rhamnosiphila*	EF418604.1	Pneumonia	Sputum	SXT (4)	Improved
5 (2004)	52/M	Nil	*N. abscessus*	GU471235.1	Brain abscess	Brain abscess aspirate	SXT (8)	Improved
6 (2006)	36/M	Chronic liver disease, AIDS	*N. asiatica*	GQ217495.1	Cutaneous infection	Skin pus	Unknown	Improved
7 (2006)	51/F	AIDS, chronic pulmonary obstructive disease	*N. transvalensis*	AB084446.1	Cutaneous infection	Skin pus	Unknown	Improved
8 (2007)	36/F	Allogeneic bone marrow transplantation, CML	*N. asiatica*	GQ217495.1	Pneumonia	Bronchial washing	IMP (0.5)	Died
9 (2007)	51/M	Dermatomyositis	*N. elegans*	GQ376166.1	Pneumonia	Sputum	SXT (8)	Improved
10 (2010)	36/M	AIDS	*N. asiatica*	GQ217495.1	Cutaneous infection	Skin pus	Unknown	Improved
11 (2010)	47/M	Nil	*N. carnea*	GU433886.1	Keratitis	Cornea	Amikacin topical	Improved

CML, chronic myelogenous leukemia; IMP, imipenem; MIC, minimum inhibitory concentration; SXT, trimethoprim–sulfamethoxazole

[a] The numbers in parentheses indicate the MIC (μg/mL) of sulfamethoxazole

cases were identified by conventional methods and 16S rRNA sequence analysis and all were susceptible to sulfamethoxazole. Two of the five patients with pulmonary infection caused by these unusual *Nocardia* species were immunocompromised and one patient died during the episode of nocardiosis. Six patients received trimethoprim–sulfamethoxazole (minimum inhibitory concentrations [MICs] of sulfamethoxazole, 2–8 μg/mL) treatment and recovered well. One patient (Patient 8) with chronic myelocytic leukemia died of *N. asiatica* pneumonia six years after bone marrow transplantation, although she had received adequate treatment with imipenem with good in vitro activity (MIC of 0.5 μg/mL) against the organism. *N. carnea* caused keratitis in one immunocompetent patient and was successfully treated by topical drugs containing amikacin.

Discussion

Current molecular methodologies provide important information on the taxonomy of *Nocardia* species, which is changing and expanding rapidly, with the recognition and description of new species [3]. This nationwide study found that the epidemiology of nocardiosis had markedly changed from previous studies in Taiwan [2, 15]. Although *N. brasiliensis* was still the most common nocardial pathogen [2], *N. cyriacigeorgica*, a previously unreported pathogen in Taiwan, was the second most common pathogen. However, these findings do not indicate that *N. cyriacigeorgica* is an emerging pathogen in Taiwan, since laboratory algorithms for the phenotypic identification of *Nocardia* species were not routinely used by most bacteriology laboratories in Taiwan, and also because *N. cyriacigeorgica* cannot be accurately identified without molecular methods. In this study, all of the *N. cyriacigeorgica* isolates were identified as non-*cyriacigeorgica Nocardia* spp. by conventional biochemical methods, and accurate identifications were made by 16S rRNA sequence analysis. In addition, almost all of the *N. asteroides* isolates initially misidentified by morphological and conventional biochemical reactions were confirmed as non-*asteroides Nocardia* by molecular methods. The identification of *Nocardia* species by routine culture and chemotaxonomic methods remains challenging, and precise identification of *Nocardia* to the species level currently requires molecular methods.

This is the first study from Taiwan to identify *N. cyriacigeorgica*. The true prevalence of this pathogen was likely underestimated in previous studies from Taiwan when molecular diagnosis was not employed. One half of the 18 patients with *N. cyriacigeorgica* infections in this study had various immunocompromised conditions, and two cancer patients died during the episodes of nocardiosis. This finding is consistent with previous reports [1, 16, 17]

and indicates that *N. cyriacigeorgica* should be considered as a possible pathogen causing human infection, especially in immunosuppressed patients.

This study is the first to report the isolation of *N. asiatica*, *N. abscessus*, *N. carnea*, *N. elegans*, and *N. transvalensis* in Taiwan and also documents the first reported worldwide instance of another rare pathogen, *N. rhamnosiphila*, as a cause of human infection. These strains caused various types of infections in 11 patients, including pneumonia, cutaneous infection, brain abscess, and keratitis. *N. elegans* was first isolated by Yassin and Brenner in 2005 [18] and its clinical significance remains unclear. This study includes the first reported case of *N. elegans* pneumonia in a patient with dermatomyositis.

N. asiatica was described for the first time in 2004, including five strains isolated in Asia over the period of 1985 to 1999 from patients with nocardiosis in Japan and from clinical specimens from Thailand. Three of the isolated strains were from sputum, one from a granuloma, and one from a trans-tracheal aspirate [19]. In the present study, six patients had clinical isolates of *N. asiatica* causing pneumonia or cutaneous infection. Importantly, four of these patients had various immunocompromised conditions, including three with HIV infection and one bone marrow recipient, which is consistent with the findings of a previous study [20]. Thus, clinicians should be aware that this rare pathogen tends to infect immunocompromised patients. *N. abscessus* was proposed as a new *Nocardia* species in 2000 [21], and this study describes the first isolates of *N. abscessus* causing brain abscess in Taiwan, a rarely reported presentation worldwide [9].

Nocardia keratitis is an uncommon clinical entity and several *Nocardia* species, such as *N. arthritidis*, *N. neocaledoniensis*, *N. asiatica*, *N. asteroides* type IV, *N. brasiliensis*, *N. pseudobrasiliensis*, *N. cyriacigeorgica*, *N. farcinica*, *N. otitidiscaviarum*, *N. amamiensis*, *N. abscessus*, *N. puris*, *N. beijingensis*, *N. thailandic*, and *N. transvalensis* were reported etiologies [22, 23]. This study adds *N. carnea* to the list of the possible etiologies of keratitis.

In conclusion, *N. brasiliensis* was the most common pathogen causing nocardiosis in Taiwan, followed by *N. cyriacigeorgica*. In addition, patients with nocardiosis caused by rare pathogens, including *N. asiatica*, *N. rhamnosiphila*, *N. abscessus*, *N. transvalensis*, *N. elegans*, and *N. carnea*, were also found. Molecular methods for identifying *Nocardia* to the species level are mandatory for better understanding the epidemiology and clinical characteristics of patients with nocardiosis.

Conflicts of interest All authors: no conflicts.

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