Observational Study

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# Characteristics of nocardiosis patients with different immune status from a Chinese tertiary general hospital during 8-year period

## A STROBE-compliment observational study

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**Abstract**

*Nocardia* is an opportunistic pathogen from environment, which is generally thought to infect immunosuppressed patients (ISPs), but recent studies showed it could also cause infections in immunocompetent patients (ICPs).

The aim of this study was to compare the clinical characteristics, patients' outcome, *Nocardia* species' identification, and antibiotic susceptibility profiles of nocardiosis between ICPs and ISPs.

The detailed clinical data were collected from all the nonrepetitive nocardiosis patients during 2011 and 2018, from a tertiary general hospital in Beijing, China. Then each *Nocardia* isolate was identified to species level by DNA sequencing. The antibiotic susceptibility testing was performed by *E* test method, and interpreted following CLSI M24 document. The clinical and microbiological characteristics between ICPs and ISPs were compared statistically.

A total of 23 nonrepetitive nocardiosis patients with detailed clinical data were enrolled in this study. Among them, 9 were ICPs and 14 were ISPs. All the skin and soft tissue infections occurred in ICPs (33.3% vs 0%, $P < .05$). Bronchiectasis occurred more frequently in ICPs (44.4% vs 21.4%), whereas chronic kidney diseases and coinfection with aspergillosis occurred more frequently in ISPs (35.7% vs 0%, 35.7% vs 0%, respectively), although they did not reach the statistical significance. There were no significant differences in other clinical characteristics, *Nocardia* species' identification, and antibiotic susceptibility between ISPs and ICPs ($P > .05$).

Nocardiosis could occur in both ISPs and ICPs. Skin and soft tissue infection and bronchiectasis occurred more frequently in ICPs. Chronic kidney diseases and co-infection with aspergillosis occurred more frequently in ISPs. These characteristics should be noticed by physicians in diagnosis of nocardiosis.

**Abbreviations:** ICPs = immunocompetent patients, ISPs = immunosuppressed patients, SXT = trimethoprim-sulfamethoxazole.

**Keywords:** immunocompetent patients, immunosuppressed patients, *Nocardia cyriacigeorgica*, *Nocardia farcinica*, nocardiosis

## 1. Introduction

*Norcardia* species are Gram-positive, aerobic, and slow-growing actinomycetes in the environment and can cause opportunistic infections. More literatures of nocardiosis were reported in recent years along with widespread use of immunosuppressive agents and organ transplantation.[1–3] However, the clinical characteristics and symptoms of nocardiosis are often nonspecific; thus, early diagnosis is often hampered. With the recent progress in genotypic identification, such as sequencing of 16S rDNA, recA, hsp65, and gyrB genes, most *Nocardia* could be identified into species level, and the knowledge about species-specific antibiotic susceptibility patterns is increasing.[4]

*Nocardia* species are usually thought to be opportunistic pathogens, and cause infections mostly in immunosuppressed patients (ISPs).[5,6] However, recent studies from Korea[7] and United States[8] showed that nocardiosis could also occur in immunocompetent patients (ICPs) with the rate of 33% and 40%, respectively. Thus comparison of the characteristics between nocardiosis patients with different immune status (ISPs and ICPs) could provide new information for early diagnosis and treatment of nocardiosis, which was a rare but potentially fatal infectious disease. The characteristics of nocardiosis from China mainland were still limited. Only a few reports[3,9] in recent years were found, and they did not involve detailed clinical characteristics, patients' treatment and outcome, *Nocardia* species' identification, or antibiotic susceptibility testing results. To the best of our knowledge, no study comparing these detailed characteristics of nocardiosis patients with different immune status in China mainland was found.

In this study, we retrospectively collected the detailed clinical data of all nocardiosis patients from a tertiary general hospital in

Editor: Gunjan Arora.

The authors have no conflicts of interest to disclose.

This study was supported by Youth Clinical Research Project of Peking University First Hospital (2018CR27) to Lei Huang.

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How to cite this article: Huang L, Sun L, Yan Y. Characteristics of nocardiosis patients with different immune status from a Chinese tertiary general hospital during 8-year period. Medicine 2019;98:45(e17913).

Received: 1 February 2019 / Received in final form: 7 October 2019 / Accepted: 13 October 2019

http://dx.doi.org/10.1097/MD.0000000000017913

Beijing, China, during 8-year period. Moreover, all the included *Nocardia* isolates were identified into species level by gene sequencing, and their antibiotic susceptibility profiles were determined. Then the clinical and microbiological characteristics between ICPs and ISPs were compared statistically.

## 2. Materials and methods

### 2.1. Patients and study design

This study was conducted at Peking University First Hospital, a 1500-bed tertiary general hospital in Beijing, China, and it was approved by the Ethic board of this hospital. All the medical records of nocardiosis patients were retrospectively reviewed from January 2011 to December 2018. The demographic data, patients' immune status, underlying diseases, co-infections, laboratory testing parameters, treatment, and outcomes were obtained.

The inclusion criteria of nocardiosis cases were as follows: at least 1 culture positive for *Nocardia* species; having compatible signs and symptoms of infection; the patients' medical records and isolated *Nocardia* strains were available for further species identification by DNA sequencing and antibiotic susceptibility testing. Those nocardiosis patients without detailed clinical information or lack of isolated *Nocardia* strains were excluded from this study.

ISPs were defined as described previously.[10] Briefly, patients with organ transplantation, malignancy, HIV infection, or any conditions requiring long-term immunosuppressive therapy (eg, use of corticosteroid or other T cell immunosupressants) before hospital visits. Other comorbidities (eg, diabetes mellitus, chronic kidney disease, or liver cirrhosis) that did not require immunosuppressive therapy were not defined as ISPs.[3] Co-infections, such as viral, bacterial, fungal pneumonia, were defined as previously described.[7] ICPs were defined following the criteria of Zea-Vera,[11] which involved not only the absence of HIV infection, but also the normal capacity to develop an immune response following the exposure to an antigen or broadly a normal immune response.

### 2.2. Nocardia species' identification and antibiotic susceptibility testing

The bacteria isolation and culture protocol were performed as described previously.[12] The presumptive identification was based on both colony morphology and microscopic examination. Definitive identification was performed by PCR amplification and sequencing the full length of 16S rDNA, hsp65, secA1, and gyrB genes.[13–16] The sequences were compared with NCBI GenBank database, and species assigning criteria were as follows: the similarity value of ≥99.6% for 16S rDNA, ≥99.0% for secA1, ≥93.5% for gyrB.[15,17] If discrepant results existed, the species assigning was determined by multilocus sequence analysis.[18]

Antibiotic susceptibility testing was performed by *E* test method as described previously for *Nocardia* species.[2] The choice of various antibiotics was based on CLSI M24–2A of the first-line and second-line drugs used for *Nocardia*,[19] including amikacin, trimethoprim-sulfamethoxazole (SXT), gentamicin, ciprofloxacin, cefepime, imipenem, ceftriaxone, amoxicillin-clavulanate, linezolid, and cefotaxime. We performed each experiment by 2 persons together to avoid mistakes in the process, and the quality controls were performed each time. If the quality controls were acceptable, and no mistake in the whole operation process was found, we just used the data from the experiment. Otherwise, we repeated the experiments until we get the acceptable results.

### 2.3. Statistical analysis

Various clinical and microbiological characteristics between ICPs and ISPs were compared. Categorical variables were compared using $\chi^2$ test or Fisher exact test. Continuous variables were compared using *t* test or Mann-Whitney *U* test. All statistical analyses were performed using SPSS version 21.0 (SPSS Inc., Chicago, IL).

### 2.4. Ethical approval

This study was approved by the ethics committee of Peking University First Hospital. Informed consents were not required, as this was a retrospective observational study and did not involve patients' privacy.

## 3. Results

### 3.1. Demographic and clinical data

During 2011 and 2018, a total of 23 patients of culture-proven nocardiosis with intact clinical and microbiological information were enrolled in this study. Their demographic and clinical characteristics were summarized in Table 1. Skin and soft tissue infection occurred more frequently in ICPs than in ISPs (33.3% vs 0%, $P < .05$). We also noticed that bronchiectasis occurred more in ICPs than in ISPs (44.4% vs 21.4%), and co-infection with aspergillosis occurred more in ISPs (35.7% vs 0%), although they did not reach statistical significance, which was mainly due to the limited sample size. A total of 21.4% (3/14) patients died in ISPs, whereas all (9/9) patients recovered in ICP group. The numbers of nocardiosis cases in both ICPs and ISPs from 2011 to 2018 were shown in Figure 1, with ISPs ranging from 0 in 2013 and 2016 to 3 in 2014, and ICPs ranging from 0 in 2014 to 2 in 2012 and 2017. The nocardiosis incidence of both ISPs and ICPs showed no obvious trend over time.

### 3.2. Laboratory testing

There was no significant difference among white blood cell, C-reactive protein, and procalcitonin levels between ICPs and ISPs ($P > .05$), which were summarized in Table 1.

### 3.3. Nocardia species' identification and antibiotic susceptibility testing

The microbiological identification of *Nocardia* to species level was confirmed by DNA sequencing, and the results were summarized in Table 2. *N farcinica* and *N cyriacigeorgica* were the most common species in our study, followed by *N otitidiscaviarum*, *N abscessus*, *N brasiliensis*, and *N nova*. There was no statistical difference in the species distribution between ICPs and ISPs.

There was also no statistically significant difference in antibiotic susceptibility testing results between ICPs and ISPs, which was shown in Table 2. Most patients were treated with >2

**Table 1**

**Demographic and clinical characteristics of included patients.**

| Characteristics | ICPs (n = 9) | ISPs (n = 14) | P* |
|---|---|---|---|
| Age, y | 53.8 ± 24.1 | 65.9 ± 8.9 | .098 |
| Male/female | 4:5 | 7:7 | 1.000 |
| Underlying diseases | | | |
| Bronchiectasis | 4 (44.4%) | 3 (21.4%) | .363 |
| Chronic kidney diseases | 0 (0%) | 5 (35.7%) | .116 |
| High blood pressure | 2 (22.2%) | 3 (21.4%) | 1.000 |
| Diabetes mellitus | 2 (22.2%) | 4 (28.6%) | 1.000 |
| Coronary heart disease | 1 (11.1%) | 1 (7.1%) | 1.000 |
| Anemia | 1 (11.1%) | 4 (28.6%) | .611 |
| Multiple organ failure (MSOF) | 1 (11.1%) | 1 (7.1%) | 1.000 |
| Co-infection | | | |
| Virus | 0 (0%) | 2 (14.3%) | .502 |
| Fungus (aspergillosis) | 0 (0%) | 5 (35.7%) | .116 |
| Other bacteria | 1 (11.1%) | 2 (14.3%) | 1.000 |
| Sites of *Nocardia* infection | | | |
| Lung | 5 (55.6%) | 10 (71.4%) | .657 |
| Skin and soft tissue | 3 (33.3%) | 0 (0%) | .047 |
| Body fluid | 1 (11.1%) | 2 (14.3%) | 1.000 |
| Disseminated | 0 (0%) | 2 (14.3%)† | .502 |
| Hospital-acquired nocardiosis infection‡ | 4 | 10 | .229 |
| Laboratory data | | | |
| White blood cell ($10^3$ cells/μL) | 10.4 ± 5.3 | 10.8 ± 3.5 | .833 |
| C-reactive protein, mg/dL | 4.9 ± 2.6 | 6.1 ± 2.9 | .306 |
| Procalcitonin, ng/mL | 0.38 ± 0.15 | 0.41 ± 0.17 | .741 |
| Outcome | | | |
| Death | 0 (0%) | 3 (21.4%) | .253 |
| Recovered | 9 (100%) | 11 (78.6%) | .253 |

ICPs = immunocompetent patients, ISPs = immunosuppressed patients.
* Due to total number <40 and some of the expected number <5, Fisher exact test's result was used.
† One disseminated case was a 68-year-old male, diagnosed as pulmonary infection, and *N farcinica* was isolated from bronchial secretion. The other case was a 73year-old male, having multiple abscesses from abdominal fluid and limbs, and *N. farcinica* was isolated from puncture fluid.
‡ Based on the criteria of "hospital-acquired infection," 14 patients were hospital-acquired, and the other 9 patients were not hospital-acquired.

kinds of antibiotic for the infections before positive culture of *Nocardia*, and SXT were used for treatment after diagnosis of nocardiosis. SXT, combined with amikacin, imipenem, or amoxillin/clavulatic acid, was the standard combination in these patients.

## 4. Discussion

Nocardiosis is a rare but potentially serious infection, which is mainly considered to be involved in ISPs.[5,6] However, recent studies showed that nocardiosis could also occur in ICPs with increasing rates.[7,8] Delay in nocardiosis diagnosis may be due to its nonspecific and variable clinical characteristics and nonspecific radiologic findings.[20] Thus comparing the characteristics of nocardiosis patients with different immune status could help in early diagnosis of nocardiosis.

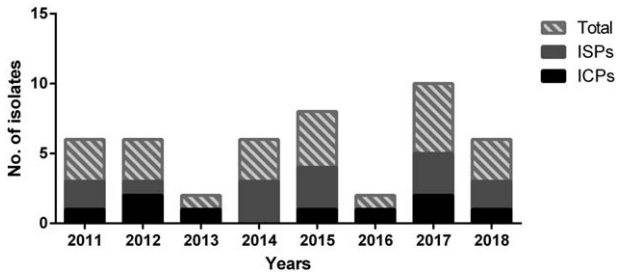


**Figure 1.** Incidence of nocardiosis in ICPs and ISPs. ICPs = immunocompetent patients, ISPs = immunosuppressed patients.

**Table 2**

***Nocardia* species identification and antibiotic susceptibilities.**

| Characteristics | ICPs (n = 9) | ISPs (n = 14) | P |
|---|---|---|---|
| Nocardia species identification | | | |
| *N farcinica* | 2 (22.2%) | 6 (42.9%) | .400 |
| *N cyriacigeorgica* | 2 (22.2%) | 5 (35.7%) | .657 |
| *N otitidiscaviarum* | 2 (22.2%) | 0 (0%) | .142 |
| *N abscessus* | 2 (22.2%) | 2 (14.3%) | 1.000 |
| *N brasiliensis* | 1 (11.1%) | 0 (0%) | .391 |
| *N nova* | 0 (0%) | 1 (7.2%) | 1.000 |
| Antibiotic resistance profiles | | | |
| SXT* | 3 (33.3%) | 2 (14.3%) | .343 |
| Amoxicillin-clavlautic acid | 2 (22.2%) | 2 (14.3%) | 1.000 |
| Ciprofloxacin | 4 (44.4%) | 8 (57.1%) | .680 |
| Ceftriaxone | 2 (22.2%) | 2 (14.3%) | 1.000 |
| Imipenem | 1 (11.1%) | 1 (7.2%) | 1.000 |
| Linezolid | 0 (0%) | 0 (0%) | >1.000 |
| Amikacin | 0 (0%) | 0 (0%) | >1.000 |
| Gentamicin | 4 (44.4%) | 3 (21.4%) | .363 |
| Cefepime | 2 (22.2%) | 2 (14.3%) | 1.000 |
| Ceftaxime | 2 (22.2%) | 3 (21.4%) | 1.000 |

ICPs = immunocompetent patients, ISPs = immunosuppressed patients.
* SXT: trimethoprim/sulfamethoxazole.

The detailed comparison of characteristics of nocardiosis between ISPs and ICPs from tertiary general hospitals was still limited. Kim et al's study[7] compared the clinical characteristics and treatment outcomes between ICPs and ISPs; however, not all *Nocardia* strains were identified to species levels and not all the strains were available for the antibiotic susceptibility results, mainly because these microbiological data were retrospectively collected, and some of them were unavailable. Thus, a total of 23 cases of culture-proven, nonrepetitive nocardiosis patients from our hospital, a 1500-bed tertiary general hospital in Beijing China, during 8-year period were characterized in our study, and we performed the *Nocardia* species identification by DNA sequencing and antibiotic susceptibility testing by *E* test method with all the available strains at the same time, instead of collecting these data retrospectively. Then these patients were divided into ISPs and ICPs groups according to the previously defined criteria,[10,11] based on their clinical characteristics. Our study showed that the 39.1% of these nocardiosis patients were ICPs and most of them recovered. Meanwhile, the overall outcome in both ICPs and ISPs was better than previous studies.[7,8]

From the data of our study, we found that most demographic features, underlying diseases, microbiological identification, and their antibiotic susceptibility were similar between the 2 groups. However, there was only 14.3% (2/14) disseminated nocardiosis patients (the detailed description of the two cases was in the notes of Table 1) in ISPs group, and it was significantly fewer than Kim et al's study,[7] which showed the disseminated cases accounted for 33% in ICPs and 36% in ISPs, respectively. It could be explained by the severity and sites of infection of included patients may be different between the 2 studies, and the nocardiosis patients in our study seem to be less severe and have better outcomes.

Among the underlying diseases we analyzed in this study, an interesting association was found between bronchiectasis and

nocardiosis in both ISPs and ICPs, with the rates of 44.4% and 21.4%, respectively, which was similar with Woodworth study of 40%.[21] Moreover, they found the increasing number of nocardiosis over time was driven by patients with noncystic fibrosis bronchiectasis. We also analyzed the incidences of nocardiosis cases among different years in both ICPs and ISPs (Fig. 1); however, due to the small sample size, we found the numbers in each year went up and down with no obvious trend over time, which was different from Woodworth et al's study,[21] while the studies from Taiwan[22] and Spain[23] showed stable case numbers over time. The difference may be explained by various population and underlying diseases among different studies.

The outcome of nocardiosis patients was better in ICPs than in ISPs; in other words, their prognosis was associated with various immune statuses. We found that the 3 cases of death were attributed to severe infections, but *Nocardia* infections were not the only reason, as they were combined with other coinfections (eg, coinfection with aspergillosis, virus, or bacteria was found in our study). The situation was reasonable, as assessment of attributable mortality in the context of complex conditions was often challenging and inaccurate.[24] The cases of nocardiosis co-infection with aspergillosis in our study were more than previous study[7], mainly in ISPs, as these patients were more prone to mixed infection that caused by multiple pathogens, which should be noticed by physicians.

The microbiological identification of *Nocardia* to species level showed that *N farcinica*, *N cyriacigeorgica*, *N otitidiscaviarum*, *N abscessus*, *N brasiliensis* distributed equally in ICPs. In contrast, *N farcinica* and *N cyriageorgica* were the predominant species in ISPs, accounting for 42.9% and 35.7%, respectively, which was different from the species distribution in the United States[25] and Taiwan[26]. The antimicrobial susceptibility testing of first-line drugs for *Nocardia* was also compared between 2 groups (Table 2), and found there was no significant difference between 2 groups. However, the resistance profiles were also different from other reports[2,25,26], which could be explained by the geographic variation to some extent.

Our study had several limitations. First, it was the study from 1 tertiary hospital in Beijing, China; thus, our results could not stand for other geographic regions of China. Second, the sample size of nocardiosis patients who met the criteria for inclusion in this study was small, compared with studies from Korea[7] and the United States[8], which may indicate the low incidence of nocardiosis in our hospital. Thus we could not get the statistically significant results in some clinical characteristics, although we could see the difference between the 2 groups of patients (eg, bronchiectasis occurred more frequently in ICPs, whereas chronic kidney diseases and co-infection with aspergillosis occurred more frequently in ISPs, although they did not reach statistical significance). Meanwhile, due to the limited sample size, we could not determine statistically whether the observed difference was attributed to compromised immune status of ISPs, and further studies with larger sample size are still needed. Third, due to the retrospective nature of the study, sample selection bias could not be avoided.

The advantage of this study was that, due to the limited data of comparison of nocardiosis in ICPs and ISPs from China, our study collected the detailed data of clinical characteristics, and performed *Noardia* species identification and antibiotic susceptibility testing, then compared these data between the 2 groups. Thus, our study added new value in the characterization of nocardiosis in China, and showed different characteristics from other geographic regions. Understanding the geographic distribution and characteristics of nocardiosis in both ISPs and ICPs would help physicians diagnose and treat nocardiosis more effectively.

In conclusion, our study showed that nocardiosis could occur in both ISPs and ICPs. Skin and soft tissue infection and bronchiectasis occurred more frequently in ICPs than in ISPs. Chronic kidney diseases and co-infection with aspergillosis occurred more frequently in ISPs than in ICPs, which should be noticed and considered by physicians in the diagnosis of nocardiosis.

## Author contributions

**Conceptualization:** Lei Huang.
**Data curation:** Lei Huang, Liying Sun.
**Methodology:** Liying Sun, Yan Yan.
**Software:** Lei Huang, Yan Yan.
**Writing – original draft:** Lei Huang.
**Writing – review & editing:** Lei Huang, Yan Yan.

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