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# Invasive Nocardiosis in Transplant and Nontransplant Patients: 20-Year Experience in a Tertiary Care Center

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## Abstract

**Objective:** To present the clinical characteristics and outcome of transplant and nontransplant patients with invasive nocardiosis.

**Patients and Methods:** We conducted a retrospective chart review of 110 patients 18 years and older diagnosed with culture-proven *invasive nocardiosis* (defined as the presence of clinical signs and/or radiographic abnormalities) between August 1, 1998, and November 30, 2018. Information on demographic, clinical, radiographic, and microbiological characteristics as well as mortality was collected.

**Results:** One hundred ten individuals with invasive nocardiosis were identified, of whom 54 (49%) were transplant and 56 nontransplant (51%) patients. Most transplant patients were kidney and lung recipients. The overall mean age was 64.9 years, and transplant patients had a higher prevalence of diabetes and chronic kidney disease. A substantial proportion of nontransplant patients were receiving corticosteroids (39%), immunosuppressive medications (16%), and chemotherapy (9%) and had chronic obstructive pulmonary disease (20%), rheumatologic conditions (18%), and malignant neoplasia (18%). A higher proportion of transplant patients (28%) than nontransplant patients (4%) received trimethoprim-sulfamethoxazole prophylaxis. In both groups, the lung was the most common site of infection. Seventy percent of all *Nocardia* species isolated were present in almost equal proportion: *N brasiliensis* (16%), *N farcinica* (16%), *N nova* (15%), *N cyriacigeorgia* (13%), and *N asteroides* (11%). More than 90% of isolates were susceptible to trimethoprim-sulfamethoxazole, linezolid, and amikacin. There was no significant difference in mortality between the 2 groups at 1, 6, and 12 months after the initial diagnosis.

**Conclusion:** The frequency of invasive *Nocardia* infection was similar in transplant and nontransplant patients and mortality at 1, 6, and 12 months was similar in both groups. Trimethoprim-sulfamethoxazole prophylaxis failed to prevent *Nocardia* infection.

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*Nocardia* species are filamentous Gram-positive bacteria found throughout the world in water, soil, and other organic matter. Generally considered an opportunistic infection of immunocompromised patients, a third of the cases of nocardiosis occur in immunocompetent hosts, most of whom have comorbidities such as chronic lung disease, chronic kidney disease, and diabetes.[1-4] *Nocardia* infections rarely occur in the immunocompetent; T cells have a direct action against *Nocardia* and also activate macrophages.[5-7] Impairment of T-cell function is the strongest risk factor for nocardiosis and is often seen in patients with solid organ and hematologic transplant.[7-9]

In nontransplant patients, long-term corticosteroid use, chemotherapy, chronic lung disease, lymphoreticular malignancy, and human immunodeficiency virus infection with CD4 count less than 100 cells/mm$^3$ are major risk factors.[1,5,6,8,10,11]

*Nocardia* infections mainly occur in the first year after transplant, but should be

considered at any time when therapeutic immunosuppression is intensified.[7] The incidence of *Nocardia* infection in recipients of solid organ transplant varies according to the transplanted organ and ranges from 1% to 4% after heart or lung transplant to less than 1% after kidney or liver transplant and only 0.3% to 2% in allogeneic hematopoietic stem cell transplant patients.[2,3]

Improved testing and identification techniques and increasing use of immunosuppressive treatments in transplant and nontransplant patients are likely responsible for the rising incidence of *Nocardia* infections.[12,13]

The main site of entry is the respiratory tract via inhalation, but skin is a common infection site. Disseminated infection preferentially affects the lungs, soft tissue, and central nervous system (CNS), but bacteremia is not common.[12-14]

Mortality from *Nocardia* infection is high, between 15% and 20% in solid organ transplant recipients and up to 30% in bone marrow transplant patients.[5,15,16] Mortality is 4 times higher in immunocompromised patients than in nonimmunocompromised patients.[5]

Our study was designed to compare the clinical, radiographic, and microbiological characteristics of transplant and nontransplant patients with invasive nocardiosis as well as outcomes in a tertiary care center over a 20-year period.

## PATIENTS AND METHODS

A single-center retrospective cohort study of patients evaluated at Mayo Clinic in Florida. The study was approved by the institutional review board (ID: 17-010028).

We reviewed all culture-positive microbiology specimens for *Nocardia* species obtained between August 1, 1998, and November 30, 2018. A total of 202 patients were identified, of whom 110 (54%) met criteria for invasive disease. *Invasive nocardiosis* is 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). *Dissemination* was defined as a positive blood culture for *Nocardia* species, infection in 2 or more noncontiguous organs, or the presence of CNS involvement. Patients with a culture-positive *Nocardia* specimen obtained in the absence of clinical and/or radiological evidence of infection were deemed to be colonized and were excluded from the analysis.

### Demographic and Clinical Data

Demographic information, comorbidities, immune status, culture results, clinical course, and treatment were obtained retrospectively through electronic medical record review. Specific information was recorded for transplant patients including type and date of transplant, time from transplant to infection, presence of acute rejection and antirejection medications used, cytomegalovirus (CMV) infection within 6 months before the diagnosis of *Nocardia* infection, and CMV serology status.

### Microbiology

The Microbiology Laboratory at Mayo Clinic in Florida first identified the organisms as "possible *Nocardia* species" after reviewing their morphology on Gram and modified acid-fast staining. Subsequently, speciation with DNA sequencing and antibiotic sensitivity testing were performed at Mayo Clinic in Rochester, Minnesota.

### Statistical analyses

Continuous variables were summarized as the sample median and range. Categorical variables were summarized as the number and percentage of patients. Comparisons of characteristics between transplant and nontransplant patients were made using a Wilcoxon rank sum test (continuous variables) or Fisher exact test (categorical variables). Survival within a year after infection (first positive culture) was estimated using the Kaplan-Meier method, in which censoring occurred on the earlier date of last follow-up or 1 year after infection. Survival was compared between transplant and nontransplant patients using Cox proportional hazards regression models; hazard ratios (HRs) and 95% CIs were estimated. *P* values less than .05 were considered statistically significant, and all statistical tests were 2-sided. Statistical analyses were performed using R statistical software (version 3.6.2, R Foundation for Statistical Computing).

**TABLE 1. Demographic Characteristics and Risk Factors[a,b]**

| Variable | N | Overall (N=110) | Nontransplant patients (n=56) | Transplant patients (n=54) | *P* value |
|---|---|---|---|---|---|
| Age (y) | 110 | 64.9 (23.9, 86.6) | 69.2 (23.9, 86.6) | 59.5 (26.4, 80.4) | .003 |
| Sex: male | 110 | 70 (63.6) | 31 (55.4) | 39 (72.2) | .077 |
| Alcohol abuse | 110 | 3 (2.7) | 2 (3.6) | 1 (1.9) | 1.00 |
| IV drug use | 110 | 1 (0.9) | 1 (1.8) | 0 (0.0) | 1.00 |
| Diabetes | 110 | 38 (34.5) | 8 (14.3) | 30 (55.6) | <.001 |
| CKD | 110 | | | | <.001 |
| Any CKD stage | | 21 (19.1) | 8 (14.3) | 13 (24.1) | |
| ESRD on dialysis | | 17 (15.5) | 0 (0.0) | 17 (31.5) | |
| Coronary artery disease | 110 | 42 (38.2) | 17 (30.4) | 25 (46.3) | .12 |
| COPD | 110 | 18 (16.4) | 10 (17.9) | 8 (14.8) | .80 |
| Liver disease | 110 | 4 (3.6) | 2 (3.6) | 2 (3.7) | 1.00 |
| Malignancy | 110 | 24 (21.8) | 10 (17.9) | 14 (25.9) | .36 |
| Solid tumors | 110 | | | | .12 |
| No tumors | | 92 (83.6) | 49 (87.5) | 43 (79.6) | |
| Localized tumor | | 12 (10.9) | 3 (5.4) | 9 (16.7) | |
| Metastatic tumor | | 6 (5.5) | 4 (7.1) | 2 (3.7) | |
| Hematologic malignancy | 110 | 7 (6.4) | 3 (5.4) | 4 (7.4) | .71 |
| Chemotherapy within 6 mo before diagnosis | 110 | 7 (6.4) | 5 (8.9) | 2 (3.7) | .44 |
| Rheumatologic disease treated with immunosuppressive therapy | 110 | 15 (13.6) | 10 (17.9) | 5 (9.3) | .27 |
| Previous trauma/surgery of the infected site | 110 | 9 (8.2) | 6 (10.7) | 3 (5.6) | .49 |
| High corticosteroid dose within 6 mo before diagnosis[c] | 110 | 23 (20.9) | 7 (12.5) | 16 (29.6) | .035 |
| Dose of methylprednisolone pulse | 21 | 60 (20, 2500) | 40 (20, 60) | 313 (20, 2500) | .012 |
| Low CD4 count before diagnosis | 110 | 15 (13.6) | 3 (5.4) | 12 (22.2) | .012 |
| Lowest CD4 count before diagnosis | 15 | 75 (1, 258) | 176 (31, 188) | 74 (1, 258) | .47 |
| TMP-SMZ prophylaxis at diagnosis | 110 | 17 (15.5) | 2 (3.6) | 15 (27.8) | <.001 |
| Taking corticosteroids | 110 | 72 (65.5) | 22 (39.3) | 50 (92.6) | <.001 |
| Daily corticosteroid dose | 72 | 10.0 (1.0, 80.0) | 20.0 (5.0, 80.0) | 10.0 (1.0, 60.0) | .003 |
| Taking immunosuppressive medications[d] | 110 | 60 (54.5) | 9 (16.1) | 51 (94.4) | <.001 |

[a]CKD = chronic kidney disease; ESRD = end-stage renal disease; COPD = chronic obstructive pulmonary disease; IV = intravenous; TMP-SMZ = trimethoprim sulfamethoxazole.
[b]Data are presented as median (minimum, maximum) or as No. (percentage). *P* values comparing nontransplant and transplant patient results from the Wilcoxon rank sum test (continuous variables) or Fisher exact test (categorical variables).
[c]High-dose corticosteroids >20 mg of prednisone equivalent daily for >1 mo.
[d]Cyclosporine, tacrolimus, azathioprine, mycophenolate mofetil, sirolimus, or other immunosuppressive medications.

## RESULTS

One hundred ten individuals with invasive nocardiosis were identified, of whom 54 (49%) were transplant and 56 nontransplant (51%) patients. Most transplant patients were kidney and lung recipients. The overall mean age was 64.9 years, but transplant patients were younger and male and had a higher prevalence of diabetes and chronic kidney disease. Demographic characteristics and risk factors are summarized in Table 1.

Of the 54 transplant patients, 51 (94%) were solid organ transplant patients and 3 (6%) were bone marrow recipients. Most solid organ transplant patients had only 1 transplant (n=47 [87%]), but 7 patients (13%) had 2.


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**TABLE 2. Clinical Symptoms**

| Clinical symptom | N | Overall (N=110) | Nontransplant patients (n=56) | Transplant patients (n=54) | *P* value |
|---|---|---|---|---|---|
| Cough | 110 | 50 (45.5) | 22 (39.3) | 28 (51.9) | .19 |
| Dyspnea | 110 | 44 (40.0) | 17 (30.4) | 27 (50.0) | .036 |
| Sputum production | 110 | 31 (28.2) | 15 (26.8) | 16 (29.6) | .74 |
| Fever | 110 | 28 (25.5) | 8 (14.3) | 20 (37.0) | .006 |
| Cutaneous lesions | 110 | 22 (20.0) | 15 (26.8) | 7 (13.0) | .07 |
| Other | 110 | 17 (15.5) | 9 (16.1) | 8 (14.8) | .86 |
| Asthenia | 110 | 16 (14.5) | 5 (8.9) | 11 (20.4) | .089 |
| Chills | 110 | 15 (13.6) | 7 (12.5) | 8 (14.8) | .72 |
| Chest pain | 110 | 9 (8.2) | 3 (5.4) | 6 (11.1) | .27 |
| Weight loss | 110 | 7 (6.4) | 5 (8.9) | 2 (3.7) | .26 |
| Focal neurological signs | 110 | 6 (5.5) | 6 (10.7) | 0 (0.0) | .013 |
| Headache | 110 | 4 (3.6) | 1 (1.8) | 3 (5.6) | .29 |
| Seizures | 110 | 2 (1.8) | 2 (3.6) | 0 (0.0) | .16 |
| Arthritis | 110 | 2 (1.8) | 2 (3.6) | 0 (0.0) | .16 |
| Acute respiratory distress syndrome | 110 | 1 (0.9) | 1 (1.8) | 0 (0.0) | .32 |
| Coma | 110 | 1 (0.9) | 1 (1.8) | 0 (0.0) | .32 |

Data are presented as No. (percentage). *P* values comparing nontransplant and transplant patient results from the Fisher exact test.

The kidney was the most frequently transplanted organ (n=26 [48%]), followed by lung (n=18 [33%]), liver, heart (n=5 [9%]), and pancreas (n=3 [6%]). The length of time between transplant and *Nocardia* infection was 1.4 years (range, 0.1-21 years).

Significant differences between transplant and nontransplant patients were observed regarding age at presentation (median, 59.5 years vs 69.2 years; *P*=.003), diabetes (56% vs 14%; *P*<.001), chronic kidney disease (57% vs 14%; *P*<.001), high corticosteroid dose within 6 months before diagnosis (30% vs 13%; *P*=.035) (>20 mg prednisone equivalent daily for more than a month), use of mycophenolate mofetil (70% vs 2%; *P*<.01), or other immunosuppressive medications (cyclosporine, tacrolimus, azathioprine, mycophenolate mofetil, and sirolimus; 94% vs 16%; *P*<.001), low CD4 count before diagnosis (22% vs 5%; *P*=.012), and trimethoprim-sulfamethoxazole (TMP-SMZ) prophylaxis (28% vs 4%; *P*<.001). Additional demographic characteristics and risk factors are summarized in Supplemental Table 1 (available online at http://www.mcpiqojournal.org).

Clinical symptoms are summarized in Table 2. Transplant patients had a higher proportion of dyspnea (50% vs 30%; *P*=.036) and fever (37% vs 14%; *P*=.006) than did nontransplant patients. Focal neurological signs were more common in nontransplant patients (11% vs 0%; *P*=.013).

A summary of diagnosis information and site of infection is given in Table 3. Most microbiological diagnoses in both groups were made from respiratory sources, and the skin was the second most common source in the nontransplant group.

No significant differences between transplant and nontransplant patients were observed regarding site of infection. The rate of dissemination was approximately 20% in both groups (20% transplant vs 21% nontransplant; *P*=>.99). In both groups, the lung was the most common site of infection (81.5% transplant vs 66% nontransplant; *P*=.084). Skin and soft tissue were important sites of infection in nontransplant patients in a proportion of 29% vs 19% in transplant patients (*P*=.26). The brain was the site of infection approximately 10% of the time (13%

**TABLE 3. Diagnosis Information and Site of Infection[a,b]**

| Variable | N | Overall (N=110) | Nontransplant patients (n=56) | Transplant patients (n=54) | *P* value |
|---|---|---|---|---|---|
| Diagnosis information | | | | | |
| First specimen source | | | | | |
| Bronchoalveolar lavage/brushing | 110 | 44 (40.0) | 15 (26.8) | 29 (53.7) | .006 |
| Sputum/induced sputum/tracheal aspirate | 110 | 19 (17.3) | 14 (25.0) | 5 (9.3) | .042 |
| Pleural fluid | 110 | 3 (2.7) | 0 (0.0) | 3 (5.6) | .12 |
| Transbronchial, surgical, or percutaneous lung biopsy | 110 | 8 (7.3) | 3 (5.4) | 5 (9.3) | .49 |
| Abscess solid organ biopsy | 110 | 1 (0.9) | 0 (0.0) | 1 (1.9) | .49 |
| Cutaneous biopsy/swab/skin abscess | 110 | 23 (20.9) | 16 (28.6) | 7 (13.0) | .060 |
| Blood culture | 110 | 7 (6.4) | 4 (7.1) | 3 (5.6) | 1.00 |
| Cerebrospinal fluid | 110 | 1 (0.9) | 1 (1.8) | 0 (0.0) | 1.00 |
| Brain abscess biopsy | 110 | 3 (2.7) | 2 (3.6) | 1 (1.9) | 1.00 |
| Other[c] | 110 | 2 (1.8) | 1 (1.8) | 1 (1.9) | 1.00 |
| Chest radiography at diagnosis | 110 | 91 (82.7) | 42 (75.0) | 49 (90.7) | .042 |
| Chest CT scan at diagnosis | 110 | 94 (85.5) | 45 (80.4) | 49 (90.7) | .18 |
| Brain CT scan at diagnosis | 110 | 46 (41.8) | 18 (32.1) | 28 (51.9) | .053 |
| Brain MRI at diagnosis | 110 | 50 (45.5) | 19 (33.9) | 31 (57.4) | .021 |
| Site of infection | | | | | |
| Disseminated infection | 110 | 23 (20.9) | 12 (21.4) | 11 (20.4) | 1.00 |
| Lung | 110 | 81 (73.6) | 37 (66.1) | 44 (81.5) | .084 |
| Skin and soft tissue | 110 | 26 (23.6) | 16 (28.6) | 10 (18.5) | .26 |
| Brain/cerebrospinal fluid/eye | 110 | 13 (11.8) | 6 (10.7) | 7 (13.0) | .77 |
| Joint | 110 | 2 (1.8) | 1 (1.8) | 1 (1.9) | 1.00 |
| Liver | 110 | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1.00 |
| Bacteremia | 110 | 3 (2.7) | 1 (1.8) | 2 (3.7) | .61 |
| Other[d] | 110 | 4 (3.6) | 1 (1.8) | 3 (5.6) | .36 |

[a]CT = computed tomography; MRI = magnetic resonance imaging.
[b]Data are presented as No. (percentage). *P* values comparing nontransplant and transplant patient results from the Fisher exact test.
[c]Endophthalmitis and peritoneal fluid.
[d]Eye, peritoneum, and salivary gland.

transplant vs 11% nontransplant; *P*=.77). Bacteremia was rare, occurring more often in transplant (4%) than in nontransplant (2%) patients (*P*=.61).

Most patients in each group had lung imaging (chest radiography, chest computed tomography [CT], or both) at the time of diagnosis. Details of radiographic findings are given in Supplemental Table 2 (available online at http://www.mcpiqojournal.org) and are similar in both groups. Imaging of the brain by CT or magnetic resonance imaging was performed more frequently in transplant than in nontransplant patients; CT was performed in 52% vs 32% (*P*=.053) and magnetic resonance imaging in 57% vs 34% (*P*=.021); abnormal findings were similar in both groups.

Table 4 displays the susceptibility of *Nocardia* species isolates to multiple antibiotics. No significant differences between transplant and nontransplant patients were observed. More than 90% of *Nocardia* specimens were susceptible to 3 antibiotics: TMP-SMZ, linezolid, and amikacin. All *Nocardia* species were susceptible to TMP-SMX except for *N pseudobrasiliensis*, which was susceptible less than 50% of the time.

Ninety percent of all species were susceptible to amikacin, except for *N amikacinotolerans* and *N wallacei*, which were resistant.

As shown in Supplemental Table 3 (available online at http://www.mcpiqojournal.org), the number of transplant patients with *Nocardia* infection increased in the past 5 years in comparison to nontransplant patients.


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**TABLE 4. *Nocardia* sp Susceptibilities[a,b,c,d]**

| *Nocardia* sp Antibiogram (invasive disease) | Total isolates | Amikacin | Amox/clavulanate | Ceftriaxone | Cefepime | Ciprofloxacin | Clarithromycin | Doxycycline | Imipenem | Linezolid | Minocycline | Moxifloxacin | TMP-SMZ | Tobramycin |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| *Nocardia brasiliensis* | 18 | 100 (16/16) | 100 (14/14) | 6 (1/17) | 0 (0/12) | 0 (0/17) | 6 (1/17 ) | 0 (0/9) | 13 (2/16) | 100 (15/15) | 19 (3/16) | 45 (5/11 ) | 100 (16/16 ) | 88 (15/17 ) |
| *Nocardia farcinica* | 18 | 100 (14/14) | 100 (14/14) | 6 (1/17) | 8 (1/13) | 71 (12/17) | 5.8 (1/17) | 0 (0/9) | 87.5 (14/16 ) | 100 (11/11 ) | 20 (3/15 ) | 100 (9/9 ) | 100 (14/14 ) | 0 (0/15 ) |
| *Nocardia nova* | 16 | 94 (15/16) | 0 (0/10) | 47 (7/15 ) | 67 (4/6 ) | 0 (0/15) | 100 (15/15) | 0 (0/6 ) | 94 (14/15) | 100 (11/11) | 7 (1/15) | 0 (0/7) | 100 (15/15) | 13 (2/16) |
| *Nocardia asteroides* (probably *cyriacigeorgica*) | 14 | 100 (10/14 ) | 50 (3/6) | 56 (5/9) | 100 (1/14) | 38 (3/8) | 67 (6/9) | 50 (1/2) | 67 (6/9) | 100 (4/4) | 22 (2/9) | 50 (1/2) | 100 (8/8) | 67 (6/9) |
| *Nocardia cyriacigeorgica* | 15 | 100 (15/15) | 2 (2/13 ) | 60 (9/15) | 15 (2/13) | 0 (0/15) | 0 (0/14 ) | 8 (1/12 ) | 100 (15/15) | 100 (15/15) | 0 (0/15) | 7 (9/14) | 100 (15/15) | 100 (15/15) |
| *Nocardia beijingensis* | 7 | 100 (7/7) | 0 (0/5) | 100 (7/7) | 33 (1/3 ) | 0 (0/7) | 57 (4/7) | 0 (0/2 ) | 86 (6/7) | 86 (6/7) | 100 (7/7) | 100 (1/1) | 100 (7/7) | 100 (7/7) |
| *Nocardia* sp | 7 | 80 (4/5 ) | 50 (1/2 ) | 33 (2/6) | 0 (0/2) | 0 (0/5) | 80 (4/5) | 0 (0/2) | 80 (4/5) | 100 (3/3) | 60 (3/5) | 50 (1/2 ) | 100 (6/6) | 60 (3/5) |
| *Nocardia pseudobrasiliensis* | 5 | 100 (5/5) | 0 (0/5) | 0 (0/5) | 0 (0/5) | 100 (5/5) | 100 (5/5) | 0 (0/5) | 0 (0/5) | 80 (4/5) | 20 (1/5) | 100 (5/5) | 40 (2/5) | 100 (5/5) |
| *Nocardia abscessus complex*[e] | 2 | 100 (2/2) | 100 (2/2) | 100 (2/2) | 100 (2/2) | 0 (0/2) | 50 (1/2) | 100 (2/2) | 0 (0/2) | 100 (2/2) | 100 (2/2) | 0 (0/2) | 100 (2/2) | 100 (2/2) |
| *Nocardia amikacinitolerans* | 2 | 0 (0/2) | 100 (2/2) | 100 (2/2) | 100 (2/2) | 0 (0/2) | 0 (0/2) | 100 (1/1) | 100 (2/2) | 100 (2/2) | 100 (2/2) | 0 (0/2) | 100 (2/2) | 100 (2/2) |
| *Nocardia asteroides complex*[f] | 2 | 100 (2/2) | 0 (0/2) | 50 (1/2) | N/A | 0 (0/2) | 100 (2/2) | N/A | 100 (2/2) | 100 (2/2) | 0 (0/2) | 0 (0/2) | 100 (2/2) | 50 (1/2) |
| *Nocardia niwae* | 2 | 100 (2/2) | 0 (0/2) | 100 (2/2) | 0 (0/2) | 0 (0/2) | 100 (2/2) | 50 (1/2) | 100 (2/2) | 100 (2/2) | 100 (2/2) | 100 (2/2) | 100 (2/2) | 100 (2/2) |
| *Nocardia veterana* | 2 | 100 (2/2) | 0 (0/2) | 0 (0/2) | 100 (2/2) | 0 (0/2) | 100 (2/2) | 0 (0/2) | 100 (2/2) | 100 (2/2) | 0 (0/2) | 0 (0/2) | 100 (2/2) | 50 (1/2) |
| *Nocardia abscessus* | 1 | 100 (1/1) | 0 (0/1) | 100 (1/1) | 100 (1/1) | 0 (0/1) | 0 (0/1) | 100 (1/1) | 100 (1/1) | 100 (1/1) | 100 (1/1) | 0 (0/1) | 100 (1/1) | 100 (1/1) |
| *Nocardia higoensis/shimofusensis* | 1 | 100 (1/1) | 0 (0/1) | 0 (0/1) | 0 (0/1) | 0 (0/1) | 0 (0/1) | 0 (0/1) | 100 (1/1) | 100 (1/1) | 0 (0/1) | N/A | 100 (1/1) | 100 (1/1) |
| *Nocardia kruczakiae* | 1 | 100 (1/1) | 0 (0/1) | 0 (0/1) | 100 (1/1) | 0 (0/1) | 100 (1/1) | 0 (0/1) | 100 (1/1) | 100 (1/1) | 100 (1/1) | 0 (0/1) | 100 (1/1) | 0 (0/1) |
| *Nocardia otitidiscaviarum* | 1 | 100 (1/1) | 0 (0/1) | 0 (0/1) | N/A | 0 (0/1) | 100 (1/1) | N/A | 0 (0/1) | 100 (1/1) | 0 (0/1) | N/A | 100 (1/1) | 0 (0/1) |
| *Nocardia transvalensis/wallacei* | 1 | 100 (1/1) | 100 (1/1) | 100 (1/1) | 0 (0/1) | 100 (1/1) | 0 (0/1) | 0 (0/1) | 0 (0/1) | 100 (1/1) | 0 (0/1) | 100 (1/1) | 100 (1/1) | 0 (0/1) |

*Continued on next page*

**TABLE 4. Continued**

| *Nocardia* sp Antibiogram (invasive disease) | Total isolates | Amikacin | Amox/clavulanate | Ceftriaxone | Cefepime | Ciprofloxacin | Clarithromycin | Doxycycline | Imipenem | Linezolid | Minocycline | Moxifloxacin | TMP-SMZ | Tobramycin |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| *Nocardia wallacei* | 1 | 0 (0/1) | 100 (1/1) | 100 (1/1) | 0 (0/1) | 0 (0/1) | 0 (0/1) | 0 (0/1) | 0 (0/1) | 100 (1/1) | 100 (1/1) | 100 (1/1) | 100 (1/1) | 0 (0/1) |
| *Nocardia yamanashiensis* | 1 | 100 (1/1) | 0 (0/1) | 0 (0/1) | 0 (0/1) | 0 (0/1) | 100 (1/1) | 0 (0/1) | 0 (0/1) | 100 (1/1) | 0 (0/1) | 0 (0/1) | 100 (1/1) | 0 (0/1) |

[a]N/A = not available; TMP-SMZ = trimethoprim-sulfamethoxazole.
[b]Data presented are percent susceptible.
[c]Only counts invasive disease and includes Clinical and Laboratory Standards Institute-listed agents.
[d]Only counts susceptible, not intermediate.
[e]*Nocardia abscessus complex* includes *N abscessus, N arthritidis, N asiatica, N beijingensis*, and *N pneumoniae*.
[f]*Nocardia aseroides complex* includes *N abscessus, N brevicatena/paucivorans, N nova complex, N transvalensis complex, N farcinica*, and *N cyriacigeorgica*.

Comparisons of *Nocardia* species between nontransplant and transplant patients are presented in Supplemental Table 4 (available online at http://www.mcpiqojournal.org). In transplant patients, *N beijingensis* (11% vs 2%; *P*=.045) and *N pseudobrasilinesis* (7% vs 0%; *P*=.038) were significantly more common, whereas nontransplant patients were more often infected with *N brasiliensis* (25% vs 6%; *P*=.005) and *N nova* (21% vs 7%; *P*=.037).

Comparisons of *Nocardia* species according to site of infection are displayed in Supplemental Table 5 (available online at http://www.mcpiqojournal.org). *Nocardia brasiliensis* infections were less common in the lung than in other sites (5% vs 45%; *P*<.01) but more common in the skin and soft tissue (54% vs 4%; *P*<.001). *Nocardia cyriacigeorgica* infections were less common in the skin and soft tissue in comparison to other sites (0% vs 17%; *P*=.038). There were no other significant differences in *Nocardia* species in relation to the site of infection (Supplemental Table 5).

Regarding outcomes, as shown in Table 5, treatment failure with need to change in antibiotics occurred more often in transplant patients (6% vs 0%; *P*=.074); however, there was no significant difference.

The median length of follow-up after infection was 2.6 years (range, 3 days to 20.8 years), and 25 patients (23%) died within a year of infection. Survival within a year after infection was similar in both groups in both unadjusted analysis (HR, 1.45; 95% CI 0.65-3.23, *P*=.36) and when analysis adjusted for age at infection (HR, 1.57; 95% CI 0.68-3.63, *P*=.29).

## DISCUSSION

Most of the available literature on nocardiosis refers to infections in solid organ transplant patients and consists of case-control studies and case series,[5,7,12,15-17] but limited data exist on the comparison between transplant and nontransplant patients.

Similarly to previous reports, we found that in our group of patients with invasive nocardiosis, half of the infections occurred in nontransplant patients who had comorbidities and immunosuppression.[1,4,6,11] The main response of the immune system against *Nocardia* is T-cell mediated; therefore, patients


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**TABLE 5. Outcomes**

| Characteristic | N | Overall (N=110) | Nontransplant patients (n=56) | Transplant patients (n=54) | *P* value |
|---|---|---|---|---|---|
| Treatment failure with need to change in antibiotics | 110 | 3 (2.7) | 0 (0.0) | 3 (5.6) | .074 |
| Survival after infection (95% CI) (%) | 110 | | | | .36 |
| 30 d | | 93.6 (89.0-98.3) | 92.6 (85.9-99.8) | 94.4 (88.5-100.0) | |
| 6 mo | | 83.3 (76.5-90.6) | 83.1 (73.7-93.8) | 83.3 (74.0-93.9) | |
| 1 y | | 76.4 (68.7-85.0) | 81.1 (71.2-92.4) | 72.0 (61.0-85.1) | |

Data are presented as No. (percentage) unless otherwise specified. *P* values comparing nontransplant and transplant patient results from the Fisher exact test (treatment failure with need to change in antibiotics) or an unadjusted Cox proportional hazards regression model (survival after infection).

receiving treatments that affect T-cell function, such as corticosteroids, calcineurin inhibitors (tacrolimus and cyclosporine), sirolimus, mycophenolate, and azathioprine carry a high risk of invasive disease.[6,12,15] The daily dose of corticosteroids was actually higher in the nontransplant group than in the transplant group.

The lung was the organ most commonly involved, and fever and respiratory symptoms, such as dyspnea, were the most common presenting symptoms, particularly in transplant patients. Most patients in both groups had abnormal imaging of the lungs that correlated with the clinical symptoms. As in previously reported series, the presence of pulmonary nodules was the most common radiographic finding. In previous studies, cavitation was less common in immunocompetent patients with *Nocardia* infections, but in our study we found that cavitation occurred almost equally in both transplant and nontransplant patients; this is likely due to the degree of immunosuppression in our nontransplant patients.[4,6,18]

Most of our patients had CT of the chest because of the enhanced level of alertness for the early diagnosis of systemic infections in immunocompromised patients at our tertiary center.

Central nervous system imaging was less common as most patients did not present with neurological symptoms, but when performed, brain abscesses were found in approximately 10% of patients in both groups and often presented as multiple lesions.

Nearly a third of nontransplant patients had skin and soft tissue infections compared with less than 20% of transplant patients. Disseminated infection occurred in 20% of patients in both groups, in agreement with the findings of other investigators in transplant patients; however, the dissemination rate in nontransplant patients was twice as high as previously reported, likely reflecting a more intense level of immunosuppression in our population.[4,6,15-17]

In our study, 5 *Nocardia* species in similar distribution accounted for 70% of the total isolates: *N brasiliensis*, *N farcinica*, *N nova*, *N cyriacigeorgia*, and *N asteroides*. Nontransplant patients had a higher incidence of *N brasiliensis* and *N nova*, whereas transplant patients had a higher incidence of *N beijingensis* and *N pseudobrasiliensis*. Some *Nocardia* species had predilection for specific target organs. *Nocardia brasiliensis* caused less pulmonary than skin disease, whereas *N cyriacigeorgica* was not responsible for a single case of skin/soft tissue infection but was found most often in the lung.

*Nocardia* species may follow a particular distribution related to geography and climate. *N brasiliensis* is more common in Taiwan, *N cyriacigeorgica* in Spain, *N nova complex* in the United States and Canada, and *N brasiliensis* in areas with tropical or subtropical climate such as the southern and southwestern United States.[11,13,19]

Empirical treatment immediately after the identification of *Nocardia* infections is of great clinical importance, as speciation and

susceptibility reporting may take several weeks. Because empirical treatment carries a risk of antibiotic resistance, a combination of antimicrobials is usually prescribed.

We found that TMP-SMZ, amikacin, and linezolid exhibited good in vitro activity against more than 90% of *Nocardia* isolates as it did in other studies, but resistant species were found.[6,13,20] More than 50% of *N pseudobrasiliensis* were resistant to TMP-SMZ, almost all *N amikacinotolerans* and *N wallacei* were resistant to amikacin, and 15% of *N beijingensis* and *N pseudobrasiliensis* were resistant to linezolid. The results with TMP-SMZ and amikacin were in line with literature reports, although a recent study by Hamdi et al[13] found no resistance to linezolid.

Imipenem, in combination with other antibiotics, is commonly used for the empirical treatment of *Nocardia* infections and was found to be, based on susceptibility, a good choice for most *Nocardia* species in our study. Ceftriaxone is not appropriate for empirical treatment because of resistance in 5 common species (*N brasiliensis*, *N farcinica*, *N asteroids*, and *N cyriacigeorgica*), but provides good coverage against *N abscessus*. Because ceftriaxone is routinely used in the treatment of pneumonia, it should be avoided when *Nocardia* infection is either suspected or already confirmed but awaiting speciation.[11] Because of its poor CNS penetration, amikacin should be avoided when *Nocardia* infection is suspected in the CNS, and other antibiotics such as imipenem should be considered.

Other groups reported that TMP-SMZ at the dose used for the prevention of *Pneumocystis jirovecii* pneumonia in hematopoietic stem cell transplant patients protects against *Nocardia* infection.[3,5,21] However, breakthroughs of *Nocardia* infection while receiving TMP-SMZ prophylaxis have been reported in solid organ transplant patients and in a mixed population of recipients of solid organ transplant and hematopoietic stem cell transplant.[12,15-17] We found that 27.8% of transplant patients and 3.6% of nontransplant patients were receiving TMP-SMZ prophylaxis and had invasive *Nocardia* infections.[1,6,18,20,22] Steinbrink et al[6] studied 112 individuals comparing immunocompetent and immunocompromised patients and found that the prophylactic use of TMP-SMZ did not provide strong protection against *Nocardia* infections. We hypothesize that the lack of protection against *Nocardia* infections may be related to the dose of TMP-SMZ and the transplant-specific duration of prophylaxis. Therefore, the diagnosis of *Nocardia* infection should not be ruled out in individuals who receive TMP-SMZ prophylaxis.

*Nocardia* infections typically occur late after organ transplant (12-34 months).[2,5,23] In our study, the mean time from transplant to infection was 17 months.

In our retrospective analysis, the number of cases of *Nocardia* infection increased in transplanted patients in the past 5 years of the study, in agreement with some of the existing literature and differing from other.[13,17,23,24] This finding may be explained by the intensive immunosuppressive treatments used including induction therapy (57% of the transplant patients), episodes of rejection requiring high dose of corticosteroids (26% of the transplant patients), and CMV infection (20% of the transplant patients) with D−/R+ or D+/R+ status (61.1% of the transplant patients), a known risk of *Nocardia* infection.[12,15,16] Our finding of a similar rate of nocardiosis in nontransplant and transplant patients highlights the degree of immunosuppression of the various regimens used for nontransplant indications.

We found that treatment failure that led to change in antibiotics occurred more often in transplant patients, but both groups had similar mortality at 1, 6, and 12 months.

One-year mortality from *Nocardia* infection in bone marrow transplant patients may be as high as 30% and between 15% and 20% in solid organ transplant recipients[5,16]; mortality in both groups neared 25% at 6 months and more than 30% at 12 months. This finding is consistent with a significant increase in the risk of infection and mortality from *Nocardia* in patients with chronic diseases, who were undergoing chemotherapy, who had low CD4 counts, and, especially, those who were using corticosteroids and immunosuppressants.

The main limitation of our study was its retrospective design, which may have introduced biases in data collection. Additionally, the long recruitment period, during which diagnostic techniques and treatments changed,


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may have made our population more heterogeneous.

## CONCLUSION

Immunocompromised patients have an increased risk of invasive nocardiosis, but our study suggests that transplant and nontransplant patients are at equal risk of mortality. Also, clinical presentation and radiographic findings are similar and prophylactic use of TMP-SMZ may not have a protective effect against *Nocardia* infection, particularly in transplant patients. Amikacin, linezolid, and TMP-SMZ are appropriate choices for empirical antibiotic therapy for *Nocardia* infections and should be initiated promptly.

## SUPPLEMENTAL ONLINE MATERIAL

Supplemental material can be found online at: http://www.mcpiqojournal.org. Supplemental material attached to journal articles has not been edited, and the authors take responsibility for the accuracy of all data.

**Abbreviations and Acronyms:** **CMV** = cytomegalovirus; **CNS** = central nervous system; **CT** = computed tomography; **HR** = hazard ratio; **TMP-SMZ** = trimethoprim-sulfamethoxazole

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