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MAJOR ARTICLE

Outcome and Treatment of Nocardiosis After Solid Organ Transplantation: New Insights From a European Study

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Background. Solid organ transplant (SOT) recipients are at risk of nocardiosis, a rare opportunistic bacterial infection, but prognosis and outcome of these patients are poorly defined. Our objectives were to identify factors associated with 1-year mortality after nocardiosis and describe the outcome of patients receiving short-course antibiotics (≤120 days).

Methods. We analyzed data from a multicenter European case-control study that included 117 SOT recipients with nocardiosis diagnosed between 2000 and 2014. Factors associated with 1-year all-cause mortality were identified using multivariable conditional logistic regression.

Results. One-year mortality was 10-fold higher in patients with nocardiosis (16.2%, 19/117) than in control transplant recipients (1.3%, 3/233, $P < .001$). A history of tumor (odds ratio [OR], 1.4; 95% confidence interval [CI], 1.1–1.8), invasive fungal infection (OR, 1.3; 95% CI, 1.1–1.5), and donor age (OR, 1.0046; 95% CI, 1.0007–1.0083) were independently associated with 1-year mortality. Acute rejection in the year before nocardiosis was associated with improved survival (OR, 0.85; 95% CI, 0.73–0.98). Seventeen patients received short-course antibiotics (median duration 56 [24–120] days) with a 1-year success rate (cured and surviving) of 88% and a 5.9% risk of relapse (median follow-up 49 [6–136] months).

Conclusions. One-year mortality was 10-fold higher in SOT patients with nocardiosis than in those without. Four factors, largely reflecting general medical condition rather than severity and/or management of nocardiosis, were independently associated with 1-year mortality. Patients who received short-course antibiotic treatment had good outcomes, suggesting that this may be a strategy for further study.

Keywords. *Nocardia*; mortality; organ transplantation; prognosis; opportunistic infections.

Nocardia spp. is a filamentous environmental gram-positive bacterium that causes infection in immunocompromised patients, such as solid organ transplantation (SOT) recipients [1]. Because inhalation is the main form of entry for *Nocardia*, lung involvement is frequent, and bacteria may subsequently spread to other organs, such as the brain [1].

Although several reports have indicated that nocardiosis is associated with increased mortality in SOT recipients, a precise assessment of its impact on outcome is still lacking [2]. Indeed, reported post-SOT nocardiosis mortality rates vary from 0% to 70%, depending on the characteristics of the studied populations and durations of follow-up [3–8]. Furthermore, prognostic factors have not been precisely identified, because only limited-size retrospective studies have been published. Of note, a univariate analysis performed in a study of 31 patients with nocardiosis (including 9 transplant recipients) suggested that dissemination and presence of brain abscesses were associated with increased mortality [9].

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Theoretically, factors that could influence the outcome of nocardiosis include its presentation (eg, presence of cerebral abscesses [9]), possible coinfections with other opportunistic pathogens (eg, *Aspergillus* and cytomegalovirus [CMV] [6]), therapeutic modalities (eg, appropriateness of antibiotics according to species identification and antimicrobial susceptibility testing [2]), occurrence of adverse effects associated with antibiotics (eg, toxicity of trimethoprim–sulfamethoxazole [SXT] [6, 10, 11]), and presence of comorbidities [12]. An improved understanding of the impact of nocardiosis on outcomes after SOT and of factors associated with outcomes may help delineate a group of patients who require a specific initial diagnostic workup, treatment, and/or follow-up.

Another challenge in the field of post-SOT nocardiosis is the optimal duration of antibiotic treatment with regard to the risk of relapse on the one hand and to the adverse effects and costs of these agents on the other. Current recommendations suggest at least 6 months of antimicrobial therapy for pulmonary or soft tissue infections and a minimum of 9–12 months for brain abscess [13]. These guidelines are based on a retrospective study of 25 pulmonary cases published in 1982 that described a high rate of relapse (60%, 3/5 patients) among patients who received only SXT for less than 4 months [14]. Strikingly, a more recent study that included 12 heart transplant recipients suggested that a shorter (≤120 days) treatment course was feasible in pulmonary nocardiosis, without relapse [15].

We recently reported the results of a multicenter case-control study conducted to identify risk factors for nocardiosis [16]. In the present study, our primary objective was to identify factors associated with all-cause mortality 1 year after diagnosis of nocardiosis in the SOT population. Our secondary objective was to assess the risk of relapse associated with short-course (≤120 days) antibiotic treatment for *Nocardia* infection.

METHODS

Study Design and Participants

In our previously published retrospective case-control study, 351 SOT recipients (117 patients with post-transplant nocardiosis and 234 matched control transplant recipients, details of whom can be found elsewhere [16]) were included from 36 hospitals in Western Europe (participating centers are listed in the Supplementary Materials and in the author list) [16]. The present study includes the same 351 patients. Patients with nocardiosis were included if they met all of the following criteria: SOT recipient, isolation of *Nocardia spp*. in a clinical sample after transplant, signs and/or symptoms suggestive of nocardiosis, and diagnosis made between January 2000 and December 2014. To avoid selection bias, cases were identified in each institution using systematic and comprehensive screening of local microbiological, pathology, and transplantation databases.

Variables

Data were collected from the patients' medical records by local investigators who used dedicated case-report forms. The date of diagnosis was defined as the day on which the first clinical sample (eg, sputum) that allowed identification of *Nocardia* spp. was collected. Variables potentially associated with patient outcome were divided into the 3 groups described below.

(1) Collected patient characteristics included: age, sex, comorbidities at time of nocardiosis (Charlson comorbidity index; Supplementary Table 1) [17], transplant details (history of previous transplant, donor age, type of donation [deceased vs living], organ transplanted), immunosuppressive regimen used, and history of acute allograft rejection and history of opportunistic infections (CMV infection and/or disease as defined elsewhere [18], CMV serostatus at time of transplantation, bloodstream infection and history of treated proven or probable invasive fungal infection in the 6 months before nocardiosis). High-dose corticosteroids were defined as >20 mg/day of prednisone for at least 1 month or >2 pulses of 500 mg of intravenous methylprednisolone. High calcineurin inhibitor trough levels were defined as >10 ng/mL for tacrolimus and >300 ng/mL for cyclosporine.

(2) Factors related to the characteristics of nocardiosis included the following: time from transplant to nocardiosis, time between occurrence of symptoms and diagnosis, sites of infection, eventual dissemination (defined as the involvement of at least 2 noncontiguous organs and/or positive blood cultures), biological blood values at the time of *Nocardia* infection (kidney function, C-reactive protein, leukocytes, neutrophils, lymphocytes), additional pathogens (identification of at least 1 other microbial pathogen at the time of *Nocardia* diagnosis), and *Nocardia* species, susceptibility to SXT.

(3) Factors associated with the treatment of nocardiosis included the antimicrobial agents used, appropriateness of the antimicrobial agents prescribed in the first 2 weeks of therapy in the initial regimen (appropriateness being defined as the administration of antibiotics with in vitro activity against the infecting strain [19]), use of bactericidal antibiotics (amikacin, carbapenems, third-generation cephalosporin restricted to ceftriaxone and cefotaxime [20]) in the first 2 weeks of treatment, occurrence of antibiotic-related adverse effects, and need for surgery due to nocardiosis. Total duration of antibiotic treatment was recorded, and a short-course was defined as ≤120 days [15].

Relapse was defined as the association of clinical and radiological signs of nocardiosis with isolation of the same *Nocardia* species found at initial diagnosis, after the cessation of antimicrobial treatment for nocardiosis. Determination of nocardiosis as the cause of death was based on physician analysis of the medical chart.

Microbiology

To identify the species of each *Nocardia* strain, amplification and sequencing of a fragment of the gene coding for the 16S ribosomal RNA (16S rRNA) or *hsp65* genes were mandatory, as

described previously [16]. Ideally, antibiotic susceptibility testing was performed by determination of the minimal inhibitory concentration (MIC) in broth microdilution [21]. However, MICs evaluated using E-test strips or antibiotic disk diffusion on agar plates were considered acceptable when performed by a trained microbiologist [22–25]. When antibiotic susceptibility testing was missing, stored strains were a posteriori sent to an expert laboratory for nocardiosis testing (Observatoire Français des Nocardioses, Lyon, France) to perform the missing tests.

Statistical Methods

Final analysis was conducted after all data had been recorded and verified. Continuous data are presented as median (range) or mean (±standard deviation), as appropriate. Categorical data are presented as numbers and percentage of total. The primary outcome was survival 12 months after diagnosis of *Nocardia* infection. Survival was assessed using Kaplan-Meier curves and compared between groups using log-rank tests. Univariate analyses were performed using Fisher exact test or χ^2 test, as appropriate, to compare categorical variables, and Student *t* tests were performed to compare continuous variables. A bilateral *P* value <.05 was considered as statistically significant. Variables with a *P* value <.2 on univariate analysis were included in the final multivariable conditional logistic regression analysis. All statistical analyses were performed using R Statistical software (version 3.2.0; R Foundation for Statistical Computing, Vienna, Austria).

Ethical Aspects

As previously described, this work was approved by local ethics committees and fulfilled the regulatory standards of each participating country [16].

RESULTS

Participants and Overall Mortality

A total of 117 SOT recipients with nocardiosis from 36 European institutions were included; full case descriptions can be found elsewhere [16]. The median duration of follow-up from the date of nocardiosis diagnosis was 45.3 (0.1–151.9) months. One-year

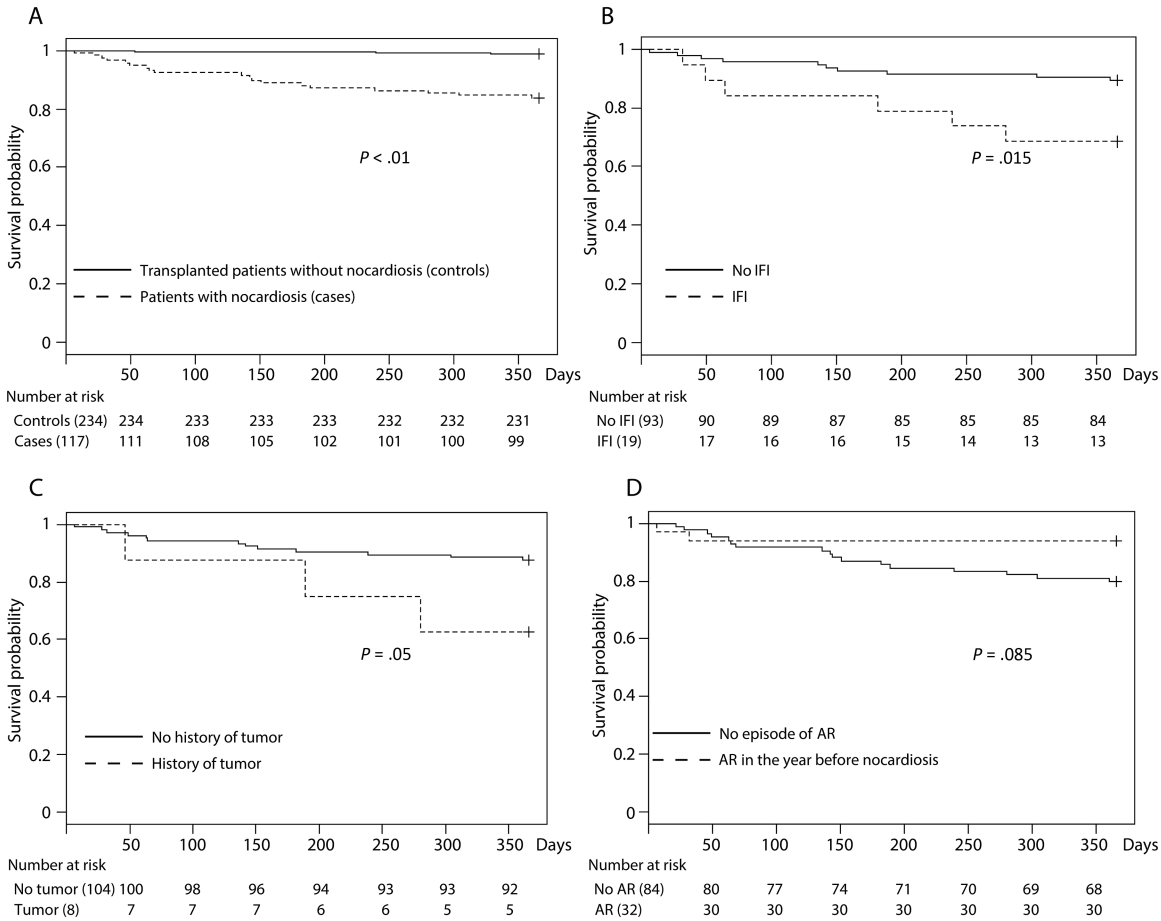

Figure 1. One-year survival curves after diagnosis of post-solid organ transplantation nocardiosis. Survival was assessed using Kaplan-Meier curves and compared among groups using log-rank tests. *A*, Survival curves of patients with nocardiosis (n = 117) and matched control transplant recipients (n = 234). *B–D*, Survival curves among patients with nocardiosis according to the presence of invasive fungal infection (including *Pneumocystis* pneumonia) in the 6 months before nocardiosis (*B*), history of tumor defined as a nonmetastatic tumor (if active or initially treated in the 5 years before diagnosis of nocardiosis) or metastatic solid tumor (*C*), and episode of acute rejection in the year before nocardiosis (*D*). Abbreviations: AR, acute rejection; IFI, invasive fungal infection.

Table 1. Factors Associated With 1-Year All-Cause Mortality in Univariate Analysis Among the 117 Patients With Post-Solid Organ Transplantation Nocardiosis

Characteristic	Dead at 1 Year, n = 19	Alive at 1 Year, n = 98	*P* Value
Clinical characteristics			
Age at diagnosis (y) (mean ± SD)	61.4 (12.3)	54.5 (13.5)	.07
Male (n, %)	14 (73.7)	60 (61.2)	.44
Charlson comorbidity index[a] at diagnosis n = 112 (mean, SD)	4.13 (1.7)	3.71 (1.8)	.34
History of tumor[b] n = 112	3 (18.8)	5 (5.2)	.08
Transplantation characteristics			
History of previous transplant	1 (5.2)	17 (17.3)	.30
Donor age (y) (mean ± SD) n = 110	54.5 (15.8)	46.0 (16.8)	.044
Deceased donor (vs living)	18 (94.7)	89 (90.8)	1
Nonthoracic (pancreas, liver, kidney) organ	12 (63.2)	66 (67.3)	.79
Immunosuppressive regimen and rejection data			
Cyclosporine A at diagnosis	4 (21.1)	17 (17.3)	.75
Tacrolimus at diagnosis	15 (78.9)	78 (80.0)	1
High calcineurin inhibitor level in the month before *Nocardia* infection	5 (26.3)	46 (46.9)	.16
Use of antiproliferative agents (azathioprine or mycophenolate mofetil) at diagnosis	14 (73.7)	81 (82.7)	.35
Corticosteroids at diagnosis (mg[c]) (mean ± SD) n = 115	7.0 (4.0)	9.1 (7.2)	.12
Acute rejection episode in the year before diagnosis n = 116	2 (10.5)	30 (30.6)	.09
Acute rejection episode in the 6 months before diagnosis n = 116	1 (5.3)	24 (24.5)	.07
High-dose steroids in the 6 months before diagnosis n = 116	1 (5.3)	19 (19.4)	.19
Plasma exchange in the 6 months before diagnosis n = 116	0 (0)	5 (5.1)	.59
Depleting antibodies[d] (antithymocyte globulin or rituximab) in the 6 months before diagnosis n = 116	0 (0)	6 (6.1)	.59
SXT prophylaxis at diagnosis	2 (10.5)	19 (19.4)	.52
Associated infectious diseases			
CMV infection in the 6 months before diagnosis	3 (15.8)	14 (14.3)	1
CMV disease in the 6 months before diagnosis	2 (10.5)	3 (3.1)	.19
CMV serostatus			.67
Low risk: D-R-	5 (26.3)	17 (17.3)	
Intermediate risk: D-R+ or D+R+	10 (52.6)	50 (51.0)	
High risk: D+R-	4 (21.1)	27 (27.6)	
Bloodstream infection in the 6 months before diagnosis	1 (5.3)	5 (5.1)	1
Additional pathogen[e] at diagnosis	12 (63.2)	28 (28.6)	<.01
Fungal infection[f] in the 6 months before diagnosis n = 112	6 (37.5)	13 (13.5)	.029
Biological characteristics			
Glomerular filtration rate[g] (mL/min/1.73 m^2) at diagnosis (mean, SD) n = 115	41.4 (24.3)	50.1 (27.6)	.19
White blood cell count at diagnosis (×1000/mm^3) (mean, SD) n = 115	11.3 (5.8)	11.5 (6.7)	.88
Neutrophil count at diagnosis (×1000/mm^3) (mean, SD) n = 105	9.5 (5.6)	9.8 (6.7)	.98
Lymphocyte count at diagnosis (×1000/mm^3) (mean, SD) n = 105	0.6 (0.4)	0.8 (0.6)	.35
C-reactive protein at diagnosis (mg/L) (mean, SD) n = 109	91.8 (67.5)	128.4 (90.9)	.13
Nocardiosis characteristics and treatment			
Time from transplantation to diagnosis (days) (mean, SD)	1611.7 (1692.7)	976.2 (1277.7)	.046
Time from symptoms to diagnosis (days) (mean, SD) n = 114	19.4 (18.4)	25.9 (24.1)	.21
Disseminated infection	9 (47.4)	41 (41.8)	.85
Lung or pleural involvement	16 (84.2)	85 (86.7)	.72
Central nervous system involvement	8 (42.1)	22 (22.4)	.13
Skin and soft-tissue involvement	5 (26.3)	32 (32.7)	.78
Bloodstream infection	2 (10.5)	7 (7.1)	.64
Nocardia species			.33
N. farcinica	8 (42.1)	33 (33.7)	
N. non-*farcinica*	11 (57.9)	65 (66.3)	
Strain susceptible to SXT n = 113	14 (73.7)	85 (86.7)	.44
Appropriate antibiotics[h] during the first 2 weeks of treatment n = 111	15 (88.2)	90 (95.7)	.23
Administration of carbapenems, 3GC,[i] amikacin, or SXT during the first 2 weeks of treatment n = 113	15 (83.3)	89 (93.7)	.15
Bactericidal antibiotic (carbapenems, 3GC,[i] amikacin) during the first 2 weeks of treatment n = 109	10 (62.5)	56 (60.2)	1

Table 1. Continued

Characteristic	Dead at 1 Year, n = 19	Alive at 1 Year, n = 98	*P* Value
Association of 2 appropriate antibiotics during the first 2 weeks of treatment n = 111	7 (41.2)	41 (43.6)	1
Antibiotic-related adverse effects n = 116	9 (47.4)	45 (46.4)	1
Need for surgery	4 (21.1)	19 (19.4)	1

Data are n (%) unless otherwise indicated. Diagnosis is the date of the diagnosis of nocardiosis, and n is the number of data analyzed (when <117).

Abbreviations: CMV, cytomegalovirus; D, donor; R, recipient; SD, standard deviation; SXT, trimethoprim–sulfamethoxazole.

[a]Apart from "history of tumor," none of the other individual variables of the Charlson comorbidity index were associated with 1-year mortality, with *P* values >.2.

[b]Defined as a nonmetastatic tumor (if active or initially treated in the 5 years before diagnosis of nocardiosis; n = 7) or metastatic solid tumor (n = 1).

[c]All corticosteroid doses are expressed in milligrams of methylprednisolone equivalent per day.

[d]In the 6 months before diagnosis of *Nocardia* infection, none of our patients received other types of lymphocyte-depleting or modulating antibodies.

[e]Fifty-one additional microbial pathogens were identified at the time of nocardiosis among 40 patients, including 19 fungi, 11 CMV, 8 gram-negative bacteria, 4 gram-positive bacteria, 3 *Clostridium difficile*, 2 *Legionella* spp., 1 human herpesvirus 8, 2 other viruses, and 1 *Toxoplasma gondii*.

[f]Nineteen patients experienced at least 1 invasive fungal infection (10 aspergillosis, 3 mucormycosis, 3 invasive candidiasis, 2 *Alternaria* spp., 1 *Fusarium* spp., 1 *Scedosporium* spp., 1 *Pneumocystis*).

[g]As estimated by modification of diet in renal disease (MDRD) formula.

[h]Appropriate antibiotic is defined as a drug with demonstrated in vitro activity against the isolated *Nocardia* strain. [i]3GC is the third-generation cephalosporin (restricted to ceftriaxone and cefotaxime).

all-cause mortality was significantly higher in patients with nocardiosis (16.2%, 19/117) than in control transplant patients (1.3%, 3/233; $P < .001$) (Figure 1A). In the nocardiosis nonsurvivors, death occurred after a median of 134 (4–359) days post-infection. Nocardiosis was listed as the cause of death in 52.6% of the nonsurvivors (10/19); when deaths related or not related to nocardiosis were compared, there was no statistically significant difference in the length of time between nocardiosis and death (100 [19–302] days vs 149 [4–359] days, $P = .57$).

Prognostic Factors

In univariate analysis (Table 1), 1-year mortality was significantly higher in patients with an additional pathogen at the time of diagnosis of nocardiosis, invasive fungal infection in the 6 months before nocardiosis, older donor age, and longer time from transplantation to nocardiosis (all $P < .05$). No therapeutic variables were associated with survival at 1 year. In multivariable analysis (Table 2), history of tumor (defined as a nonmetastatic tumor [if active or initially treated in the 5 years before diagnosis of nocardiosis] or metastatic solid tumor), invasive fungal infection in 6 months before nocardiosis, and older donor age were independently associated with increased 1-year mortality. Conversely, acute rejection in the year before nocardiosis was associated with a better survival. Survival analyses are shown in Figure 1B–D.

Description of Initial Management

During the first 2 weeks of treatment, appropriate antibiotics were prescribed in 94.6% of the patients (105/111) based on results of antibiotic susceptibility testing (Supplementary Tables 2 and 3). Bactericidal antibiotics were used as initial therapy in 66/109 of the patients (60.6%) and 2 simultaneous appropriate antibiotics in 48/111 (43.2%). At least 1 antibiotic-attributed adverse effect was reported in 46.6% of the patients (54/116), affecting the bone marrow (n = 24), kidneys (n = 22), digestive system (n = 11), and/or skin (n = 5). Twenty-three patients required surgery (23/117, 19.7%).

Risk of Relapse and Short-Course Antibiotic Treatment

Twenty-seven patients (23.0%) received short-course antibiotic treatment. However, the impact of antibiotic duration on the risk of relapse could only be assessed in 17 patients, as death occurred within 120 days in 10 of these patients (37.0%). These 10 patients died while still receiving active antimicrobial therapy against *Nocardia*, and half of these deaths (5/10) were directly attributed to nocardiosis. A detailed description of the 17 analyzable patients is provided in Table 3; the median duration of antibiotic treatment was 56 (24–120) days. Compared with the entire cohort, the 17 patients in whom antibiotics were deliberately given for ≤120 days were less likely to have disseminated

Table 2. Factors Associated With 1-Year All-Cause Mortality After Multivariable Conditional Logistic Regression Analysis Among 117 Patients With Nocardiosis After Solid Organ Transplantation

Characteristic	Odds Ratio (95% Confidence Interval)	*P* Value
History of tumor[a]	1.4 (1.1–1.8)	.02
Fungal infection[b] in the 6 months before diagnosis	1.3 (1.1–1.5)	<.01
Donor age (per year)	1.0046 (1.0007–1.0083)	.02
Acute rejection episode in the year before diagnosis	0.85 (0.73–0.98)	.03

[a]Defined as a nonmetastatic tumor (if active or initially treated in the 5 years before diagnosis of nocardiosis; n = 7) or metastatic solid tumor (n = 1).

[b]Nineteen patients experienced at least 1 invasive fungal infection (10 aspergillosis, 3 mucormycosis, 3 invasive candidiasis, 2 *Alternaria* spp., 1 *Fusarium* spp., 1 *Scedosporium* spp., 1 *Pneumocystis*).

Table 3. Description of Patients With Post-Solid Organ Transplantation Nocardiosis Receiving Short-Course Antibiotic Treatment (≤120 Days)

Patient	Age at Time of Diagnosis	Lung Involvement[a]	Disseminated Infection	Central Nervous System Infection	Skin and Soft-Tissue	Type of Positive Sample	*Nocardia* Species	Antibiotic Treatment Duration (days)	Outcome at 1 Year	Secondary Prophylaxis With Trimethoprim–Sulfamethoxazole, dose[b], duration	Length of Follow-up (months)
1	52	Multilobar, bilateral	No	No	No	Sputum, bronchial aspirate, BAL and pleural fluid	ND	42	Alive, no relapse	Yes, 2800, till death	41
2	67	None	No	No	Yes	Abscess fluid	*N. farcinica*	90	Alive, no relapse	Yes, 5600, 6 mo	49
3	50	Unilobar, unilateral	Yes	No	No	Bronchial aspirate, BAL and blood	*N. nova* complex	47	Alive, no relapse	Yes, 2400, 12 mo	48
4	63	Multilobar, bilateral	No	No	No	Sputum	*N. farcinica*	24	Alive, no relapse	Yes, 1600, ND	132
5	36	Multilobar, bilateral	No	No	No	Sputum	*N. abscessus*	51	Relapse, alive at 1 year	Yes, 1600, ND	26
6	56	Multilobar, bilateral	No	No	No	Bronchial aspirate and BAL	*N. nova* complex	39	Alive, no relapse	Yes, 1200, ND	62
7	65	Multilobar, unilateral	No	No	No	Bronchial aspirate and BAL	*N. farcinica*	76	Alive, no relapse	Yes, 2400, 4 mo	22
8	69	Multilobar, bilateral	No	No	No	Bronchial aspirate and BAL	*N. farcinica*	70	Alive, no relapse	No	63
9	80	None	No	No	Yes	Skin biopsy	*N. flavorosea*	56	Alive no relapse	No	27
10	71	None	No	No	Yes	Abscess fluid	*N. farcinica*	102	Dead, no relapse[c]	Yes, 5600, 5 mo	6
11	30	Unilobar, unilateral	No	No	No	BAL	*N. farcinica*	45	Alive, no relapse	No	23
12	60	Multilobar, bilateral	No	No	No	BAL	*N. farcinica*	33	Alive at 1 year, no relapse	Yes, 2400, until death	136
13	32	None	No	No	Yes	Skin biopsy	*N. abscessus*	90	Alive at 1 year, no relapse	No	72
14	60	Unilobar, unilateral	Yes	Yes	Yes	Abscess fluid	*N. cerradoensis*	47	Alive at 1 year, no relapse	Yes, 2400, until death	15
15	40	Multilobar, bilateral	No	No	No	Pleural fluid	ND	90	Alive at 1 year, no relapse	No	133
16	67	None	No	No	Yes	Skin biopsy	*N. anaemiae*	105	Alive at 1 year, no relapse	No	86
17	56	Unilobar, unilateral	No	No	No	Sputum and BAL	ND	120	Alive at 1 year, no relapse	ND	90

Abbreviations: BAL, bronchoalveolar lavage; ND, not determined.

[a]Lung involvement was assessed with lung computed tomography scan for all patients except patients 1 and 9.

[b]Dose was expressed as sulfamethoxazole weekly dose in milligrams.

[c]Death unrelated to nocardiosis.

disease (2/17 [11.8%] vs 50/117 [42.7%], $P < .01$) and tended to less frequently have central nervous system (CNS) infection (1/17 [5.9%] vs 30/117 [25.6%], $P = .12$). After a median follow-up of 49 (6–136) months, 15 of the 17 patients were cured (88.2%, including 2/2 with disseminated infection, 1/1 with CNS infection, and 11/12 with lung infection), 1 died within the first year (5.9%) and 1 relapsed (5.9%). The patient who died had *Candida* bloodstream infection at the time of diagnosis. Among the 15 patients who did not relapse despite administration of short-course antibiotics, all received appropriate initial antibiotics (15/15, 100%). However, the percentages of patients who received bactericidal antibiotics (7/15, 46.7%) or an association of 2 appropriate antibiotics (5/15, 33.3%) in the first 2 weeks of treatment were not significantly different from those observed in the entire cohort ($P = .46$ and $P = .65$, respectively). After cessation of therapy, secondary prophylaxis with SXT was given to 62.5% (10/16) of the patients who had received short-course antibiotics.

Seven patients (7/117, 6.0%) had a relapse during follow-up. These patients had a median duration of treatment of 165 [51–501] days, with 1 patient receiving short-course treatment (51 days). This patient, who had isolated lung infection, had relapsing nocardiosis despite the use of appropriate and bactericidal antibiotics in the first 2 weeks of treatment. Among the 7 patients who relapsed, only 1 died within 1 year due to an episode of acute allograft rejection.

Among 98 survivors at 1 year, 92 (93.9%) had no relapse after a median follow-up of 4.3 (1–12.6) years. Among these survivors, the median duration of treatment was 195 (24–1981) days. Duration of antibiotic treatment was significantly longer in patients with disseminated or CNS nocardiosis (Supplementary Figure 1).

In the 8/117 patients who had an infection limited to the skin and soft tissues (6.8%), the median duration of antibiotic treatment was 103 (35–351) days, and 6 of these patients (75.0%) required surgery. Cure was achieved in 7 patients (87.5%, including 4 patients with short-course antibiotics), and 1 patient (12.5%) relapsed 137 days after the end of therapy (which included >4 months of antibiotics and no surgery).

DISCUSSION

In our European cohort, 1-year all-cause mortality was more than 10 times higher in the 117 SOT recipients with nocardiosis than in control transplant recipients. The following 4 factors were independently associated with risk of death 1 year after nocardiosis: a history of tumor, invasive fungal infection in the 6 months before nocardiosis, donor age, and absence of acute organ rejection in the year before nocardiosis.

The mortality rate observed in our study (16.2%, 19/117) is comparable to that seen in a previous study reporting on 35 patients with post-SOT nocardiosis (6-month mortality = 14.3%, 5/35) [6] but appears to be lower than what has been reported in other studies (~30%) [4, 5]. This apparent discrepancy may be explained by the different outcome periods used in the various studies and the large proportion of lung recipients in the 2 latter studies. Higher mortality rates have been reported in patients with fungal opportunistic infections after SOT, including pneumocystosis (90-day mortality 23.1%, 6/26) [26], aspergillosis (12-week mortality, 39.3%, 44/112) [27], and mucormycosis (90-day mortality 58.2%, 57/105) [27]. We were therefore not surprised to observe that occurrence of an invasive fungal infection in the 6 months prior to nocardiosis (reported in 17.0% of our cohort and in 37.5% of the patients who died) was independently associated with an increased risk of death, as has been suggested previously [8].

Other patient characteristics were also independently associated with death after nocardiosis. First, we observed that a history of tumor was an independent prognostic factor after nocardiosis. Second, donor age was independently associated with 1-year mortality, an observation that is in agreement with data from the French transplantation agency (Agence de la Biomédecine) showing that donor age was associated with reduced graft and recipient survival after heart, lung, liver, and kidney transplantation [28].

Of interest, we observed significantly lower mortality among patients who experienced an acute rejection episode in the year before nocardiosis. Although this observation may appear surprising, these patients tended to have received higher doses of corticosteroids in the 6 months before diagnosis and to more frequently have a high calcineurin inhibitor level, suggesting that although a higher degree of immunosuppression may increase the risk of post-SOT nocardiosis, it is associated with a better outcome [16]. This association may be explained by the fact that patients with a high degree of immunosuppression are more closely monitored and promptly investigated in case of fever or respiratory symptoms, leading to earlier diagnosis. However, one can also hypothesize that a greater inflammatory response may be associated with a worse prognosis in *Nocardia* infection.

Strikingly, no therapeutic variable was associated with patient survival. Because of the noninterventional design of our study, we cannot rule out a beneficial effect of the early use of appropriate antibiotics or the impact of using antibiotic combinations or bactericidal vs bacteriostatic antibiotics. Expert recommendations regarding the initial choice of antibiotics [13] should therefore be followed, initially using antibiotics active against a broad spectrum of *Nocardia* species, such as SXT, amikacin, third-generation cephalosporins (restricted to ceftriaxone and cefotaxime), carbapenem (restricted to imipenem and meropenem), or linezolid. Antibiotic combinations that include bactericidal antibiotics should be considered for severe cases, including CNS nocardiosis. Treatment should be adapted as soon as possible to molecular biology–based species identification and results of antimicrobial susceptibility testing.

A somewhat controversial finding when considering current recommendations is our data regarding the duration of treatment for nocardiosis. Guidelines propose at least a 6-month antibiotic course for nocardiosis, but few data are available to support this statement. In 1982, Wallace et al reported 25 cases of pulmonary nocardiosis (in patients without SOT) and described a higher rate of relapse among patients receiving less than 4 months of treatment [14]. Almost 30 years later, in a retrospective description of 12 cases of nocardiosis after heart transplantation who received short-course (≤120 days) antibiotic treatment, Tripodi et al [15] reported that none of their patients who were treated with 3–4 weeks of intravenous bactericidal antibiotics followed by 1–3 months of oral antibiotic relapsed. Reducing antibiotic treatment duration could have potential benefits, such as cost savings and reduction in the risk of adverse events, especially among transplant recipients. Indeed, 46.5% of our patients experienced at least 1 drug-related adverse effect. Among 17 analyzable patients (including only 2 with disseminated infection and 1 with CNS infection) receiving short-course antibiotic treatment frequently followed by secondary prophylaxis with SXT, we observed an 88.2% cure rate without relapse, 1 nocardiosis-independent death, and 1 relapse. Our results should be interpreted with caution because of the risk of selection bias associated with the nonrandomized design. However, together with the findings of Tripodi et al [15], our results support the need for a randomized, controlled trial on the duration of antibiotic treatment for nocardiosis. Such a study should take into account important factors that were not available in our study (eg, dosing of antibiotics, potential reduction or tapering of immunosuppressive drugs, patient compliance). However, the relatively low number of events (<20% deaths at 1 year and rare relapses) observed in our study and the rarity of nocardiosis after SOT would make such a trial difficult to perform.

Once therapy is stopped, the role of secondary prophylaxis using low-dose SXT has not yet been determined. Secondary prophylaxis with SXT was prescribed to 62.5% (10/16) of our patients receiving short-course antibiotic treatment, which may explain the low incidence of relapse. However, we and others have shown that the low doses of SXT used to prevent pneumocystosis after SOT are not effective as primary prophylaxis against nocardiosis [16]. Because such prophylaxis is usually well tolerated and also prevents other opportunistic infections, we would recommend its use at higher dosage (800 mg sulfamethoxazole per day) as secondary prophylaxis.

Our study has several limitations, including its retrospective design, lack of data regarding reduction or tapering of immunosuppressive drugs or compliance to therapy, and the fact that antibiotic dose adjustment to body weight or kidney function was not taken into account. The limited size of our study and its design may explain the absence of a significant association between the severity of nocardiosis (eg, presence of brain abscess) and mortality [9]. Antibiotic susceptibility testing was not standardized, with only 40% of the bacterial strains sent to the French expert laboratory, and most tests were performed by antibiotic disk diffusion on agar plates. However, although disk diffusion is not considered a gold standard by the Clinical and Laboratory Standards Institute, it has been shown to have a high percentage of agreement with reference methods [21, 22].

In conclusion, we provide the first assessment of factors associated with 1-year mortality after post-SOT nocardiosis. Our findings support the suggestion that short-course antibiotic treatment may be a strategy for further study.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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APPENDIX

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