Nocardia Infection in Heart-Lung Transplant Recipients at Alfred Hospital, Melbourne, Australia, 1989–1998

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***Nocardia* infections are uncommon in recipients of heart, lung, or heart-lung transplants, but such infections are well described. Frequent episodes of rejection, high-dose prednisolone treatment, renal impairment, and prolonged respiratory support have all been shown to increase the risk of *Nocardia* infection in this group. In this retrospective review of 540 recipients of heart, lung, or heart-lung transplants, 10 patients developed *Nocardia* infection (frequency, 1.85%). Infection occurred at a mean ± standard deviation of 13 ± 14.5 months after transplantation. All patients had pulmonary disease with no evidence of extrapulmonary disease. The *Nocardia* infection did not contribute directly to patient deaths. Coinfection with other pathogens was present in 6 patients, and 2 patients had sequential infections. Radiological findings varied. All isolates were susceptible to trimethoprim-sulfamethoxazole, amikacin, and imipenem. Treatment regimens varied. Two (30%) of 6 patients treated with trimethoprim-sulfamethoxazole developed adverse reactions, which necessitated a change in antibiotic therapy. The optimal treatment regimen, which comprises both the antimicrobial agent and the length of treatment, is unclear.**

Nocardiosis is a localized or disseminated infection caused by a soilborne aerobic actinomycete. Infection is commonly introduced through the respiratory tract, and pulmonary disease is the most common presentation. Hematogenous dissemination occurs, particularly involving the nervous system and skeletal soft tissue structures. *Nocardia* infections occur uncommonly in recipients of solid-organ transplants, and they predominantly affect patients who undergo renal and heart, lung, or heart-lung transplantation. However, <4% of these patients will develop this type of infection [1–6]. Cardiac transplant recipients with a history of high-dose prednisolone treatment, renal impairment, prolonged respiratory support, and frequent episodes of rejection have an increased risk of infection [7]. Two small study series, which had a total of 54 patients, looked at infectious complications in heart-lung transplant recipients and reported no cases of *Nocardia* infection [8, 9]. Isolated case reports [10, 11] of mixed infections with *Nocardia* species and other pathogens have been reported in transplant recipients.

The present study is a retrospective review of *Nocardia* infection in patients undergoing heart-lung transplantation at Alfred Hospital. Although there are a number of published study series evaluating infectious complications in this group, to our knowledge, there are only 2 other study series looking specifically at *Nocardia* infections [7, 12] in this group of patients.

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Methods

Alfred Hospital is a tertiary-referral, university-affiliated hospital in Melbourne, Australia. From February 1989 through June 1998, a total of 540 heart-lung transplantations were performed at Alfred Hospital. A total of 385 were performed on patients from the state of Victoria, and 155 were performed on patients from other states or territories within Australia or from New Zealand. After transplantation and once they were stable, patients remained in Victoria for 3 months before returning home. All further follow-up took place at the initial referring center.

The records of the Microbiology and Infectious Diseases Department were reviewed, and the medical records of those patients who had undergone heart-lung transplantation and from whom *Nocardia* species had been isolated were reviewed. Patient demographics, date of transplantation, organs transplanted, immunosuppression regimen at the time of isolation of *Nocardia* species, concurrent use of trimethoprim-sulfamethoxazole (TMP-SMZ) for *Pneumocystis carnii* pneumonia prophylaxis, presence of rejection within the preceding 6 months, concurrent or sequential pathogens, and patient outcome were recorded. The site of infection, type of specimen from which *Nocardia* species were isolated, radiological findings at the time of isolation, antibiotic susceptibility profile, treatment, and treatment-related adverse reactions were also recorded.

Isolates were identified provisionally as *Nocardia* species by their ability to grow aerobically and by colonial and microscopic morphology and demonstration of partial acid-fast staining by use of a modified acid-fast staining method. Confirmation of identification and speciation was performed at the Microbiology Diagnostic Unit, Melbourne. Antibiotic susceptibility testing was performed for 9 isolates by use of the Etest method [13]; 1 isolate was tested retrospectively, and the other 8 were tested prospectively. For the remaining isolate, susceptibility testing was done by use of the agar dilution method [14]. The definitions of the terms "susceptible,"

"moderately susceptible," and "resistant" were based on the definitions of the National Committee for Clinical Laboratory Standards (NCCLS) for organisms grown aerobically [15].

Results

During the 112-month study, *Nocardia* species were isolated from 10 of 540 patients undergoing heart-lung transplantation. The medical records of these 10 patients were reviewed. The medical records of 1 patient were incomplete, because information on episodes of rejection, use of TMP-SMZ prophylaxis, and length of treatment for the *Nocardia* infection was not available. The patient demographics, date of transplantation, organs transplanted, immunosuppression regimen, episodes of rejection, and use of TMP-SMZ for *P. carnii* pneumonia prophylaxis are shown in table 1.

Infection occurred at a mean ± SD of 13 ± 14.5 months (range, 0–38 months) after transplantation. In 1 patient, *Nocardia farcinica* was isolated from bronchial washings of the transplanted donor lung 1 day after transplantation. This may have been a contaminant, but the patient was included in this series because she received prophylactic treatment to prevent infection. The infection occurred within 1 month of transplantation in 2 other patients, between 2 and 6 months after transplantation in 1 patient, and >6 months after transplantation in the other 6 patients.

All patients had pulmonary disease. The isolates, the specimen from which the culture was isolated, the radiological findings, and concurrent or sequential pathogens are shown in table 2. *Aspergillus* was the most common associated pathogen; 6 patients were coinfected with *Aspergillus* and *Nocardia* species, and 1 patient experienced a sequential *Aspergillus* infection. Three patients were coinfected with 3 pathogens. One of these patients had *Nocardia, Aspergillus,* and *Toxoplasma* species isolated from sputum and from a bronchoalveolar lavage specimen. The other 2 patients had *Nocardia, Aspergillus,* and *Scedosporium* species isolated from sputum, and 1 of these 2 patients had *Aspergillus* and *Scedosporium* species isolated from brain tissue at postmortem examination. All 3 patients died as a consequence of overwhelming infection. Three of 6 patients with mixed infections had supporting histopathological evidence. Two patients (patients 8 and 9) had evidence of extensive cerebral infarction secondary to angioinvasive aspergillosis. Postmortem findings in patient 6 were consistent with fungal pneumonitis. A lung-mass biopsy specimen taken from patient 10 was considered inadequate for histological examination, and appropriate histopathological specimens were not sent for the remaining 2 patients.

Chest radiological findings at the time of isolation of the *Nocardia* species varied. Four patients had areas of diffuse infiltrates and pleural fluid on chest radiographs. Three had ill-defined opacities, and 1 of these 3 had multiple lesions. One patient had a diffuse reticular nodular pattern throughout both lung fields, and the other patient, in whom *N. farcinica* was isolated 1 day after transplantation, had a normal chest radiograph. Radiological findings were not available for 1 patient.

Seven patients died. Four patients died within 6 months of the isolation of *Nocardia* species. These 4 patients included the 3 patients coinfected with 3 pathogens and 1 patient who died of disseminated *Aspergillosis* infection. Although *Nocardia* species were isolated from all 4 patients, it was not directly responsible for patient death. The remaining 3 deaths occurred >6 months after the isolation of *Nocardia* species. Death was attributed to renal failure (1 patient), respiratory failure (1 patient) and disseminated *Aspergillus* infection (patient 1).

Treatment regimens varied. Three people died while still receiving treatment for *Nocardia* infection. For 1 patient who died, the diagnosis was made at postmortem examination. The treatment details for another patient were not known. Five patients completed their treatment courses and were considered cured. One patient received a 6-month course of oral amoxicillin for treatment of the *Nocardia* infection. Another patient began receiving iv TMP-SMZ; however, 2 days after the start of treatment, a rash developed, necessitating a change to use of imipenem as antibiotic treatment. Imipenem was given for 2 weeks, and then treatment was changed to oral roxithromycin for a total of 6 months. The other 3 patients were treated with a carbapenem for 1–2 weeks and then were switched to treatment with oral TMP-SMZ (2 patients) or roxithromycin (1 patient).

Table 1. Clinical data for 10 heart-lung tranplant recipients in whom *Nocarida* infection developed after transplantation.

Patient	Sex	Age, y	Date of transplantation	Organs transplanted	Immunosuppression	TMP-SMZ	Episodes of rejection within 6 months
1	F	49	27/07/92	Heart and lung	Cyclosporine, azathioprine, prednisolone	Yes	Yes
2	M	57	30/06/92	Heart	Cyclosporine, azathioprine, prednisolone	Yes	Yes
3	M	59	20/09/92	Heart	Cyclosporine, azathioprine, prednisolone	No	Yes
4	M	53	21/12/92	Heart	Cyclosporine, azathioprine, prednisolone	NA	NA
5	M	43	01/08/91	Heart and lung	Cyclosporine, azathioprine, prednisolone	No	Yes
6	M	46	03/06/94	Bilateral sequential lung	Cyclosporine, azathioprine, prednisolone	No	No
7	F	60	06/01/96	Single lung	Cyclosporine, azathioprine, prednisolone	No	No
8	M	56	24/03/97	Heart	Cyclosporine, azathioprine, prednisolone	No	Yes
9	F	49	10/10/92	Bilateral sequential lung	Cyclosporine, methotrexate, prednisolone	Yes	Yes
10	F	26	10/04/94	Bilateral sequential lung	Cyclosporine, methotrexate, prednisolone	No	Yes

NOTE. F, female; M, male; NA, not available; TMP-SMZ, trimethoprim-sulfamethoxazole.

Table 2. Isolates from 10 heart-lung tranplant recipients in whom *Nocardia* infection developed after transplantation.

Patient	*Nocardia* isolate	Specimen	Radiological findings	Concurrent pathogen	Sequential pathogen
1	*N. asteroides* type IV	BAL/sputum/lung tissue	Pleural effusion, opacification	*Aspergillus, Toxoplasma*	—
2	*Nocardia* species	Sputum	Right lower lobe collapse and effusion	—	Cytomegalovirus
3	*N. nova*	Lung tissue	Ill-defined nodule	—	—
4	*N. nova*	BAL/sputum	NA	—	—
5	*N. nova*	BAL	Opacification and effusion	—	*Aspergillus*
6	*N. asteroides*	Sputum	Reticular-nodular pattern	*Aspergillus, Scedosporium*	—
7	*N. farcinica*	Sputum	Normal	*Aspergillus*	—
8	*N. nova*	Lung tissue	Nodule	*Aspergillus*	—
9	*N. nova*	Lung tissue	Diffuse opacification	*Aspergillus, Scedosporium*	—
10	*N. nova*	BAL/lung tissue	Multiple ill-defined nodules	*Aspergillus*	—

NOTE. BAL, bronchoalveolar lavage; NA, not available; NPI, no pathogen isolated. Lung tissue was obtained by biopsy or at postmortem examination.

Two patients, both of whom were receiving TMP-SMZ therapy, developed adverse drug reactions, necessitating a change in therapy. As described above, 1 patient developed a rash, and the other patient, who died before completion of treatment, developed neutropenia. The rash and neutropenia resolved after a change of therapy.

All isolates were susceptible to TMP-SMZ, amikacin, and imipenem (MICs, $\leq$2 mg/L, $\leq$4 mg/L, and $\leq$4 mg/L, respectively). All isolates were susceptible to erythromycin (MIC, $\leq$0.5 mg/L), with the exception of *N. farcinica.* Five of 6 *Nocardia nova* isolates were tested against amoxicillin/clavulanate, and all were resistant (MIC, $\geq$8 mg/L). All isolates were resistant to ciprofloxacin (MIC, $\geq$4 mg/L), with the exception of *N. farcinica,* and all showed reduced susceptibility or were resistant to tetracycline or doxycycline (MICs, 4 mg/L or $\geq$8 mg/L, respectively).

Discussion

Nocardia infections are uncommon in heart-lung transplant recipients at our hospital; only 10 (1.85%) of 540 patients developed *Nocardia* infection. This may be an underestimation of the rate of infection, because not all patients were followed at Alfred Hospital. Seven of the 10 patients died; in all 7 patients, the cause of death was unrelated to the *Nocardia* infection. This is consistent with the findings from other published series [7, 12]. We did not assess whether the acquisition of infection affected the overall survival of this group of patients; this has been shown not to be the case in 1 other series [7].

The first 6 months after transplantation is the period of greatest risk for the development of infection [3, 16, 17]. During this time, the risk of acute rejection necessitates the need for induction immunosuppression. Four patients in our series acquired their infection within the first 6 months after transplantation, and 3 of the 4 then died of overwhelming infection.

Risk factors for *Nocardia* infection in heart-lung transplant recipients include a history of high-dose prednisolone treatment, renal impairment, prolonged respiratory support, and frequent episodes of rejection [7]. In our series, 7 of 9 patients for whom such information was available had episodes of acute rejection that required escalation of their immunosuppression regimens within the 6 months preceding the isolation of the *Nocardia* species. All 10 patients were treated with cyclosporine-containing regimens; 8 patients received azathioprine, cyclosporine, and prednisolone, and the other 2 patients received methotrexate, cyclosporine, and prednisolone. Heart transplant recipients treated with cyclosporine have been shown to have a lower rate of infectious complications than those treated with a non–cyclosporine-containing regimen [2], and this may explain the low rate of *Nocardia* infection that we saw. A review of *Nocardia* infections in renal transplant recipients was unable to show a similar decrease in rates of infection associated with the use of cyclosporine [3].

The lungs were the primary sites of infection in all 10 patients, and no evidence of dissemination to other sites was documented. Eight of 9 patients for whom chest radiographs were reviewed had abnormal findings. Unfortunately, the presence of copathogens in 6 of these 9 patients makes it difficult to draw definite conclusions about the radiological findings. Only 3 patients had ill-defined nodules, and 2 of these patients were coinfected with *Aspergillus* species. There is no characteristic picture of pulmonary nocardiosis [18, 19]. A review [20] of the cause of lung nodules and masses that occurred in 25 of 257 cardiac transplant patients at one institution found *Aspergillus* species (9 patients; 3.5%) and *Nocardia* species (7 patients; 2.7%) to be the most frequently isolated pathogens. In another series [21] from the same institution, 2 patients developed *Nocardia* infection. Analysis of chest radiographs confirmed that both patients had nodules present. In one series [22] looking at the radiological changes seen in 77 lung transplantation patients with opportunistic bronchopulmonary infections, a diverse range of radiological changes was seen; unfortunately, there were no cases of *Nocardia* infection.

Coinfection with other pathogens, either sequentially or concurrently, can occur [7, 10–12]. Six patients in our series had concurrent infections, and 2 had sequential infections with other pathogens. Five of the 6 patients with concurrent infections had recent episodes of acute rejection and a resulting increase in their levels of immunosuppression. Three patients had histopathological evidence supporting the presence of mixed infections.

The administration of TMP-SMZ prophylactically has been

shown to reduce the occurrence of *P. carinii* pneumonia and toxoplasmosis in heart transplant recipients [6, 23–25]. The use of TMP-SMZ was thought to contribute to the absence of *Nocardia* infection in 1 group of patients [26]; however, the number of patients in the series was small (62 patients), and there was no control group. Three patients in our series were taking TMP-SMZ prophylaxis; all 3 were receiving 160 mg of TMP and 800 mg of SMZ 3 times weekly.

There are no controlled trials comparing the various treatment regimens. Despite the lack of conclusive data to support the need for the combination of TMP-SMZ, a published series [27] evaluating TMP-SMZ treatment and several recent reviews [17, 19, 28] have stated that TMP-SMZ, rather than SMZ only, remains the treatment of choice. The recommended daily dose of SMZ varies from 25 mg/kg to 75 mg/kg [17, 19]. When susceptible strains of the *Nocardia asteroides* complex are treated either with this combination or with sulfonamides only, 90%–95% of pleuropulmonary disease responds favorably [27]. However, in patients who have disseminated disease, depressed cell-mediated immunity, or both, side effects occur frequently. Approximately 44%–80% of HIV-infected individuals and organ transplant recipients experience fever, skin rash, neutropenia, or some combination of these [19]. In our series, 2 (30%) of 6 patients treated with TMP-SMZ experienced side effects that were considered serious enough to warrant a change of therapy. Because of concerns about side effects in this group of patients, it has been suggested that the optimal choice of parenteral drug for initial therapy is amikacin in combination with imipenem [19]. All isolates in our series were susceptible to both agents; 6 patients in our series were initially treated with a carbapenem (imipenem or meropenem) without adverse events occurring.

There is heterogeneity within the species *N. asteroides.* Biochemical tests, growth requirements, and antibiotic susceptibility profiles have allowed for the further identification of *N. asteroides* complex isolates as *N. farcinica, N. nova,* and *N. asteroides* sensu stricto [29, 30]. Antimicrobial susceptibility testing of 78 consecutive clinical isolates of *N. asteroides* complex identified 95% of isolates exhibiting 1 of 5 patterns [31]. The 14 isolates that showed the group 3 pattern (susceptibility to ampicillin and erythromycin but resistance to carbenicillin) are now identified as *N. nova.* Nine of 10 isolates were further identified: 6 were identified as *N. nova*, 2 as *N. asteroides* sensu stricto, and 1 as *N. farcinica*. All isolates of *N. nova* were susceptible to erythromycin but were resistant to ciprofloxacin and to tetracycline, doxycycline, or both. All 5 isolates of *N. nova* tested against amoxicillin/clavulanate were resistant. Separate testing against ampicillin was not performed. The reason for susceptibility to ampicillin but resistance to amoxicillin/clavulanate relates to the presence of an inducible membrane-bound β-lactamase that is induced by carbenicillin and clavulanate but not by ampicillin [30]. Resistance to ceftriaxone was higher (5 of 6 patients; 83%) than was reported in other series [32]. *N. nova* encompasses ~20% of isolates previously identified as *N. asteroides* [29]. It was the predominant isolate in our small series, accounting for 60% (6 of 10) of all isolates. We do not have an explanation for this.

Antimicrobial susceptibility testing was done by use of the Etest method [13]. This method has been shown to have excellent correlation when compared with the microbroth dilution method performed as described by the NCCLS [15].

In conclusion, nocardiosis remains an important but uncommon cause of morbidity in the heart-lung transplant recipient. The overall mortality of nocardial infection in general is 35% [33]. Although the mortality rate was high in this series, *Nocardia* infection did not directly contribute to it. Mortality is likely influenced by the severity of the immunosuppression of the host and by the extent of the infection. Although TMP-SMZ remains the treatment of choice recommended by some authors [18, 32], the high incidence of adverse events in the immunosuppressed group of patients makes other alternative regimens, such as imipenem and amikacin, seem more appealing. Further study comparing the 2 regimens is needed.

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