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# Experience with linezolid for the treatment of nocardiosis in organ transplant recipients

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**Summary** *Objectives:* Combination therapy with amikacin is recommended for treatment of nocardiosis in severely ill solid organ transplant recipients (SOT), but its use is complicated by nephrotoxicity. Linezolid has shown promise as an alternative in the empiric therapy of nocardiosis, but little is known about its effectiveness and safety in this setting. We describe the experience with linezolid for nocardiosis in SOT.
*Methods:* Retrospective review of cases of nocardiosis in SOT at a large center from 2006 to 2012.
*Results:* Nineteen cases were identified, 15/19 in lung transplant recipients. Median creatinine clearance at diagnosis was 56 ml/min. Eighteen patients were treated: 17/18 (94%) received trimethoprim/sulfamethoxazole and 15/18 (83%) received linezolid. Median duration of linezolid treatment was 21 days and it was discontinued in 10/15 (67%) due to side effects. Thrombocytopenia and anemia occurred in 14/15 (93%) and 9/15 (60%) of patients on linezolid, respectively, and were not different from patients not on linezolid. Cure was observed in 16/19 (84%), 33% of deaths were related to nocardiosis.
*Conclusions:* Linezolid was acceptable as initial empiric therapy for nocardiosis. Myelosuppression was a limiting factor, but not exclusive to patients on linezolid and could have been aggravated by concomitant use of other myelosuppressive drugs.


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## Introduction

*Nocardia* species are ubiquitous and belong to a diverse group of bacteria known as aerobic actinomycetes. Disease occurs primarily in immunocompromised hosts[1] and usually constitutes a serious infection with high risk of dissemination. The overall incidence of *Nocardia* infection has been increasing, mostly due to an expanding population of transplant recipients and increased use of immunomodulatory agents.[2–4] Nocardiosis occurs in 0.6% of solid organ transplant (SOT) recipients.[5] The prevalence is higher in lung transplant recipients (3.5%) and lower in liver transplant recipients (0.1%). A previous study from our center identified the following independent risk factors for *Nocardia* infection in SOT recipients: treatment with high-dose steroids, cytomegalovirus (CMV) disease, and high levels of calcineurin inhibitors.[5] In the same study, overall mortality at 6 months was 14% and 80% of deaths were attributable to *Nocardia*.

Sulfonamides are generally the preferred choice for treating most cases of nocardiosis.[6,7] For initial therapy of cerebral, disseminated disease, or very ill patients, combination therapy with carbapenem and amikacin with or without trimethoprim/sulfamethoxazole (TMP/SMX) is recommended. These recommendations also apply to SOT recipients.[7] However, there are shortcomings in the aforementioned approach. Underlying renal dysfunction is common in SOT recipients, which represents a safety barrier for employing amikacin in severe disease. Therefore, alternative treatment approaches can sometimes be necessary. The advent of linezolid in the last decade created a potential opportunity for developing an alternative treatment for nocardiosis. Linezolid has acceptable *in vitro* activity against all *Nocardia* species,[8] its oral bioavailability is close to 100%, and it has excellent cerebrospinal fluid (CSF) penetration.[9] However, there is very little published experience with this agent for this type of infection. Isolated case reports of successful treatment of nocardiosis with linezolid, including disseminated disease, have been published.[10,11] However, whether the clinical success observed in those reports can be generalized remains uncertain. Safety remains a theoretical concern since long-term linezolid treatment can be complicated by toxicity, primarily bone marrow suppression. Therefore, the usefulness of linezolid for nocardiosis warrants further investigation given the lack of data on its efficacy and safety for the treatment of nocardiosis in SOT.

We reasoned that linezolid might be a reasonable alternative for initial empiric therapy until susceptibility results are available. In this manuscript, we describe the clinical experience of linezolid in the treatment of *Nocardia* infections in SOT recipients in one of the largest transplant centers in the United States. To our best knowledge, this is the largest case series of linezolid for the treatment of *Nocardia* infections in the SOT population.

## Methods

### Patients and study design

The study was approved by the University of Pittsburgh Institutional Review Board. We retrospectively reviewed all cases of nocardiosis in SOT at the University of Pittsburgh Medical Center from 2006 to 2012. Cases were included if they had a positive culture for *Nocardia*. Cases were initially identified from the hospital's microbiology database and this was followed by a detailed review of the patient's medical records. The clinical data collected included demographics, transplant data such as type and date of transplant, underlying illness, immunosuppressive regimen, rejection episodes and treatment, and prophylaxis; laboratory and radiographic findings; signs and symptoms at the time of diagnosis; length of hospital stay; occurrence of CMV disease and invasive fungal infections; *Nocardia* susceptibility results; antimicrobial therapy; and clinical and microbiological outcomes.

### Definitions

*Nocardia* infection was defined as a positive culture in the presence of clinical and/or radiological features of infection. Disseminated infection was defined as involvement of $\geq$2 non-contiguous sites or central nervous system (CNS) involvement.[12] Neutropenia was defined as a neutrophil count $<$1000/$\mu$L and severe neutropenia as a neutrophil count $<$500/$\mu$L. Thrombocytopenia was defined as a platelet count $<$150,000/$\mu$L. Anemia was defined as a drop in hemoglobin greater than 2 g/dL from baseline while on therapy. CMV infection was defined as evidence of CMV viral replication via detection of CMV DNA. Invasive fungal infection was defined as proven or probable as per ESOT/MSG criteria.[13] Creatinine clearance (CrCl) at baseline was calculated by the Cockcroft-Gault formula. Acute kidney injury (AKI) was defined as a 50% decrease in clearance from baseline. Clinical cure was defined as resolution of signs, symptoms and radiographic findings of infection.

### Statistics

Discrete variables were expressed as number (*n*) and percentages. Continuous variables were reported as mean $\pm$ SD (or range), or median (range). Proportions were compared by Fisher's *Z*-test. *P*-values $<$0.05 were considered significant by two-tailed tests. Statistical analysis was conducted with SigmaStat (Systat Software, Inc., San Jose, CA).

## Results

We identified 19 SOT patients with nocardiosis (Table 1). Median age at diagnosis was 60 years (range 26–80), 14/19 (73.7%) were male and 15/19 (78.9%) were lung transplant recipients. All patients were on a tacrolimus-based immunosuppressive regimen and 13/19 (68.4%) were on TMP/SMX prophylaxis. Sixteen (84.2%) patients had GFR $<$90 ml/min, and 10 (52.6%) had GFR $<$60 ml/min. Median CrCl at time of diagnosis was 56 ml/min (range 19–116).

### Clinical characteristics of *Nocardia* infections

The most common site of infection was pulmonary in 15/19 (78.9%), followed by disseminated disease in 3/19 (15.8%).