

Nocardiosis: Updates and Clinical Overview

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CME Activity

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Abstract

Nocardia, a gram-positive bacillus with the microscopic appearance of branching hyphae, can produce considerable disease in the appropriate host. The taxonomy of *Nocardia* continues to evolve; more than 50 species have been described. Early recognition and effective therapy are imperative to achieve successful outcomes. Although nocardiosis typically occurs in patients with cell-mediated immunosuppressive conditions, infection may occasionally develop in immunocompetent patients as well. This review addresses the microbiology of *Nocardia*, risk factors for infection, clinical presentations, and management strategies.

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The genus *Nocardia* is a ubiquitous group of environmental bacteria that usually manifest as an opportunistic infection in immunocompromised hosts. *Nocardia* can be found in soil, decomposing vegetation, and other organic matter, as well as in fresh and salt water. Both *Nocardia* and *Rhodococcus* are members of the family Nocardiaceae, which belongs to a suborder of “aerobic actinomycetes” that also includes *Mycobacterium*, *Corynebacterium*, *Gordona*, and *Tsukamurella*.

The taxonomy of *Nocardia* has been challenging because numerous revisions have been made with the identification of more than 50 species. What was originally referred to as *Nocardia asteroides* was later found to be a group of bacteria with a heterozygous pattern of antimicrobial drug susceptibilities.¹ Subsequently named *N asteroides* complex, this group of bacteria is responsible for most clinical human nocardial infections. *N asteroides* complex was later

separated and reorganized into different species on the basis of drug susceptibility patterns: *Nocardia abscessus*, *Nocardia brevicatena-paucivorans* complex, *Nocardia nova* complex (which includes *N nova*, *Nocardia veterana*, *Nocardia africana*, *Nocardia kruczakiae*), *Nocardia transvalensis* complex, *Nocardia farcinica*, and *N asteroides*.² *Nocardia cyriacigeorgica* was recently differentiated from *N asteroides* and is becoming a more frequently identified clinically relevant pathogen.³

Nocardia is a gram-positive bacterium that grows aerobically. Unlike other gram-positive bacteria, *Nocardia* appears as a filamentous bacterium with hyphaelike branching on direct microscopy. *Nocardia* exhibits varying degrees of acid-fastness, depending on the mycolic acid composition in the cell wall and type of stain used.² The modified Kinyoun acid-fast stain uses 1% sulfuric acid as a decolorizer (instead of the more potent hydrochloric acid used in the decoloration step in the Ziehl-

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TABLE 1. Select Differential Diagnoses of Nocardiosis

Pulmonary disease
<ul style="list-style-type: none"> • Fungal infections, including (depending on the host) aspergillosis, mucormycosis, histoplasmosis, blastomycosis, cryptococcosis • Actinomycosis, <i>Rhodococcus equi</i>, and other bacterial infections • Mycobacterial infections, including <i>Mycobacterium tuberculosis</i> and nontuberculosis mycobacterial infections • Lung malignancy (primary or secondary)
Cutaneous disease
<ul style="list-style-type: none"> • Lymphocutaneous disease: sporotrichosis, <i>Mycobacterium marinum</i> infection • Superficial cellulitis: group A streptococcus, <i>Staphylococcus aureus</i>, <i>Erysipelothrix</i> species, and <i>Francisella tularensis</i> infections • Mycetoma (late stage): actinomycosis, fungal infections (<i>Pseudoallescheria</i> species and other molds) • Other: cutaneous leishmaniasis, cryptococcosis, infections with rapidly growing mycobacteria (eg, <i>Mycobacterium fortuitum</i>, <i>Mycobacterium chelonae</i>)
Central nervous system disease
<ul style="list-style-type: none"> • Malignancy (primary or secondary) • Bacterial abscess (single or multiple) • Vascular infarction • Other (depending on host): toxoplasmosis, <i>M tuberculosis</i>, fungal infection (including cryptococcosis, aspergillosis, mucormycosis), cysticercosis

Neelsen staining procedure), which enhances the ability of *Nocardia* to retain the colored fuchsin.⁴ Unlike mycobacteria, *Nocardia* has a “beaded” acid-fast appearance on microscopy. *Nocardia* can resemble *Actinomyces* species on Gram stain; however, *Actinomyces* species are not acid-fast and grow under anaerobic conditions.

RISK FACTORS FOR INFECTION

Nocardia usually is an “opportunistic pathogen,” with the majority of infections occurring in patients with immunosuppressive conditions. Up to one-third of patients with nocardiosis, however, are immunocompetent.⁵ Irrespective of a patient’s immunologic status, the isolation of *Nocardia* from the respiratory tract or other body source should not be regarded as a contaminant or commensal organism. Patients with depressed cell-mediated immunity especially are at high risk for infection, including those with lymphoma, other selected malignancies, human immunodeficiency virus infection, and solid-organ or hematopoietic stem cell transplant and those receiving long-term treatment with steroids or other medications that suppress cell-mediated immunity.^{6,7}

Patients with allogeneic hematopoietic stem cell transplants are at much higher risk for nocardiosis than those with autologous hematopoietic stem cell transplants.^{8,9} The development of graft-vs-host disease and subsequent additional immunosuppressive treatments may account for much of the increased risk in allogeneic hematopoietic stem cell

transplant patients. Among these patients, nocardiosis can develop at varying time periods, which range from 2 to 3 months to 1 to 2 years after stem cell infusion.^{8,9} Among solid organ transplant recipients, *Nocardia* infection has a frequency of 0.6% to 3% and has been well described in kidney, heart, and liver recipients.¹⁰⁻¹² A recent review of 5126 solid organ transplant recipients, however, found lung transplant recipients to have the highest incidence of *Nocardia* infection, followed by recipients of heart, small bowel, kidney, and liver transplants.¹² Although the use of cyclosporine has been associated with the development of nocardiosis,^{13,14} combination therapy with cyclosporine and prednisone in some patient groups may pose less risk than azathioprine and prednisone or high-dose prednisone alone.^{15,16} Solid tissue cancers with associated chemotherapy also represent another novel category for *Nocardia* disease development. Comorbidities and concurrent infections, including diabetes, cytomegalovirus infection, and alcoholism, contribute as well. Chronic obstructive pulmonary disease has a common association with pulmonary nocardiosis, but usually in the setting of concurrent corticosteroid use.¹⁷

CLINICAL PRESENTATIONS

Pulmonary nocardiosis is the most common clinical presentation of infection because inhalation is the primary route of bacterial exposure. The onset of symptoms may be subacute to more chronic and can include productive or nonproductive cough, shortness of breath, chest pain, hemoptysis, fever, night sweats, weight loss, and progressive fatigue. The chest radiograph can be variable, displaying focal or multifocal disease with nodular and/or consolidation infiltrate as well as cavitary lesions.^{18,19} Pleural effusions can develop in up to one-third of patients. It can be very difficult clinically and radiographically to differentiate *Nocardia* from filamentous fungal (eg, aspergillosis, mucormycosis) or mycobacterial disease (Table 1). Occasionally, *Nocardia* may be identified from the respiratory tract in a person without apparent pulmonary infection. *Nocardia* isolation without apparent pulmonary infection can be encountered in patients with underlying structural lung disease, such as bronchiectasis and cystic fibrosis,² and should be interpreted cautiously. The identification of *Nocardia* from an immunocompromised patient should never be ignored, especially if any abnormal clinical or radiologic pulmonary findings are present.

Extrapulmonary nocardiosis is relatively common and can occur through hematogenous dissemination or a contiguous spread of necrotizing pneumonitis into the pleura, pericardium, mediastinum, and vena cava. Abscess formation is characteristic of extrapulmonary nocardiosis and can resemble a pyogenic bacterial process or evolve into a chronic granulomatous or mixed progressive inflammatory mass. The central nervous

system (CNS) is the most common extrapulmonary location for nocardiosis (up to 44% in one series).¹⁸ Patients may have 1 or more brain abscesses and present with headache, nausea, vomiting, seizures, or alteration in consciousness.² Neurologic symptoms typically develop gradually, although an acute presentation with rapid progression may occur occasionally. Cerebral nocardiosis commonly accompanies pulmonary disease, but isolated CNS disease may occur. In immunocompetent patients, cerebral nocardiosis is less common and may resemble a brain tumor or vascular infarct.^{20,21} Central nervous system imaging should be considered for patients with any adverse neurologic symptoms, severe pulmonary nocardiosis, or significant immunosuppression.

Primary cutaneous and soft tissue nocardiosis can result from traumatic injury to the skin that involves contamination with soil.²² Unlike other forms of nocardiosis, primary cutaneous disease usually develops in immunocompetent hosts. After skin inoculation, a superficial abscess or localized cellulitis can develop. Cutaneous nocardiosis can resemble soft tissue infections produced by *Staphylococcus aureus* or streptococci (Table 1); however, this form of nocardial disease is usually more indolent.¹⁸ The infection can spread to the regional lymph nodes and produce a single or linear chain of nodular lesions. Lymphocutaneous nocardiosis is often called *sporotrichoid nocardiosis*, given the similar presentation of sporotrichosis. In more advanced disease, a mycetoma can develop with sinus tract development. *Nocardia brasiliensis* is the most common *Nocardia* species in cutaneous disease (especially progressive and lymphocutaneous disease), although *N asteroides* and *Nocardia otitidiscaviarum* have also occasionally been isolated.²²

Nocardia bacteremia is less often encountered. In one review of *Nocardia* bacteremia, 64% patients had concurrent pulmonary nocardiosis, 28% had concurrent cutaneous disease, and 19% had concurrent CNS disease.²³ *Nocardia* bacteremia associated with central venous catheter infections has been reported.^{24,25} Polymicrobial bloodstream infections with *Nocardia* and gram-negative bacilli have also been identified. Hematogenously disseminated nocardiosis has led to infection in the eyes (keratitis), heart valves, liver, spleen, adrenal glands, thyroid gland, and organ tissues.

TREATMENT CONSIDERATIONS

General treatment recommendations for nocardiosis are hindered by the lack of prospective controlled trials. Optimal antimicrobial treatment regimens have not been firmly established. *Nocardia* displays variable in vitro antimicrobial susceptibility patterns, and management of nocardial infections must be individualized.²⁶ The Clinical and Laboratory Standards Institute has published recommendations for antimicrobial susceptibility testing for *Nocardia* and other aerobic actinomycetes.²⁷ *Nocardia*

isolated from clinically significant infections should undergo antimicrobial susceptibility testing to assist in treatment decisions. Drug susceptibility patterns for major *Nocardia* species are listed in Table 2.

Sulfonamides, including sulfadiazine and sulfisoxazole, have been the antimicrobials of choice to treat nocardiosis for the past 50 years despite bacteriostatic activity.²⁸ Trimethoprim-sulfamethoxazole (TMP-SMX) is the most commonly used sulfonamide preparation in the United States, although the benefit of the trimethoprim component is unclear. Divided doses of 5 to 10 mg/kg per day of the trimethoprim component (or 25 to 50 mg/kg per day of sulfamethoxazole) are recommended to produce sulfonamide serum concentrations between 100 and 150 $\mu\text{g/mL}$. Adverse reactions to high-dose TMP-SMX therapy are frequent and include myelosuppression, hepatotoxicity, and renal insufficiency. Trimethoprim-sulfamethoxazole is active against most *Nocardia* species; however, *N otitidiscaviarum* is commonly resistant to TMP-SMX, and *N nova* and *N farcinica* are occasionally resistant.^{22,28}

Alternative antimicrobial agents with activity against *Nocardia* include amikacin, imipenem, meropenem, ceftriaxone, cefotaxime, minocycline, moxifloxacin, levofloxacin, linezolid, tigecycline, and amoxicillin-clavulanic acid. Imipenem is more active than either meropenem or ertapenem against most *Nocardia* species.²⁹ Ertapenem should not be used as a replacement for imipenem or meropenem. Of the tetracyclines, minocycline appears to have the best activity against *Nocardia* and is an alternative oral agent in patients allergic to sulfonamides. Tigecycline, a glycylcycline, appears to be active in vitro against most *Nocardia* species. Of the fluoroquinolones, moxifloxacin is fairly active in vitro against *N asteroides* complex.^{29,30} Linezolid, an oxazolidinone, is quite active against virtually all known pathogenic *Nocardia* species and has successfully been used in treatment of patients with disseminated and CNS nocardiosis.³¹ Problems with linezolid, however, include its high cost and significant toxicities, including myelosuppression, peripheral neuropathy, and lactic acidosis. Amoxicillin-clavulanic acid is moderately active against many strains of *N asteroides*, *N farcinica*, and *N brasiliensis*, but inactive against most strains of *N nova*, *N otitidiscaviarum*, and *N transvalensis*.²² Among the *Nocardia* species, *N farcinica*, *N brasiliensis*, and *N otitidiscaviarum* tend to have higher degrees of multidrug resistance.^{2,32}

Combination therapy with imipenem and cefotaxime, amikacin and TMP-SMX, imipenem and TMP-SMX, amikacin and cefotaxime, or amikacin and imipenem may provide enhanced activity.³³ In mouse models, the combination of amikacin and imipenem was more effective in the treatment of cerebral and pulmonary nocardiosis than TMP-SMX alone.^{34,35} For most forms of nocardiosis, initial combination drug therapy is recommended. In patients

TABLE 2. Select *Nocardia* Species and Corresponding Antimicrobial Susceptibility Patterns^a

Species	Antimicrobial susceptibility patterns									
	Sulfa-methoxazole	Ampicillin	Amoxicillin-clavulanate	Ceftriaxone	Linezolid	Amikacin	Imipenem	Fluoroquinolone	Clarithromycin	Other ^b
<i>Nocardia asteroides</i> complex ^c										
<i>N. abscessus</i>	+	+	+	+	+	+	–	–	–	
<i>N. asteroides</i>	+	–	+/–	+	+	+	+	–	–	
<i>N. brevicatena</i> and <i>N. paucivorans</i>	+	+	+	+	+	+	–	+	–	
<i>N. cyriacigeorgica</i>	+	+/–	+/–	+	+	+	+	+/–	–	^d
<i>N. farcinica</i>	+/–	–	+/–	–	+	+	+	+	–	^e
<i>N. nova</i> complex	+	+/–	–	+	+	+	+	–	+	
<i>N. transvalensis</i> complex	+	–	+/–	+	+	–	+	+	–	^f
Other <i>Nocardia</i> species										
<i>N. brasiliensis</i>	+	–	+	–	+	–	–	–	–	
<i>N. otitidiscaviarum</i>	+/–	–	–	–	+	+	–	+	–	
<i>N. pseudo-brasiliensis</i>	+	–	–	–	+	–	–	+	+	

^a + = active; – = less active or inactive; +/- = may be active, but resistance is common; no entry = variable susceptibility results or insufficient information.

^b Minocycline, moxifloxacin, and tigecycline are active against selected *Nocardia* species.

^c *Nocardia asteroides* complex is a group of bacteria that have a heterozygous pattern of antimicrobial drug susceptibilities and are responsible for the majority of clinical human *Nocardia* infections.

^d *N. cyriacigeorgica* may be reported as *N. asteroides* by some laboratories unless additional testing is performed.

^e Usually susceptible to amikacin; resistant to other aminoglycosides.

^f Usually resistant to amikacin and other aminoglycosides.

with CNS disease, therapy should include drugs with favorable CNS penetration (eg, TMP-SMX and ceftriaxone). Patients with severe nocardiosis may benefit from the addition of a third agent, such as linezolid. Combination therapy should continue until clinical patient improvement occurs and *Nocardia* species identification and antimicrobial drug susceptibility information can be confirmed. Single-drug therapy may suffice thereafter. Duration of treatment is generally prolonged to minimize risk of disease relapse. Immunocompetent patients with pulmonary or multifocal (non-CNS) nocardiosis may be successfully treated with 6 to 12 months of antimicrobial therapy. Immunosuppressed patients and those with CNS disease should receive at least 12 months of antimicrobial therapy with the appropriate clinical monitoring.

Trimethoprim-sulfamethoxazole provides effective prophylaxis to prevent *Pneumocystis* pneumonia and also can decrease the risk of nocardial infections. Daily TMP-SMX prophylaxis most reliably prevents nocardiosis and may also account for the decreased prevalence of nocardiosis in patients with advanced human immunodeficiency virus infection.³⁶ Intermittent therapy with oral TMP-SMX (2 double-strength tablets twice weekly or 1 single-

strength tablet 3 times weekly) is less protective against nocardiosis.^{8,15,16} Breakthrough nocardial infections in the setting of intermittent TMP-SMX prophylaxis, however, may still remain susceptible.

CONCLUSION

Increases in the number of patients receiving immunosuppressive therapies for solid organ or hematopoietic stem cell transplants, hematologic and solid tissue cancers, and autoinflammatory conditions, ensure that *Nocardia* will remain a formidable pathogen. Although this organism is capable of producing serious and metastatic disease in the appropriate host, early recognition and initiation of appropriate treatment can lead to successful outcomes.

Abbreviations and Acronyms: CMI = cell-mediated immunity; COPD = chronic obstructive pulmonary disease; CNS = central nervous system; TMP-SMX = trimethoprim-sulfamethoxazole

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