253 *Nocardia* Species

Sharon C-A. Chen, Matthew R. Watts, Susan Maddocks, and Tania C. Sorrell

SHORT VIEW SUMMARY

Definition

- Nocardiosis results from infection by members of the genus *Nocardia,* which are ubiquitous environmental saprophytes that cause localized or disseminated disease in humans and animals.

Microbiology and Epidemiology

- Microscopically, *Nocardia* appear as gram-positive, beaded, weakly acid-fast, branching rods.
- Molecular speciation has revolutionized taxonomy by identifying several new species and reassigning species, especially from the commonest pathogenic group, the former *Nocardia asteroides* complex.
- Infection arises by direct inoculation through the skin or by inhalation.
- Mycetomas from *Nocardia* spp., most often caused by *N. brasiliensis,* primarily affect immunocompetent hosts in tropical countries.
- Immunocompromise, alcoholism, and certain lung diseases predispose patients to pulmonary and disseminated nocardiosis, most often due to *N. cyriacigeorgica, N. nova,* or *N. farcinica.*

Clinical Manifestations

- Primary skin infection may be manifested as superficial cellulitis or pyogenic abscess(es), lymphocutaneous (spirotrichoid) infection, or chronically progressive, destructive disease with sinus tract formation (mycetoma), usually on a distal limb.
- Presentation of lung disease may be subacute or chronic, with productive or nonproductive cough, dyspnea, hemoptysis, and fever, and other systemic symptoms. Cavity formation within the pneumonia or spread to the central nervous system (CNS), or both, are suggestive of nocardiosis. Isolated CNS lesions also occur, and their presentation can be insidious.

Diagnosis

- Cerebral imaging, preferably magnetic resonance imaging, should be performed in all cases of pulmonary and disseminated nocardiosis to rule out insidious CNS disease.
- The microbiology laboratory should be informed of suspected nocardiosis because it may not be detected by routine laboratory methods. Respiratory secretions, skin biopsies, or aspirates from deep collections are the most useful diagnostic specimens and are typically positive on Gram stain. Modified acid-fast stain of sputum or pus is helpful in suggesting the diagnosis. Growth of *Nocardia* spp. may take 48 hours to several weeks but usually 3 to 5 days.
- Species identification may be predictive of antimicrobial susceptibility; it often requires molecular identification based on nucleic acid technology (NAT, DNA sequencing).
- Recently, mass spectrometry analysis using matrix-assisted laser desorption/ionization time-of-flight mass spectrometry has been reported to be a reliable and more rapid alternative to NAT, but species identification is contingent on a reliable mass spectral database.

Therapy and Follow-Up

- Trimethoprim-sulfamethoxazole (TMP-SMX) is the mainstay of treatment, and monotherapy is usually successful in patients with isolated skin infection or mycetomas that are not extensive (see Table 253.3).
- In infection spread beyond the lung, speciation and/or susceptibility testing results should guide definitive combination therapy. TMP-SMX is usually included in initial therapy.
- Empirical therapy with TMP-SMX plus amikacin (with imipenem or meropenem) is recommended in immunocompromised patients or those with disseminated disease but no brain involvement.
- For isolated cerebral disease, empirical TMP-SMX plus imipenem or meropenem are suitable.
- When additional sites are involved or the patient has life-threatening disease, empirical three-drug regimens, such as TMP-SMX, meropenem or imipenem, and amikacin (or ceftriaxone in patients with renal failure), are preferred. Initial adjunctive therapy with linezolid is an option, especially if one of these classes of drug is contraindicated.
- Clinical improvement is generally evident within 3 to 5 days or, at the most, 7 to 10 days after initiation of appropriate therapy.
- Prolonged therapy is necessary to prevent relapse.
- Surgical excision or drainage of pus may be required, depending on the extent and site of the lesions or the response to medical therapy, or both.
- Patients with deep-seated infection should be monitored clinically and radiologically during and for up to 12 months after cessation of therapy.

Nocardia is a genus of aerobic actinomycetes responsible for localized or disseminated infections in animals and humans. The genus is named after Edmond Nocard, who in 1888 described the isolation of an aerobic actinomycete from cattle with bovine farcy. The first human case of nocardiosis was reported by Eppinger in 1890. Cases of human disease have increased substantially in the past 2 decades, in association with an increasing population of immunocompromised hosts and improved methods for detection and identification of *Nocardia* spp. in the clinical laboratory. In parallel, an increasing number of novel species of *Nocardia* has been recognized as human pathogens.

CLASSIFICATION

The aerobic actinomycetes are a large and diverse group of gram-positive bacteria[1] that appear on microscopy as branching, filamentous cells. Members of the group are often only distantly related phylogenetically. A subgroup, classified in the suborder Corynebacterineae, is the most important cause of human and veterinary infection and includes the genera *Mycobacterium, Corynebacterium, Nocardia, Rhodococcus, Gordonia,* and *Tsukamurella.*[1] All members of the group have cell walls containing meso-diaminopimelic acid, arabinose, galactose (type IV cell wall[1]), and mycolic acids of various chain lengths. The latter are

responsible for varying degrees of acid fastness on modified acid-fast staining. In this chapter the genus *Nocardia* is discussed in the context of human infection.

Previous taxonomic classifications have relied on traditional phenotypic methods to assign nocardiae to both genus and species. *Nocardia* spp. are characterized by an ability to form aerial hyphae and to grow in media containing lysozyme and by an inability to grow at 50°C.[1,2] Speciation using biochemical reactions has been largely superseded due to their frequent inability to distinguish between species, especially those that are phylogenetically closely related.[1,2]

Molecular Identification and Taxonomy

Molecular techniques are now preferred for accurate species determination. In addition, matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS) has proven useful for identification of clinically relevant *Nocardia* spp.[3,4]

The application of molecular methods[2,5,6] has greatly expanded the spectrum of pathogenic nocardiae and has led to significant taxonomic changes and species reassignment within the genus. This is particularly evident among isolates formerly assigned to the *Nocardia asteroides* complex.[2] More than 100 *Nocardia* spp. have now been identified (National Center for Biotechnology Information—taxonomy for *Nocardia:* www.ncbi.nlm.nih.gov/Taxonomy/, and www.bacterio.net/nocardia.html), many of which have been implicated in human disease (Table 253.1).[2,6,7] The nomenclature of isolates formerly in the *N. asteroides* complex is summarized in Table 253.2 and includes *Nocardia cyriacigeorgica,*[8] *Nocardia abscessus,*[9] the *Nocardia nova* complex, and the *Nocardia transvalensis* complex. Other major human pathogens include *Nocardia*

TABLE 253.1 Current Classifiable *Nocardia* Species Names

NOCARDIA SPECIES[a]	FREQUENCY[b]	*NOCARDIA* SPECIES[a]	FREQUENCY[b]
Nocardia abscessus	22	*Nocardia donostiensis*	
Nocardia acidovorans		*Nocardia elegans*	12
Nocardia africana		*Nocardia endophytica*	
Nocardia alba		*Nocardia exalbida*	4
Nocardia alboflava		*Nocardia farcinica*	160
Nocardia altamirensis		*Nocardia flavorosea*	
Nocardia amamiensis		*Nocardia fluminea*	
Nocardia amikacinitolerans		*Nocardia fusca*	
Nocardia anaemiae		*Nocardia gamkensis*	
Nocardia aobensis	5	*Nocardia globerula*	
Nocardia araoensis	1	*Nocardia goodfellowii*	
Nocardia argentinensis		*Nocardia grenadensis*	
Nocardia arizonensis		*Nocardia harenae*	
Nocardia artemisiae		*Nocardia heshunensis*	
Nocardia arthritidis	4	*Nocardia higoensis*	1
Nocardia asiatica	21	*Nocardia ignorata*	
Nocardia asteroides	2	*Nocardia inohanensis*	1
Nocardia beijingensis	24	*Nocardia interforma*	
Nocardia bhagyanarayanae		*Nocardia iowensis*	
Nocardia blacklockiae		*Nocardia jejuensis*	
Nocardia boironii		*Nocardia jiangxiensis*	
Nocardia brasiliensis	71	*Nocardia jinanensis*	
Nocardia brevicatena		*Nocardia kruczakiae*	
Nocardia caishijiensis		*Nocardia lasii*	
Nocardia callitridis		*Nocardia levis*	
Nocardia camponoti		*Nocardia lijiangensis*	
Nocardia canicruria		*Nocardia lillensis*	
Nocardia carnea	3	*Nocardia mexicana*	
Nocardia casaurinae		*Nocardia mikamii*	
Nocardia caverna		*Nocardia miyunensis*	
Nocardia cerradoensis		*Nocardia neocaledoniensis*	
Nocardia coeliaca		*Nocardia niigatensis*	4
Nocardia concava	3	*Nocardia ninae*	
Nocardia coubleae		*Nocardia niwae*	
Nocardia crassostreae		*Nocardia nova*	81
Nocardia cummidelens		*Nocardia novocastrensa*	
Nocardia cyriacigeorgica	60	*Nocardia otitidiscaviarum*	14
Nocardia devorans		*Nocardia paucivorans*	1

TABLE 253.1 Current Classifiable *Nocardia* Species Names—cont'd

NOCARDIA SPECIES[a]	FREQUENCY[b]	*NOCARDIA* SPECIES[a]	FREQUENCY[b]
Nocardia pigrifrangens		*Nocardia takedensis*	
Nocardia pneumoniae		*Nocardia tartaricans*	
Nocardia polyresistens		*Nocardia tenerifensis*	
Nocardia pseudobrasiliensis	2	*Nocardia tengchongensis*	
Nocardia pseudosporangifera		*Nocardia terpenica*	1
Nocardia pseudovaccinii		*Nocardia testacea*	2
Nocardia puris	4	*Nocardia thailandica*	1
Nocardia rayongensis		*Nocardia thraciensis*	
Nocardia rhamnosiphila		*Nocardia transvalensis*	13
Nocardia rhizosphaerae		*Nocardia uniformis*	
Nocardia rhizosphaerihabitans		*Nocardia vaccinii*	
Nocardia roseoalba		*Nocardia vermiculata*	
Nocardia salmonicida		*Nocardia veterana*	3
Nocardia salmonicolor		*Nocardia vinacea*	3
Nocardia seriolae		*Nocardia violaceofusca*	
Nocardia shimofusensis		*Nocardia vulneris*	
Nocardia sienata	1	*Nocardia wallacei*	10
Nocardia soli		*Nocardia xestospongiae*	
Nocardia speluncae		*Nocardia xishanensis*	
Nocardia strombolensis		*Nocardia yamanashiensis*	
Nocardia sungurluensis		*Nocardia zapadnayensis*	
Nocardia sylvodorifera			

[a]Species names in http://www.ncbi.nlm.nih.gov/Taxonomy/Browser/wwwtax.cgi. Accessed January 22, 2018.
[b]Frequency of classifiable isolates at Chiba University, Medical Mycology Center, 1999–2007.
Data from Mikami U. [Recent progress in taxonomic studies on pathogenic Nocardia *and usefulness of the bacteria for the studies on secondary metabolites and antibiotic resistant mechanisms].* Nihon Ishinkin Gakkai Zasshi. *2010;51:179–192 [in Japanese].*

TABLE 253.2 *Nocardia asteroides* Complex: Major Changes in Taxonomic Categories

FORMER SPECIES OR SPECIES GROUP ASSIGNMENT	CURRENT SPECIES GROUP DESIGNATION	CURRENT SPECIES DESIGNATION
N. asteroides drug pattern I	—	*N. abscessus*
N. asteroides drug pattern II	*N. paucivorans*/*N. brevicatena* complex	*N. paucivorans*[b] *N. brevicatena*[b]
N. asteroides drug pattern III	*N. nova* complex[c]	*N. nova* sensu stricto, *N. africana* *N. aobensis* *N. elegans*, *N. kruczakiae*, *N. veterana*
N. asteroides drug pattern IV[d]	*N. transvalensis* complex	*N. wallacei*, *N. transvalensis* sensu stricto, *N. blacklockiae*
N. asteroides drug pattern V		*N. farcinica*
N. asteroides drug pattern VI		*N. cyriacigeorgica*

[a]*N. brevicatena* and *N. paucivorans* are not new species names; they have been reclassified.
[b]*N. asteroides* sensu stricto is rarely pathogenic.
[c]It is uncertain to which species the former *N. asteroides* drug pattern III isolates now correspond.
[d]Only *N. wallacei* is designated as the former "*N. asteroides* drug pattern IV." The other members of the *N. transvalensis* complex are previously either separate as "*N. asteroides* complex" or are recently identified species.
Data from Conville PS, Witebsky FG. Nocardia, Rhodococcus, Gordonia, Actinomadura, Streptomyces*, and other aerobic actinomycetes. In: Jorgensen JH, Pfaller MA, Carroll KC, et al., eds.* Manual of Clinical Microbiology. *Washington, DC: American Society for Microbiology Press; 2015.*

otitidiscaviarum, Nocardia farcinica, and *Nocardia brasiliensis.*[2] Some more recently described or reclassified species have been reported to cause human infection. They include *Nocardia paucivorans* (*Nocardia brevicatena/paucivorans* complex[2,10]), *Nocardia africana,*[11] *Nocardia veterana*[12] (*N. nova* complex[2]), *Nocardia wallacei*, and *Nocardia blacklockiae* (*N. transvalensis* complex).[13] The terminology "*N. asteroides* spp. complex" is no longer used because it encompasses such a heterogenous group of organisms.

ECOLOGY AND EPIDEMIOLOGY

Nocardia spp. are ubiquitous environmental saprophytes, occurring in soil, organic matter, and aquatic habitats, including in waste-water systems.[1,2] Human infection usually arises from direct inoculation of the skin or soft tissues or by inhalation. *N. brasiliensis* is the commonest cause of mycetoma due to nocardial infection in immunocompetent hosts reported from tropical regions of the southern United States, Mexico, Central and South America, and Australia. Worldwide, respiratory and disseminated infections occur predominately in immunosuppressed hosts, and although species distribution varies with geographic region, infections are most often due to *N. cyriacigeorgica*, *N. nova, N, abscessus*, *N. brasiliensis,* and *N. farcinica.*[1,2,14,15]

Nocardia spp. are well-recognized causes of infection in animals, with bovine mastitis being the most common.[2] There are no reports of animal-to-human transmission nor of person-to-person transmission. However, clusters of invasive nocardiosis acquired by patients in oncology and transplantation units, presumed to be associated with inhalation of contaminated air or dust, have been described.[2] Transmission via the hands of staff or contaminated fomites appeared likely in one outbreak.[2] Hospital construction work may have been a risk factor in separate clusters of postsurgical wound infections due to *Nocardia* spp.[2,16] Cases of indwelling intravenous (IV) line–associated bloodstream

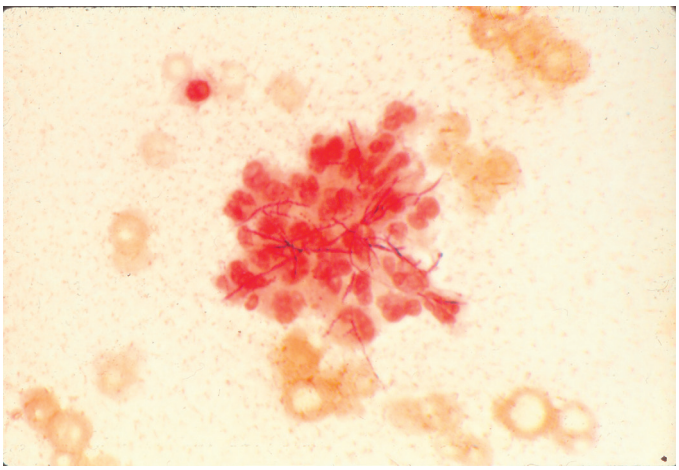

FIG. 253.1 Pulmonary nocardiosis. Photomicrograph of direct Gram-stained smear from a patient with pulmonary nocardiosis, showing typical branching rods.

infection, mostly due to members of the *N. asteroides* spp. complex or *N. nova,* have been reported occasionally in immunosuppressed patients.[17] A community cluster of *N. cyriacigeorgica* infection associated with unlicensed cosmetic procedures has also been described.[18] In a recent study, hospital environmental reservoirs of *Nocardia*, including dust on window frames and equipment and potable water sources were described.[19] Pulsed-field gel electrophoresis,[16] random amplification of polymorphic DNA fingerprinting,[20] and multilocus sequence typing[18] have been used to confirm clusters and define common sources.

PATHOLOGY

Sections of tissues infected with *Nocardia* usually show an acute pyogenic inflammatory reaction. Gram stains (Fig. 253.1) of specimens may reveal branching, beaded, filamentous bacteria, similar to those seen in smears taken from cultures, within abscesses. "Sulfur granules" (bacterial macrocolonies), similar to those seen in actinomycosis, may be found in nocardial mycetomas. *Nocardia* spp. usually stain acid-fast in tissue sections if a method such as that of Fite-Faraco is used, whereas *Actinomyces* spp. do not.[1]

PATHOGENESIS

Disease manifestations of nocardiosis are determined by the portal of entry, tissue tropism, growth rates in vivo, ability to survive phagocyte attack, the nature of the host immune reaction, and the characteristics of the infecting strain.

Immune Response to *Nocardia* Infection

After IV inoculation into mice, virulent *Nocardia* are cleared from the blood within a few hours and localize in a number of organs (lung, brain, kidneys, liver, and spleen). Innate immune function is important in the initial response to infection. In an intranasal mouse model of pulmonary nocardiosis, effective clearance was dependent on early neutrophil recruitment initiated by interleukin-17 (IL-17) production by γδT lymphocytes.[21] Early neutrophil mobilization appears to retard the process until lymphocyte-mediated cytotoxicity and activated macrophages effect a definitive response.[22,23] In human infection *Nocardia*-induced granulocyte-macrophage colony-stimulating factor (GM-CSF) production may also be a key cytokine response mediator.[24] Protective immune responses to *Nocardia* spp. are primarily T-cell–mediated. Nocardiosis is more problematic in patients with impaired cell-mediated immunity, eliciting little in the way of an effective humoral response.[22] Healing is associated with strong, sustained rises in interferon-γ (IFN-γ) in animal models, and IFN-γ may have a therapeutic role in humans with chronic granulomatous disease.[25]

Specific Virulence Determinants

The nocardial envelope of the Corynebacterineae suborder, which includes *Mycobacterium* spp. and *Nocardia* spp., is an asymmetrical bilayer composed of inner-leaflet mycolic acids and assorted noncovalently bound outer-layer glycolipids. A substantial proportion of the cell wall mass is composed of peptidoglycan.[26] Mycolic acid polymers are found in many actinomycetes, including *Nocardia* spp., and are associated with virulence.[27] Outer-layer lipids induce production of proinflammatory cytokines IL-1β and IL-6 by macrophages and are likely to be responsible for the powerful granulomatous reaction to *N. brasiliensisis* infection,[28] but they are also implicated in the immunosuppressive microenvironment generated later.[29]

Nocardia spp. contain no cell wall lipopolysaccharide, exopolysaccharide capsule, or surface fimbriae. Strain-dependent specific adhesins and invasive properties influence the outcome of infection in animal models.[30,31] Specific toxins, including hemolysins and proteases, have been identified, but these are not thought to be widespread or particularly significant virulence factors.[22,32,33] Highly pathogenic members of the *N. asteroides* complex secrete superoxide dismutase into growth media, whereas nonpathogenic *Nocardia* spp. do not.[34] Catalases, superoxide dismutase, and two types of putative determinants of mammalian cell entry, secreted siderophores and toxins, are present in the genomes of pathogenic *Nocardia*.[35]

Host Cell–*Nocardia* Interactions

Virulent strains of *N. asteroides* are relatively resistant to neutrophil-mediated killing.[36] Patients with specific defects in the phagocyte oxidative burst (e.g., chronic granulomatous disease)[14,25] or with anti–GM-CSF neutralizing antibodies in their serum may be more vulnerable to this infection.[24]

Virulent *Nocardia* inhibit phagosome-lysosome fusion more successfully in vitro,[37] giving rise to cell wall–deficient forms (L-forms) that persist within macrophages.[38] Such forms ("filterable *Nocardia*") are readily cultured from in vitro broth filtrates, especially when supplemented with erythrocytes,[39] and L-forms have been isolated from animal infections.[40,41]

Ciliated epithelia appear relatively resistant to invasion by *Nocardia* spp. However, a range of susceptible lung- and airway-associated cell types has been observed in rat models.[31] Tropism for cerebral tissue is evident experimentally, but neuroinvasiveness and macrophage penetration vary significantly between strains. Electron microscopic studies of infected macrophage and astrocytoma-derived or astrocytoma-related cell lines suggest that the penetration competence of invasive *N. asteroides* spp. complex is localized to the bacterial apex.[32] Specific lectins have been shown to determine site specificity in the murine brain,[32] intrinsic differences in expression of which may contribute to variations in host susceptibility.[42]

Biofilms

Although IV catheter–associated bloodstream infections are rare in clinical practice, nocardiae promote heavy growth of biofilms, both on the surface of central venous catheter segments in vitro and in a biofilm model.[17] When embedded in such a matrix, the organisms are resistant to antimicrobial drugs unless exposed to very high local concentrations, such as can be achieved with intraluminal antimicrobial lock therapy.[17]

CLINICAL EPIDEMIOLOGY

Nocardia Species and Disease Associations

Members of the former *N. asteroides* spp. complex are responsible for about 80% of noncutaneous invasive disease and for most systemic and central nervous system (CNS) disease.[22,43] *N. farcinica* is also an important pathogen, notable for its relatively greater resistance to antibiotics. There is also evidence from mouse models that it may be more virulent than other *Nocardia* spp.[44] *N. brasiliensis* is the most often reported cause of cutaneous and lymphocutaneous disease, particularly in tropical areas. *N. pseudobrasiliensis,* a species now separated from *N. brasiliensis,* appears to be associated with disseminated, including CNS, infections.[1,45] Pulmonary disease is the most frequent presentation of nocardiosis caused by the less common pathogens *N. transvalensis*[46] and *N. otitidiscavarum,*[22] although both may cause severe cutaneous infection.[47] Superficial nocardiosis after implantation is not necessarily

associated with compromised cell-mediated immunity but may progress to disseminated disease in that setting.[47]

Immunocompromise as a Risk Factor for Nocardiosis

Immunocompromise is a well-established risk factor for nocardiosis. *Nocardia* spp. may therefore be considered as opportunistic pathogens, which cause serious and disseminated disease in settings such as organ transplantation and lymphoreticular neoplasia. The relative risk for progressive disease reflects the level of immunosuppression. A compilation of more than 1000 randomly selected cases from the literature in the early 1990s showed that greater than 60% of all reported cases of nocardiosis were associated with preexisting immune compromise, ranging from alcoholism and diabetes to chronic granulomatous disease, organ transplantation, and acquired immunodeficiency syndrome (AIDS).[22] In a recent northern Australian study, greater than one-third (36%) of patients with nocardiosis were immuncompromised.[43] Among recipients of solid-organ transplants with nocardiosis, significant risk factors include receipt of high-dose corticosteroids at time of onset, cytomegalovirus disease within the preceding 6 months, high serum trough levels of calcineurin inhibitors within the preceding 30 days, use of tacrolimus, patient age, and length of stay in the intensive care unit postoperatively.[15,48] Use of low-dose trimethoprim-sulfamethoxazole (TMP-SMX) for *Pneumocystis* prophylaxis, such as one double-strength tablet twice a week, did not prevent nocardiosis in either solid-organ or hematopoietic stem cell transplant (HSCT) recipients.[48–50] Breakthrough nocardiosis remains susceptible to TMP-SMX.[49] The use of anti–tumor necrosis factor-α agents has been associated with disseminated nocardial infections.[51,52] Although cases of nocardiosis have been described in patients with AIDS, the overall incidence is low and not fully explained by the use of sulfonamide prophylaxis against *Pneumocystis jirovecii* pneumonia.[53]

Chronic Lung Disease as a Risk Factor for Nocardiosis

Persons with chronic lung disorders, such as pulmonary alveolar proteinosis, and almost any condition requiring long-term corticosteroid use are also at risk. Other chronic airway conditions that may predispose to colonization with *Nocardia,* with the potential, albeit low, for subsequent infection include cystic fibrosis (CF) and non-CF bronchiectasis. In one study the incidence of nocardiosis among patients with bronchiectasis rose significantly between 1996 and 2013.[54]

CLINICAL MANIFESTATIONS

Primary Cutaneous Nocardiosis

Primary cutaneous nocardiosis may manifest as superficial cellulitis or abscess, lymphocutaneous (spirotrichoid) infection, or mycetoma. Unlike other forms of nocardiosis, this usually develops in immunocompetent hosts.[55] Superficial infection often follows relatively trivial inoculation injuries (Fig. 253.2), which may vary from insect and animal bites to puncture wounds and contaminated abrasions. The lymphocutaneous form includes a rare variant, cervicofacial nocardiosis, which is associated with prominent localized lymphadenitis.[56] Members of the former *N. asteroides* complex more commonly cause superficial infections, whereas *N. brasiliensis* is the most common cause of progressive cutaneous and lymphocutaneous disease.[22] Because the initial response to *Nocardia* is pyogenic, localized skin lesions may initially be treated as staphylococcal or streptococcal in origin; however, nocardial disease is usually more indolent. In advanced disease a mycetoma can develop with sinus tract formation. Mycetomas are a chronically progressive, destructive disease, occurring days to months after inoculation, and are typically located distally on the limbs. Eumycetoma (of fungal etiology) and actinomycetoma (due to actinomycetes) are equally prominent in the literature, the epidemiology varying with geographic location (see Chapter 261). Overall, *Streptomyces* and *Actinomadura* spp. appear to be of equal or greater importance than *Nocardia* spp. as causative agents of actinomycetoma. Suppurative granulomas, progressive fibrosis and necrosis, sinus formation with destruction of adjacent structures, and macroscopically visible infective granules (grains) are regular features of nocardial mycetoma.

FIG. 253.2 Skin lesions. Nocardial skin lesions due to direct inoculation in an immunosuppressed landscape gardener.

Pulmonary Disease

Pulmonary disease is the predominant clinical presentation of nocardiosis and is acquired through inhalation of organisms from the environment.[15,22] Any species may cause lung infection, although the most common are *N. cyriacigeorgica*, *N. nova,* and *N. farcinica*. Onset of symptoms may be subacute or chronic and include one or more of productive or nonproductive cough, dyspnea, hemoptysis, and fever and other systemic symptoms. In patients with malignancy, radiologically evident pulmonary infiltrates commonly herald the presence of nocardiosis.[57] Established infection may include endobronchial inflammatory masses, pneumonia, lung abscess, and cavitary disease with contiguous extension to surface and deep structures, including effusion and empyema.

Radiologic Manifestations of Pulmonary Nocardiosis

These include irregular nodules (usually cavitating when large), reticulonodular or diffuse pneumonic infiltrates, and pleural effusions (Fig. 253.3). High-resolution computed tomography (CT) of pulmonary lesions most often shows them to be dense, well-circumscribed nodules or masses, often with central cavitation. Interlobar septal thickening around the lesion or ground-glass infiltrates may also be seen.[58] The "halo sign," considered characteristic of aspergillosis in neutropenic patients, has been described. Progressive fibrotic disease may develop in the immunocompetent host, and diagnosis is often difficult. Pulmonary nocardiosis may occasionally complicate advanced human immunodeficiency virus (HIV) infection (most commonly when the CD4 count is <200/mm^3), where it often presents with alveolar infiltrates that progress during therapy rather than as cavitary disease.[59]

Differential Diagnosis of Pulmonary Nocardiosis

Nocardiosis should always be considered in the differential diagnosis of indolent pulmonary disease, particularly in the setting of cellular immune compromise, along with other actinomycetes (e.g., mycobacteria, *Actinomyces* spp.) and fungi (e.g., *Cryptococcus neoformans, Aspergillus* spp.). Pneumonia may have subacute presentation, resembling staphylococcal pneumonia. Clues to a nocardial etiology include spread to contiguous structures, especially with soft tissue swelling or external fistulae, and to the CNS. Invasive diagnostic procedures, including bronchoalveolar lavage for pneumonia, should be considered early in the immunocompromised host because disease may be rapidly progressive; in patients with severe immunodeficiency, coexisting pathology with similar clinical characteristics (e.g., aspergillosis, tuberculosis, malignancy) is well documented.[60]

Central Nervous System Nocardiosis

CNS involvement was recognized in greater than 44% of cases of all systemic nocardiosis in an early survey[22] compared with 4% to 33% in

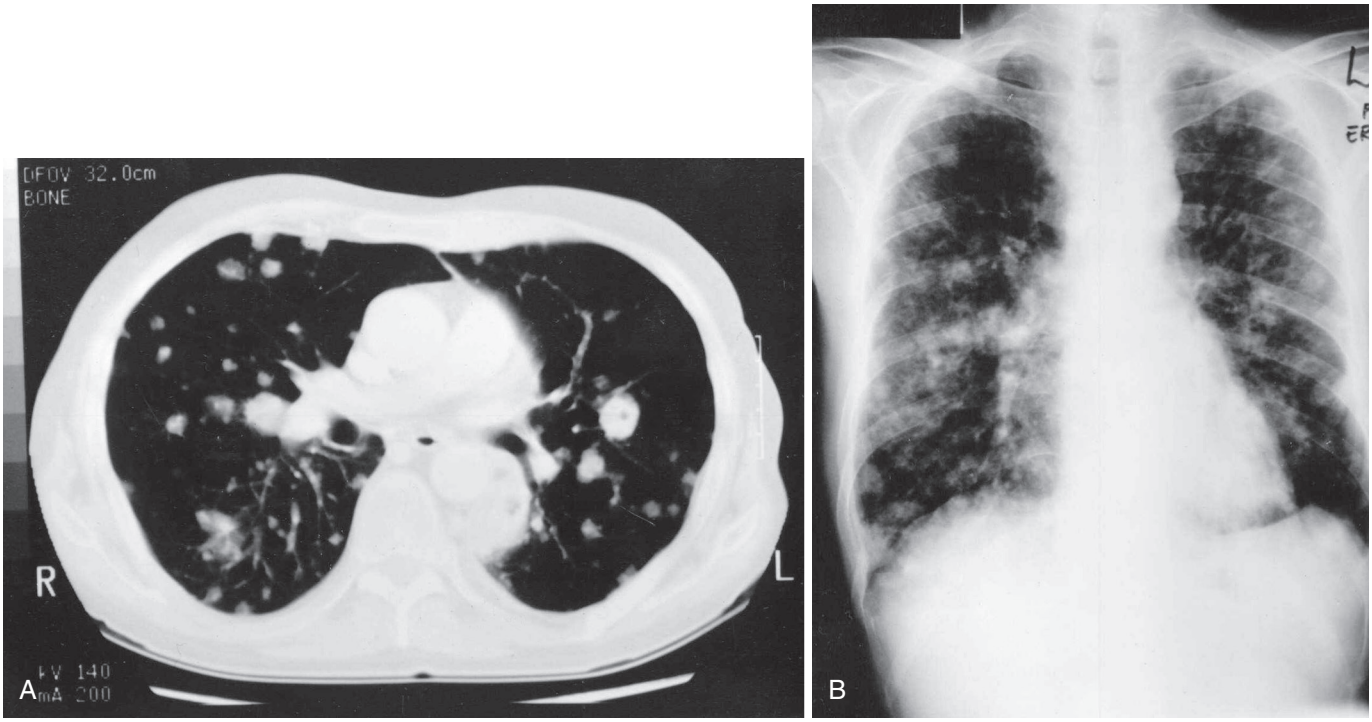

FIG. 253.3 Pulmonary nodules. Multiple pulmonary nodules, demonstrated by computed tomography (A) and chest radiograph (B), in an immunosuppressed patient with disseminated nocardiosis.

FIG. 253.4 Brain abscess. Magnetic resonance image showing *Nocardia* brain abscess.

FIG. 253.5 Skin lesion. Skin lesion from disseminated *Nocardia farcinica* infection.

more recent series.[48,57,61] Clinical manifestations usually result from local effects of granulomas or abscesses in the brain and, less commonly, the spinal cord or meninges (Fig. 253.4). These include headache, focal neurologic signs, seizures, confusion, and depressed consciousness. Multiple brain lesions are common. CNS nocardiosis should always be considered in patients with pulmonary or disseminated disease. Indeed, clinically silent brain abscess is sufficiently common that cerebral imaging, preferably magnetic resonance imaging (MRI), should be performed routinely in such cases.[48,49] Isolated CNS disease can also occur.[17,62,63] Insidious presentations are often mistaken for neoplasia because of the paucity of clinical and laboratory signs of inflammation; silent invasion and persistence make diagnosis and management more difficult.[14,22] Tissue diagnosis of a cerebral mass in the setting of proven pulmonary nocardiosis is not always necessary.[14] However, cerebral biopsy or aspiration should be considered early in the immunocompromised patient because of the higher incidence of serious coexisting pathology and a more aggressive course than that ascribed traditionally to cerebral nocardiosis. *N. farcinica* has a particular association with CNS (and skin) disease.[48,57]

Disseminated Nocardiosis

Disseminated infection is characterized by sites widespread abscess formation. The most commonly reported sites include the CNS (see earlier) and eye (particularly the retina), skin and subcutaneous tissues, kidneys, joints, bone, and heart (Fig. 253.5). Occasional cases of IV catheter–associated bacteremia have also been reported. Bacteremia is uncommon. *N. nova* was the predominant bloodstream pathogen in cancer patients and recipients of HSCT.[49,57]

Keratitis

Nocardia keratitis is well described in Asia and has been reported in travelers returning from Asia.[62,64] Although uncommon in most parts of the world, the entity is increasingly recognized, largely due to the availability of molecular diagnostic methods in many laboratories (see later). It is an aggressive ocular infection, typically after corneal trauma or minor surgical procedures to the eye. If the diagnosis is delayed, the infection can lead to corneal scarring.[62] Although the most commonly identified agents are from the former *N. asteroides* complex and *N. brasiliensis*, a broad range of species have now been implicated.[63] With appropriate therapy, keratitis resolves with good visual outcomes.[62]

Colonization

Occasional instances of transient colonization of the respiratory tract and skin by *Nocardia* spp. have been reported and appear to represent aerosol contamination or soil-derived contamination. Colonization of the sputum may be found in patients with underlying pulmonary pathology (e.g., bronchiectasis) or cystic fibrosis who are not receiving steroid therapy and requires no specific therapy. To be considered significant, *Nocardia* should be visible on Gram or modified acid-fast stain, produce a pure or predominant growth in culture, and be isolated repeatedly from clinical specimens. However, the extent to which spontaneously resolving or subclinical pulmonary infection occurs in the population is ill-defined, and at least one leading authority warns against dismissing positive sputum cultures as harmless.[22] The isolation of *Nocardia* from any site in an immunocompromised patient must never be ignored and should prompt appropriate investigations for invasive infection.

LABORATORY DIAGNOSIS

Nocardia spp. are most frequently isolated from respiratory secretions, abscess aspirates, and biopsy specimens. In pulmonary nocardiosis the diagnostic yield is increased by testing repeated sputum specimens, bronchoalveolar lavage, and biopsies.[1] For cutaneous nocardiosis, tissue biopsies are preferred for culture.[1] Specimens should be transported in sterile containers, and the microbiology laboratory should always be informed when nocardiosis is suspected, as the diagnosis may be missed by routine laboratory methods.

Direct smears from such specimens typically show gram-positive, beaded, fine, right-angled branching filaments (<1 µm diameter). Filaments may fragment to form rods and cocci of varying sizes. They are characteristically acid fast by methods such as the modified Kinyoun technique.[2] *Nocardiae* can be identified directly from clinical specimens using nucleic acid tests,[65,66] which may be particularly useful when there has been preexisting antimicrobial therapy or when biopsy specimens have been embedded in paraffin for histopathology.

Standard blood culture media support the growth of nocardiae, but prolonged incubation (up to 2 weeks) and blind subcultures may be required for their detection.[1] Bacteremia, as demonstrated by positive blood cultures, is rare in patients with nocardiosis.[2] In general, *Nocardia* spp. will grow on nonselective media used routinely for culture of bacteria, fungi, and mycobacteria. However, in specimens containing mixed flora (e.g., respiratory secretions), *Nocardia* colonies are easily obscured by those of more rapidly growing bacteria, and the yield is increased by use of selective media, such as Thayer-Martin agar with antibiotics[67] or paraffin agar.[68] Buffered charcoal-yeast extract medium, which is commonly used for selective growth of *Legionella* spp., may also be used for the isolation of *Nocardia* spp. from respiratory specimens.[69] Decontamination methods used for mycobacterial culture are too harsh for *Nocardia* spp. and may substantially reduce the numbers of viable organisms present in the specimen.[70]

Growth of *Nocardia* spp. on solid media take 48 hours to 14 days, but typical colonies are usually seen after 3 to 5 days. They appear as either buff or pigmented, waxy, cerebriform colonies (Fig. 253.6) or have a dry, chalky-white appearance if aerial hyphae are produced.[1] They have a characteristic earthy odor. Smears from cultures often show greater fragmentation of filaments than direct smears from clinical specimens.

Presumptive *Nocardia* isolates were previously classified on the basis of biochemical tests that were relatively expensive, slow, and limited by their inability to differentiate between members of the *N. asteroides* and *N. nova* complexes or to identify newly described species.[1,2] Molecular testing and MALDI-TOF MS can be used to identify *Nocardia* to a genus or species level and, where necessary, isolates should be referred to a reference laboratory.

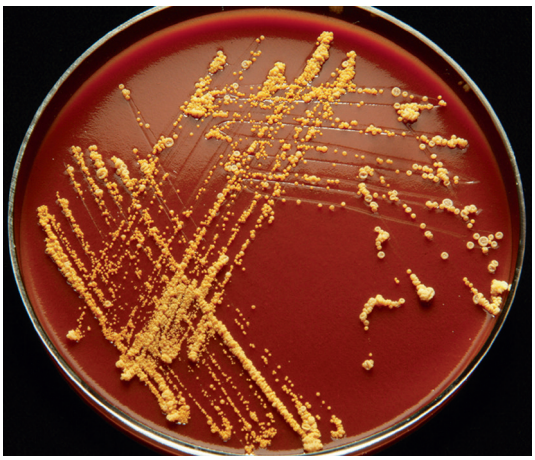

FIG. 253.6 Culture. Typical colonies of *Nocardia* spp. growing on selective media.

Identification of *Nocardia* Species

Molecular techniques can provide definitive identification of most *Nocardia* isolates and recognize new species. An accurate species identification allows the prediction of antimicrobial susceptibilities in many cases.[1] Polymerase chain reaction–amplified DNA can be characterized, analyzed, and compared with archived sequences. Although sequencing of the first 500 to 606 base pairs (bp) of the 5′ end of the 16S ribosomal RNA (rRNA) gene contains sufficient sequence variability for species identification,[2,5,6] sequence analysis of longer gene fragments (e.g., 999–1400 bp) is necessary to distinguish between closely related species, most notably *N. abscessus*/*N. asiatica*/*N. arthritidis, N. africana*/*N. elegans,* and *N. veterana*.[5] Although guidelines of the Clinical and Laboratory Standards Institute (CLSI) recommend that greater than 99.6% similarity is needed for species identification, Conville and associates[1,71] recommend greater than 99.8% homology to differentiate between some species, including those within the *N. nova* complex.

Although housekeeping gene sequences, such as *hsp65, secA1, gyrB, rpoB,* and *sodA,* can improve phylogenetic resolution,[1,72,73] the accuracy of species identification is also dependent on the quality of sequences in gene repositories,[74] and inaccuracies have been found in public databases.[75] Thus comparison with sequences of well-characterized type strains of a species and/or with those in a curated database (e.g., the SmartGene [SmartGene GMbH, Zug, Switzerland]) is necessary for correct identification. Errors may also arise because multiple but different 16S rRNA genes are present in certain *Nocardia* spp., such as *N. nova*.[74–76] Multiple copies of the *gyrB* and *rpoB* genes have also been identified.[77]

Multilocus sequence analysis (MLSA) is a molecular identification technique that uses concatenated sequences from a number of gene targets to clarify the phylogenetic relationships of closely related species.[1] This is regarded as a more effective method of identification, as single-gene targets may be susceptible to recombination, gene transfer, and stochastic variation.[77] MLSA has been useful for the identification of known *Nocardia* spp. and demonstrated the clustering of previously uncharacterized clinical isolates.[4,77–79] Although whole-genome analysis of clinical isolates would be the gold standard in terms of *Nocardia* identification and allow the detection of resistance genes, current limitations to routine laboratory usage include cost, access to next-generation sequencing, and the need to manipulate and analyze large datasets.[80]

MALDI-TOF MS compares the spectra produced by bacterial proteins with a library generated from well-characterized organisms, allowing rapid identification. In a European study, performed after optimization of the spectral library, MALDI-TOF MS identified 91% of 171 isolates

to the species level and 6% to the genus level; species were confirmed by molecular testing.[81] In a multicenter trial the use of three combined libraries resulted in identification at species level in 84% and at genus level in 6%.[3] Reextraction of specimens with a low MALDI-TOF MS identification score (<2.0) and modification of extraction methods have also improved identification.[3,82] In two studies, where in-house libraries were developed, identification to species level was made in 95% and 90.6% of isolates and to genus level in an additional 5% and 9.4%, respectively.[4,82] A strategy for improved *Nocardia* identification would be to use MALDI-TOF MS technology for rapid identification of the majority of isolates and, when identification is uncertain, perform nucleic acid–based molecular identification.[82]

MANAGEMENT

Antimicrobial Selection

Successful management of *Nocardia* infection requires the use of antimicrobial drugs, often in combination, and, where appropriate, surgical drainage or débridement. As there are no randomized trials to determine optimal regimens, recommendations are based on retrospective and observational data, animal studies, in vitro susceptibility profiles, and expert opinion.

Initial selection of a therapeutic regimen should be based on the species of *Nocardia*, the site and severity of infection, the host immune status, and potential drug interactions or toxicity. As clinical isolates of *Nocardia* exhibit variable resistance to antimicrobial agents, antimicrobial susceptibility testing is advised. Although there is a lack of data directly correlating in vitro susceptibility with clinical outcome, with the exception of CNS disease,[83] therapy based on in vitro susceptibility is often effective.

In Vitro Susceptibility Testing

The CLSI has approved broth microdilution methods for antimicrobial susceptibility testing of aerobic actinomycetes and has set interpretive breakpoints for commonly used antimicrobials.[84] Other available methods include the E-test (AB Biodisk; Solna, Sweden) and BACTEC radiometric methods. Both correlate well with broth microdilution results and are easier to use in the routine clinical laboratory.[85]

Susceptibility profiles for commonly isolated *Nocardia* spp. are summarized in Table 253.3. Although resistance patterns can be predicted for some *Nocardia* spp., geographic variability has been reported, and new species for which susceptibility data is lacking continue to be identified.[86]

Discrepancies in susceptibility testing between laboratories have also been well-documented, particularly with testing of TMP-SMX.[86–90] These are largely due to technical issues inherent in broth microdilution methodology and include inoculum preparation, end-point determination, and lack of standardized interlaboratory proficiency testing programs.[87,91] For these reasons, referral of isolates to a specialized reference laboratory is recommended in the following circumstances: if local susceptibility testing is performed and yields data contrary to that expected from published literature, for patients with deep-seated or disseminated infection, for patients intolerant of treatment with TMP-SMX, and for those who fail therapy or relapse after therapy. Isolates of newly described species and of *Nocardia* spp. known to be more inherently resistant should also be considered for susceptibility testing in a reference laboratory.[86,91]

Antimicrobial Regimens

Sulfonamides, most recently in the form of TMP-SMX, have been the mainstay of therapy for *Nocardia* infection since their introduction in the 1940s and have substantially improved outcomes. In cases of disseminated (including CNS) disease and in immunosuppressed patients, mortality rates with sulfonamide monotherapy are greater than 50%,[92–94] and combination antimicrobial therapy is recommended. This should be commenced empirically pending susceptibility results. Amikacin combined with imipenem or meropenem, or three-drug regimens consisting of TMP-SMX, amikacin, and a carbapenem or third-generation cephalosporin, have been used for high-risk patients.[14,15] Increasing experience with linezolid suggests it is effective in combination with the above agents and may have a useful role in initial empirical management of disseminated or CNS *Nocardia* infection pending susceptibility results.[92–94] TMP-SMX, linezolid, carbapenems, and ceftriaxone may be preferred to amikacin-containing regimens in solid-organ transplant populations because of the high incidence of renal impairment in this group.[15] Other agents that have been used in combination regimens include broad-spectrum quinolones, minocycline, and tigecycline.

Trimethoprim-Sulfamethoxazole

TMP-SMX, available in the fixed ratio of 1:5, is the sulfonamide preparation preferred for management of *Nocardia* infection. Synergistic activity between the two drug components has been demonstrated against the majority of *Nocardia* spp. in vitro,[95,96] giving this formulation an advantage over older sulfonamide agents, such as sulfadiazine and sulfisoxazole. Although it is not known whether synergy occurs in vivo, optimal ratios of TMP to SMX for demonstration of synergy in vitro vary from less than 1:5 to 1:10.[96,100] Drug levels in serum and CSF are estimated to reach 1:20[95] and 1:7 or less in tissues and pus, including cerebral abscesses.[96,97]

The recommended dose of TMP-SMX in adults with normal renal function and localized disease is 5 to 10 mg/kg/day TMP and 25 to 50 mg/kg/day SMX given in two to four divided doses, depending on extent of disease.[96] Although use of 5 mg/kg/day (TMP component), together with surgical débridement, is considered sufficient for effective

TABLE 253.3 Antimicrobial Susceptibility of Selected *Nocardia* Species

	N. cyriacigeorgica	*N. farcinica*	*N. nova complex*	*N. transvalensis complex*	*N. brasiliensis*
Trimethoprim-sulfamethoxazole (TMP-SMX)	S	S[a]	S	S	S
Amoxicillin clavulanate	R	S	R	V (0%–53% R)	S
Ceftriaxone	S	R	V (25%–53% R)	V (15%–37% R)	V (13%–66% R)
Imipenem	V (3%–57% R)	V (4%–67% R)	S	R	R
Amikacin	S	S	S	R	S
Linezolid	S	S	S	S	S
Moxifloxacin	R	S,?V[b]	R	S	S
Clarithromycin	R	R	S	R	R
Minocycline	V (15%–95% R)	R	V (44%–88% R)	R	V (23%–76% R)
Tigecycline	V	R	V	ND	S

[a]Recent studies suggest resistance rates of 0.5%–6% to TMP-SMX in *N. farcinica;* however, rates of 45% have been described in Spain.
[b]Generally active with variable resistance in some reports.
ND, No data; *R,* generally inactive; *S,* generally active (some isolates may be resistant); *V,* variable resistance in vitro (published ranges in parentheses).

management of primary cutaneous infection,[96] doses of 15 mg/kg/day TMP and 75 mg/kg/day SMX are used in severe or extensive infection, disseminated infection, cerebral abscess, or AIDS.[60,95] Lower doses of TMP-SMX have been used successfully to treat infection in some immunocompromised patients; for example, 5 mg/kg/day of the TMP component given daily in two doses has successfully treated pulmonary infection in renal transplant recipients. In these cases, however, TMP-SMX was usually prescribed as only one component of a combination therapy regimen.[83,99] Lower-dose regimens using 10 mg/kg/day[100,101] or less[102] of the TMP component have also successfully cured cases of cerebral abscess. Dose reduction of TMP-SMX is recommended in renal impairment.

Therapeutic drug monitoring of serum sulfonamide levels may have a role where absorption from the gastrointestinal tract is uncertain, in patients who require high doses of TMP-SMX and are at risk of dose-related toxicity (renal failure and bone marrow impairment), and in cases of poor therapeutic response. The recommended therapeutic level of sulfonamide, measured 2 hours after an oral dose at steady state, is 100 to 150 mg/L[103]; however, there are minimal data equating sulfonamide levels to toxicity or efficacy.[98]

The decision to use sulfonamides in therapy will in part depend on the causative species of *Nocardia*. Although sulfonamide-resistant *Nocardia* have been reported (see Table 253.3), resistance of *Nocardia* spp. overall to TMP-SMX appears to be between 2% to 3%.[78,86,87] Alternative antimicrobial agents should be considered in infections caused by *Nocardia* demonstrated to be sulfonamide-resistant, in patients who are clinically failing sulfonamide therapy, and in those intolerant of sulfonamide-containing regimens due to hypersensitivity or toxicity. Sulfonamide intolerance has been reported in 3.4% to 8% of exposed non–HIV-infected patients[104,105] and in up to 55% of AIDS patients.[106] Desensitization to TMP-SMX may be considered for those with hypersensitivity, to enable ongoing treatment with sulfonamides. Patients receiving other myelosuppressive agents, such as azathioprine,[107] or nephrotoxic agents, such as calcineurin inhibitors, are at increased risk of sulfonamide-induced myelotoxicity and nephrotoxicity, respectively.

Other Regimens

The choice of alternative therapeutic agents is based on in vitro susceptibility data; efficacy in animal models, primarily short-term murine models of pulmonary and cerebral nocardiosis[108,109]; and published case reports and case series. Assessment of the efficacy of these regimens is complicated by the relative rarity of infection, the diversity of agents that have been used either in combination or sequentially, the variability in host populations studied, and the variable chronic course of *Nocardia* infection.

Amikacin and Carbapenems

Most clinical experience to date has been with amikacin and imipenem. Amikacin exhibits excellent activity in vitro against most species of *Nocardia*, with the exception of *N. amikacinitolerans*, *N. pseudobrasiliensis*, and *N. transvalensis complex,* with resistance to amikacin demonstrated in 57%, 31%, and 72% of isolates, respectively, in one study.[86] Imipenem has good in vitro activity against *N. nova* and many other *Nocardia* spp.; however, resistance has been reported in up to 100% of strains of *N. pseudobrasiliensis* and *N. brasiliensis* and in moderate-to-high numbers of isolates within the *N. transvalensis* complex, *N. otididiscaviarum*, *N. farcinica*, *N. cyricageorgica,* and *N. abscessus*.[86,110] Synergy between amikacin and TMP-SMX has been demonstrated in vitro; with imipenem, the effectiveness is primarily additive.[111]

Amikacin and imipenem have been successfully used, together or in combination with sulfonamides or other agents, in both immunocompromised patients and in patients with *Nocardia* infection involving different body sites.[15,112,113] In one study cure was achieved in seven of eight patients who received amikacin in combination with agents that demonstrated synergy in vitro.[113] Amikacin and imipenem in combination have been recommended as initial parenteral therapy in pulmonary *Nocardia* infection[114] and in severe infection,[14] particularly where there may be concerns regarding TMP-SMX susceptibility or toxicity; however, there are no clinical trials to support this approach. Once-daily dosing regimens of amikacin make it attractive for in-home IV therapy programs; however, the potential for amikacin to cause ototoxicity and nephrotoxicity makes its use problematic in many risk groups that have underlying poor renal function.

Limited data are available on the use of alternative carbapenems (meropenem, ertapenem) in *Nocardia* infection. Meropenem is clinically appealing as it is associated with a lower incidence of seizures compared with imipenem, achieves good CSF penetration, and is active in vitro activity against several *Nocardia* spp.[110,115] Of note, susceptibility of *Nocardia* isolates to meropenem cannot be inferred from susceptibility to imipenem. Imipenem appears to be the most active carbapenem in vitro against *N. farcinica* and *N. otidiscaviarum*,[110,115] whereas meropenem has demonstrated more activity than imipenem in vitro against *N. abscessus* and the *N. transvalensis* complex.[110] Ertapenem demonstrates poor activity against *Nocardia* spp. generally, although some have observed that *N. nova* isolates may be susceptible to all carbapenems, including ertapenem in vitro.[110] A single study of 51 isolates of *Nocardia* spp. concluded that overall meropenem is 4 times less active and ertapenem 16 times less active than imipenem against the species tested.[116] Published reports of the use and efficacy of meropenem in nocardiosis have been in the setting of combination therapy.[15,117–119]

Third-Generation Cephalosporins

The third-generation cephalosporins ceftriaxone, cefotaxime, and cefuroxime exhibit in vitro activity against a variety of *Nocardia* spp., but *N. farcinica* isolates are typically resistant, and variable levels of resistance have been demonstrated in isolates of the *N. transvalensis* complex, *N. pseudobrasiliensis,* and *N. otidiscaviarum*. Greater than 10% of isolates of *N. brasiliensis* and the *N. nova* complex are resistant to ceftriaxone in vitro (see Table 253.3). Synergy between cefotaxime and imipenem has been demonstrated against susceptible strains of *Nocardia* in a murine model of cerebral *Nocardia* infection, where the combination of cefotaxime and imipenem was more effective at reducing colony counts at 72 hours than either agent given alone.[120] Synergistic activity has also been described in vitro between cefuroxime and amikacin.[113]

Oxazolidinones: Linezolid and Tedizolid

The oxazolidinone linezolid exhibits excellent in vitro activity against all known species of *Nocardia*.[86,121,122] and has excellent oral bioavailability and good CNS penetration.[123] Increasing clinical experience suggests that it is efficacious when used in combination with another anti-*Nocardia* agent[92–94,124]; however, its toxicity profile precludes long-term usage. When given for more than 14 days, linezolid is associated with an increased risk of hematologic toxicity,[125] lactic acidosis, retrobulbar optic neuritis, peripheral neuropathy, and the serotonin syndrome. There is some evidence that therapeutic drug monitoring of plasma linezolid levels may reduce the incidence of toxicity; however, results are conflicting.[126–128] In 18 cases of solid-organ transplant recipients treated for *Nocardia* infection, in whom 17 of 18 received TMP-SMX and 15 of 18 received linezolid, the median duration of therapy with linezolid was 21 days.[94] Ten of the 15 (67%) ceased linezolid due to adverse events; thrombocytopenia was noted in 14 of 15 (93%) and anemia in 9 of 15 (60%). However, these rates were similar to those in patients who did not receive linezolid.

Given its potential for toxicity, linezolid may not be appropriate for long-term therapy of *Nocardia* infections. However, it may be useful in initial and empirical management of infection or in combination with other agents, particularly when amikacin may not be an option due to nephrotoxicity, while results of susceptibility tests are pending.

Limited available data suggest that tedizolid, a second-generation oxazolidinone, has greater efficacy than linezolid in vitro with minimal inhibitory concentrations twofold to threefold lower than linezolid against many *Nocardia* spp.[129] Although phase III studies comparing tedizolid with linezolid demonstrated a lower incidence of thrombocytopenia with tedizolid (3.2% vs. 5.6%),[130] there is insufficient clinical experience to recommend its use.[131]

Minocycline and Amoxicillin-Clavulanate

The most frequently used oral alternatives to sulfonamides include minocycline and amoxicillin-clavulanate. Minocycline has the best in

vitro activity of the tetracyclines and has shown efficacy when used alone, in combination with other antimicrobials, as sequential therapy, and in patients intolerant of sulfonamides.[132–134] Reports of failure when used as monotherapy in immunocompromised patients, however, have also been reported.[135]

Amoxicillin-clavulanate has been effective in individual cases when used in combination with other agents or as sequential therapy.[136,137] It may be particularly useful in the treatment of cutaneous infection due to *N. brasiliensis*, a consistent β-lactamase producer, and is the preferred oral agent for this species in patients who cannot tolerate sulfonamides.[138] A case of acquired resistance to β-lactam and β-lactamase inhibitor antibiotics has been described, however, resulting in relapse during therapy of *N. brasiliensis* with amoxicillin-clavulanate.[139] Other species with susceptibility to amoxicillin-clavulanic acid include *N. abscessus* and *N. farcinica*.[2] The use of amoxicillin-clavulanate should be guided by in vitro susceptibility results; demonstration of β-lactamase production is not necessarily predictive of resistance to β-lactam drugs, and isolates of the *N. nova* complex can test ampicillin susceptible/intermediate but may be resistant to amoxicillin-clavulanic acid.[2]

Fluoroquinolones, Macrolides, and Tigecycline

In vitro susceptibility results should also be used to guide the choice of alternative agents for which few clinical data are available, such as the macrolides, fluoroquinolones, and tigecycline. Moxifloxacin demonstrates activity against several *Nocardia* spp., including *N. farcinica*, the *N. transvalensis* complex, *N. pseudobrasiliensis,* and *N. brasiliensis*, and has greater activity in vitro than ciprofloxacin.[86,140] Published clinical experience in patients treated with moxifloxacin has mainly been as salvage therapy in infections due to *N. farcinica*, or in combination with other agents or surgical débridement. Results have been mixed, with both successful and poor outcomes reported.[141,142]

Clarithromycin is the macrolide most commonly used for treatment of *Nocardia* infections and exhibits good activity in vitro against *N. nova*.[143] This agent has been used successfully to treat *N. nova* infections as part of combination therapy, as sequential therapy, and in cases of sulfonamide intolerance.[144,145] Limited in vitro data on use of the IV drug tigecycline suggest that it has activity against a variety of *Nocardia* spp., including imipenem-resistant and TMP-SMX–resistant isolates; however, no clinical efficacy data are available.[116,146]

Superficial Infection and Mycetoma

Localized or isolated cutaneous disease in the immunocompetent host may be treated with monotherapy. Oral TMP-SMX is preferred; however, other agents, including minocycline, amoxicillin-clavulanate, fluoroquinolones, and macrolides, have been used depending on isolate susceptibility.

Nocardia Intravascular Catheter-Related Bloodstream Infection

Nocardia central line–associated bloodstream infections are rare and occur primarily in immunocompromised patients. Early line removal, together with combination antimicrobial therapy, is recommended.[17]

Severe Infection

Empirical Therapy

Although TMP-SMX as monotherapy may be successfully used in mild pulmonary infection with no evidence of dissemination, combination antimicrobial therapy with at least two agents is recommended for immunocompromised hosts, those with more than one site of infection not involving the CNS, and any patient with severe pulmonary involvement or isolated CNS disease. Recommended regimens include amikacin and imipenem or meropenem, or amikacin and TMP-SMX. Although two-drug therapy may be suitable in cases of isolated cerebral disease, when additional sites are involved, or infection is life threatening, three-drug regimens that cover all likely pathogenic *Nocardia* spp. are recommended, for instance, TMP-SMX plus imipenem or meropenem, plus amikacin or ceftriaxone (or linezolid in patients with renal failure). Empirical therapy should be modified after *Nocardia* speciation and susceptibility results.

Surgical Management

The need for surgical management of *Nocardia* infection depends on the site and extent of disease.

Surgery in Extraneural Nocardiosis

In extraneural infection, indications for aspiration, drainage, or excision of abscesses are similar to those for other chronic bacterial infections. Thick-walled, multiloculated abscesses are unlikely to be managed successfully with therapeutic aspiration alone.[147]

Surgery in Cerebral Nocardiosis

Surgical management is advised for brain abscesses that are accessible and relatively large, if the patient's condition deteriorates or lesions progress within 2 weeks of therapy, or when there is no reduction in abscess size within a month.[148] Stereotactic aspiration is useful for decompression of cerebral abscesses, but cure is often achieved only after craniotomy and complete excision of the abscess.[147] Small cerebral abscesses may be cured by prolonged antimicrobial therapy. As cerebral abscesses can progress despite appropriate therapy, all patients should be monitored with regular cerebral CT scans or MRI. Surgical intervention may be required for successful management of empyemas and mediastinal collections. Pericarditis complicating pulmonary *Nocardia* infection is often fatal unless pericardial drainage is performed.[149]

Keratitis and Other Eye Infections

Keratitis

In localized *Nocardia* keratitis, such as infection after LASIK (laser-assisted in situ keratomileusis) surgery, topical amikacin (1.5%–2.5% solution) has most commonly been used[62] due to its activity in vitro against *Nocardia* spp., its good corneal penetration with high local concentrations in the eye, and its safety profile.[55] In a series of 111 cases of culture-proven *Nocardia* keratitis in India, 89.7% of isolates were reported as amikacin susceptible.[150] Treatment consisted of topical amikacin 2.5% eye drops administered hourly with the addition of oral TMP-SMX in cases where response was slow or symptoms worsened; 82% resolved with medical treatment alone. The average duration of treatment for keratitis was 38 days.

Other antimicrobials that have been used topically in *Nocardia* keratitis include TMP-SMX preparations, tobramycin, ciprofloxacin (0.3%), and moxifloxacin (0.5%).[151] Pretreatment of *Nocardia* keratitis with topical quinolone preparations has been associated with increased resistance to moxifloxacin in *Nocardia* spp. in vitro.[152] Topical corticosteroids should be used with caution in *Nocardia* keratitis. In a randomized, placebo-controlled trial comparing topical corticosteroid use with placebo in bacterial keratitis, corticosteroids were associated with worse clinical outcomes at 3 months and with larger scar size at 12 months in patients with *Nocardia* keratitis compared with those who did not receive topical prednisolone.[153]

The use of systemic (oral or IV) antimicrobial therapy depends on the clinical context.

Endophthalmitis

Nocardia is a rare cause of endophthalmitis, either exogenous from surgery or trauma, or, even less commonly, hematogenous. Relatively poor outcomes have been noted after use of intravitreal amikacin in patients with *Nocardia* endophthalmitis despite susceptibility of the causative species to amikacin in vitro (100% and 90%, respectively).[62] Thus systemic TMP-SMX is usually given. Antimicrobial choice depends on species and results of susceptibility testing (see Table 253.3). Intravitreal amikacin carries with it a small risk of macular infarction.[154]

Duration of Therapy and Prognosis

Clinical Responses to Therapy

Clinical improvement is generally evident within 3 to 5 days[108] or, at most, 7 to 10 days after the initiation of effective therapy.[101] Parenteral therapy can usually be safely changed to an oral regimen after 3 to 6 weeks, depending on clinical response. Initial high doses of TMP-SMX may also be reduced at this time. Patients with extensive infection, necrotic foci not amenable to surgery, or those who respond slowly may benefit from prolongation of parenteral and subsequently oral therapy.[14]

Causes of Therapeutic Failure

Lack of response to initial therapy may be due to primary drug resistance; inadequate penetration of drug into sites of infection (dependent on dose, bioavailability of oral drugs, abscess location and pathology, and patient compliance); the presence of a sequestered abscess requiring surgical drainage; and, in an immunocompromised host, overwhelming nocardial infection or a coexisting or secondary opportunistic infection.

Management of Immunosuppressive Drug Therapy in Patients With Nocardiosis

Reduction or cessation of immunosuppressive drugs may be required if *Nocardia* infection is uncontrolled or progressive despite therapeutic serum levels of antimicrobial agents.

Duration of Therapy in Immunocompetent Hosts

Recommendations for the duration of therapy are empirical and based primarily on reports of relapse after sulfonamide therapy of different durations.[a] Isolated cutaneous infection, including sporotrichoid nocardiosis and superficial ulcers, can be cured with 1- to 3-month courses of therapy.[96] Prolonged therapy is required in patients with mycetoma.[147] Immunocompetent patients with pulmonary or systemic *Nocardia* infection and without CNS involvement should be treated for a minimum of 6 months. Those with CNS infection should be treated for 12 months.[14]

Duration of Therapy in Immunosuppressed Hosts

HIV-negative, immunosuppressed patients with isolated pulmonary disease should be treated for at least 6 months and those with disseminated disease for 6 to 12 months, depending on the degree of immunosuppression and response to therapy. Therapy should be continued for 12 months or longer if there are intercurrent increases in immunosuppression (e.g., due to episodes of graft rejection). For patients who must be maintained on steroid or cytotoxic therapy after successful treatment of *Nocardia* infection, prolonged low-dose, maintenance antimicrobial therapy or secondary prophylaxis may be required (see section "Prophylaxis").

In patients with AIDS, early institution of a prolonged primary course of antinocardial therapy is essential, as treatment of patients with late presentations or of those with relapsed nocardial infection has usually been unsuccessful.[59] Although secondary prophylaxis has traditionally been recommended in patients with AIDS at the completion of *Nocardia* therapy, restoration of the immune system with antiretroviral therapy has been associated in one report with clinical cure of *Nocardia* infection in the absence of appropriate therapy, suggesting immune restoration may abrogate the need for secondary prophylaxis.[157]

Short-Course Therapy

Cure of extrapulmonary abscesses has been described in a few cases treated with a short course of amikacin (7–8 weeks) with amikacin and surgical drainage[43,158] or, in a case of cerebral nocardiosis, amikacin plus ceftriaxone.[159]

Prophylaxis

Primary Prophylaxis

Primary prophylaxis against *Nocardia* infection is not usually recommended for immunosuppressed patients posttransplantation as the incidence of infection is low. Of note, prophylaxis against *P. jirovecii* infection is often prescribed in this patient group using TMP-SMX two or three times weekly. This regimen does not prevent infection with *Nocardia,* and substantial numbers of patients develop nocardiosis after solid-organ or stem cell transplantation while on such prophylaxis.[15,48,146,160,161]

Secondary Prophylaxis

The efficacy of secondary prophylaxis to prevent relapse or recurrence of *Nocardia* infection has not been determined. It may be considered for patients with persisting immunosuppression, once therapy for *Nocardia* infection is completed. TMP-SMX at a dose of one double-strength tablet daily (800 mg SMX component) has been used; however, there are no efficacy or outcome data to support this approach.[102,116]

[a]References 59, 95, 96, 100, 155, 156.

Clinical Outcomes

The clinical outcome of *Nocardia* infection depends on underlying host factors, site and extent of disease, the infecting *Nocardia* spp., and duration of therapy.

Worse outcomes have been reported in immunosuppressed patients compared with nonimmunosuppressed patients. A mortality of 70% was described in one study of 27 HIV patients with advanced immunosuppression; however, all but one patient had received monotherapy for their *Nocardia* infection.[59] Mortality rates of 55% have been reported in immunocompromised patients with CNS disease compared with 20% in nonimmunocompromised patients.[148] *Nocardia* infection of the CNS has been associated with worse outcomes in general when compared with other sites of infection. Mortality rates of 47.8% have been reported in CNS infection compared with 7.6% with pulmonary infection alone.[156] Cure rates of up to 80% were described in disseminated disease compared with 60% in CNS disease in another study.[95] Isolated cutaneous disease generally has a 100% cure rate. Mortality rates are higher in immunocompromised patients with *Nocardia* infection than in matched controls without *Nocardia* infection. A case-control study of 35 solid-organ transplant recipients demonstrated a 6-month mortality rate of 14% compared with 4% in non-*Nocardia* control subjects. Cure rates of 89% were described in the study regardless of site of infection, although those with disseminated infection received prolonged therapy (median, 7.5 months) compared with those with nondisseminated infection (median, 6 months).[15] A recent case-control study of 117 solid-organ transplant recipients showed a mortality rate of 16.2% at 1 year compared with 1.3% in non-*Nocardia* control subjects.[119] A multivariate analysis of this population revealed that a history of tumor, invasive fungal infection in the preceding 6 months, and donor age were independent risk factors for mortality from *Nocardia* infection at 1 year (rather than site, dissemination, or antimicrobial regimen). Of interest, a prior episode of acute rejection was associated with improved survival from *Nocardia* infection. Exposure to high-dose steroids, cytomegalovirus infection in the preceding 6 months, and high median calcineurin levels within 30 days have previously been identified as independent risk factors for the development of *Nocardia* infection in organ transplant recipients.[15]

Although immunosuppressive therapy increases the risk of pulmonary and disseminated nocardiosis in recipients of organ transplants, it is not clear to what extent continuation of immunosuppressive therapy during treatment of nocardiosis has an impact on outcome. Most patients can be cured with appropriate antimicrobial therapy even if immunosuppressive drugs are continued, provided that the diagnosis is made early and appropriate full-dose antinocardial therapy is continued for an adequate period of time.[136,160] On the other hand, delay in diagnosis and early cessation of therapy have been associated with increased rates of relapse and worse outcomes.[59,96,156]

Effect of *Nocardia* Species on Outcome

Some *Nocardia* spp. may be more virulent and associated with worse clinical outcomes. Isolates of *N. farcinica* were more virulent than other species in a mouse model,[44] and in a series of 20 microbiologically confirmed cases of CNS nocardiosis, 6 of 7 deaths reported at 1 year were attributed to *N. farcinica*.[162] Multidrug-resistant isolates may also be predicted to have worse outcomes, depending on the availability of effective antimicrobial choices.

Summary of Management

The choice and dose of antimicrobial drugs and the duration of therapy depend on the sites and extent of infection, underlying host factors, the species of *Nocardia*, and the clinical response to initial management. TMP-SMX remains the mainstay of therapy. Initial combination therapy is indicated in patients who are immunosuppressed or who present with brain involvement or disease involving multiple sites. Oral maintenance therapy can be initiated after 4 to 8 weeks, depending on the severity of infection and the clinical response. Newer, orally active drugs may be of value as short-term adjunctive or salvage therapy (linezolid), or as salvage or maintenance therapy when supported by susceptibility testing (late-generation quinolones or macrolides).

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The complete reference list is available online at Expert Consult.

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