Clinical Infectious Diseases

STATE-OF-THE-ART REVIEW

State-of-the-Art Review: Modern Approach to Nocardiosis—Diagnosis, Management, and Uncertainties

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Nocardiosis is an uncommon yet potentially devastating infection. *Nocardia* tends to affect individuals with chronic lung disease or immunocompromising conditions, 2 groups increasing in number. Incidence of nocardiosis is likely to increase as well, and it is vital to have an approach to this complex disease. Here, we aim to review the presentation, diagnosis, and management of *Nocardia* in the modern era. We will also highlight areas of uncertainty in our understanding of nocardiosis and propose a general approach to nocardiosis therapy, accounting for response and tolerance of *Nocardia* treatment.

Keywords. brain abscess; bronchiectasis; immunosuppression; *Nocardia*; trimethoprim-sulfamethoxazole.

Nocardia is a genus of aerobic, partially acid-fast, gram-positive bacilli that are commonly found in the environment [1]. Nocardiosis preferentially affects people with chronic lung disease or immunocompromising conditions, 2 populations that are increasing over time [2, 3]. Accordingly, the incidence of *Nocardia* infections has also increased and will likely continue to rise, with annual incidence rates as high as 0.87 per 100 000 people in North America [4, 5]. However, data regarding nocardiosis incidence are limited and some areas may differ, particularly arid climates where *Nocardia* is more prevalent in the environment [1].

Diagnosis and management of nocardiosis is challenging and requires multidisciplinary collaboration. Patients with *Nocardia* infection are often first evaluated by pulmonologists, transplant practitioners, or specialists in managing immunosuppression. Laboratory methods for identifying and testing *Nocardia* isolates are highly specialized and require close collaboration with the microbiology laboratory. Antimicrobial management of nocardiosis can also be complex and is best handled via partnership between infectious diseases physicians and pharmacists.

In this review, we aim to outline the complexities in diagnosis and management of nocardiosis among at-risk populations. We will highlight common clinical challenges in longitudinal care of patients with this infection and provide an overall framework for approaching this complex disease.

EPIDEMIOLOGY AND CLINICAL PRESENTATION

Who Is at Risk for Nocardiosis?

It is important to consider predisposing conditions when evaluating a patient with possible nocardiosis. Patients with nocardiosis typically have chronic pulmonary disease or are immunocompromised, if not both [6, 7]. Iatrogenic immunosuppression, through transplantation, anti-neoplastic therapy, or treatment of autoimmune disease, is easily the most common cause of immunocompromised status among patients with nocardiosis [6–8]. Primary immunodeficiencies are also associated with nocardiosis, most notably chronic granulomatous disease [9]. However, invasive nocardiosis requires compromised cellular immunity [10], and isolated suppression of humoral immunity (such as with anti-CD20 antibodies) does not appear to predispose to nocardiosis [6, 11, 12]. With the development of effective antiretroviral therapy, people with human immunodeficiency virus (HIV) do not have high rates of nocardiosis, though those who develop *Nocardia* infection typically have severely depressed CD4 cell counts [13].

Comorbid pulmonary disease is typically one of the obstructive lung diseases, such as bronchiectasis or chronic obstructive pulmonary disease [6, 14]. While uncommon, pulmonary alveolar proteinosis (PAP) is associated with multiple opportunistic pathogens, the most prevalent being *Nocardia* species [15, 16]. PAP can be categorized as autoimmune, hereditary, congenital, or secondary depending on etiology. Autoimmune PAP, the most common form in adults, is associated with anti–granulocyte-macrophage colony-stimulating factor (GM-CSF) autoantibodies [17]. This is notable as anticytokine antibodies, including anti-GM-CSF autoantibodies, are

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associated with immunodeficiency irrespective of autoimmune PAP [18, 19], and most patients with anti-GM-CSF autoantibodies who develop nocardiosis do not have PAP [20].

Importantly, nondisseminated cutaneous nocardiosis is commonly the result of direct inoculation, either through trauma or environmental skin disruption (eg, contact with a thorn). Accordingly,

patients with nondisseminated cutaneous nocardiosis are commonly immunocompetent without apparent predisposing condition [21].

Presenting Characteristics

Nocardia species can affect essentially any anatomic site; thus, nocardiosis can have various manifestations. That said, *Nocardia* is typically acquired through either inhalation or traumatic disruption of the skin and correspondingly often presents with pulmonary or cutaneous disease [6,7, 22]. However, isolated nonpulmonary, noncutaneous disease does occur and may be the result of dissemination with an unrecognized or clinically resolved primary site.

Pulmonary nocardiosis often presents with progressive pulmonary symptoms such as cough and dyspnea. Common findings on computed tomography (CT) include pulmonary nodules (with or without cavitation), pulmonary consolidation, and tree-in-bud opacification. Ground-glass opacification is frequently seen but typically in conjunction with other findings. Pleural effusions may be present and could represent pleural space infection. There are 2 common phenotypes. Immunocompetent patients with chronic lung disease may experience a more indolent course of progressive respiratory symptoms over weeks to months [6, 23]. This resembles other chronic pulmonary infections such as *Mycobacterium avium* complex and may also be difficult to distinguish from progression of their underlying pulmonary disease in the setting of colonization [24]. This is contrasted by the presentation typically associated with immunocompromised populations, where symptom progression is more rapid, often in the order of days to weeks. This may resemble other invasive infections, such as invasive molds. However, exceptions to these patterns exist and likely represent a spectrum of disease [25]. It is important to note that *Nocardia* species may colonize the airways, particularly among patients with chronic pulmonary disease [26]. Identification of *Nocardia* in respiratory culture or by molecular methods does not prove pulmonary infection in isolation and needs to be considered in the context of the patient's symptomatology, radiographic findings, and comorbid conditions.

Primary cutaneous nocardiosis takes 3 main forms: mycetoma, lymphocutaneous disease, and superficial skin infections. Mycetoma is most common in tropical regions and presents as a chronic, progressive, destructive lesion that may involve deeper structures or form fistulae [27]. Lymphocutaneous infection leads to nodules or pustules tracking proximally along lymphatic channels, usually on an extremity [28]. This is also referred to as sporotrichoid spread and is seen with multiple fungal and mycobacterial pathogens. Superficial skin infections have been described as nonspecific skin abscess or cellulitis. These may be clinically indistinguishable from "typical" bacterial cellulitis or abscess and should be considered among patients who do not respond to first-line therapy [29].

Table 1. Diagnostic Considerations for Pulmonary Nocardiosis

Patient Factor	Considerations	Comments
Clinical	Progressive pulmonary symptoms with or without systemic symptoms	While not required for diagnosis of pulmonary nocardiosis, screen for signs or symptoms of other sites of nocardiosis and evaluate accordingly.
Radiologic	Nodular pulmonary parenchymal changes with or without cavitation or pulmonary consolidation	CT of the chest is preferred to chest radiography[a].
Microbiologic	Isolation of a *Nocardia* sp or positive *Nocardia*-specific or broad-range bacterial PCR with sequence identification from a respiratory specimen	Multiple respiratory cultures isolating *Nocardia* is ideal but not required.
Predisposing conditions	Chronic pulmonary disease Use of immunosuppressing medications Primary immunodeficiency	Predisposing conditions are not necessary for diagnosis, though a large majority of patients with pulmonary nocardiosis will have either chronic pulmonary disease or an immunocompromising condition. In select circumstances, nocardiosis may be a presentation of an underlying immunodeficiency or pulmonary disease.
Alternative etiologies	Evaluate and rule out alternative causes of presenting signs and symptoms	In patients with chronic pulmonary disease, it may be difficult to discern the cause of respiratory symptoms between nocardiosis and progression of underlying disease.

Abbreviations: CT, computed tomography; PCR, polymerase chain reaction.

[a]Patients diagnosed with pulmonary nocardiosis who are immunocompromised or have signs of neurologic involvement should also undergo brain imaging, preferentially with magnetic resonance imaging.

Other forms of nocardiosis are most commonly part of disseminated infection. The most common site of dissemination is the central nervous system (CNS), typically manifesting as cerebral abscesses [6, 7, 22]. CNS nocardiosis commonly presents with multiple supratentorial abscesses, usually in the frontal or temporal lobes [30, 31]. However, a sizable proportion will have a single brain abscess, and abscesses have been reported in all regions of the CNS [30, 32]. CNS nocardiosis requires a high index of suspicion, as up to half of immunocompromised patients with CNS involvement have no CNS symptoms [22, 33]. When CNS symptoms occur, they are often headache, focal neurologic deficits, seizure, or altered mentation [6, 22].

Nocardia can affect essentially any other site, albeit less commonly than lungs, skin, and CNS. Other sites include intra-

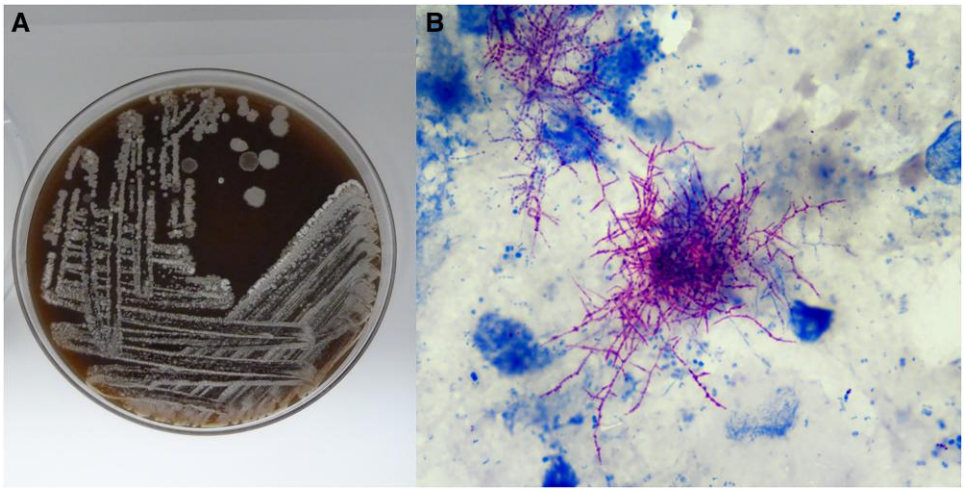

Figure 1. *A*, Culture colonies of *Nocardia cyriacigeorgica* on a 5% sheep blood agar plate, 6 days' growth after incubation at 37°C. *B*, Modified Ziehl-Neelsen stain of a *Nocardia cyriacigeorgica* isolate at ×1000 magnification showing thin, beaded, branching filaments typical of *Nocardia* species.

abdominal abscess, infective endocarditis, osteomyelitis, septic arthritis, keratitis, and retinitis [6]. While dissemination is the result of bacteremia, identification of *Nocardia* bloodstream infection is rare, even among patients with proven dissemination [34]. *Nocardia* bacteremia is seen in less than 10% of all patients, though rates up to 29% have been reported among allogeneic stem cell transplant recipients [6, 22, 33]. Patients with *Nocardia* isolated in blood cultures should undergo evaluation for other sites of infection, though central line–related primary bacteremia does rarely occur [35]. Additionally, nocardiosis in uncommon sites should prompt evaluation for more foci of infection. Small nosocomial outbreaks have also been reported [36, 37].

DIAGNOSTIC APPROACH

There are no standardized criteria for diagnosing nocardiosis. However, the diagnostic approach for pulmonary nocardiosis is like that of nontuberculous mycobacterial (NTM) pulmonary disease [38]. Patients with compatible respiratory symptoms, nodular or other consistent changes on chest imaging, microbiologic confirmation of *Nocardia* by culture or polymerase chain reaction (PCR), and lack of a more plausible explanation for the findings can be diagnosed with pulmonary nocardiosis (Table 1). In contrast to NTM pulmonary disease, multiple sputum cultures growing *Nocardia* may not necessarily be required. However, repeating sputum cultures can be useful to confirm nocardiosis when there is uncertainty regarding the pathogenicity of a single positive culture. It is important to note that roughly 20% of patients with culture growth of *Nocardia* will be classified as colonized rather than clinically infected [6, 26]. Patients deemed to have *Nocardia* colonization and not treated have similar outcomes to those treated for nocardiosis, suggesting that presence of *Nocardia* is not always pathogenic among patients with underlying pulmonary disease [39]. Full history, symptom assessment, and radiographic review is necessary to distinguish between *Nocardia* colonization and pulmonary infection necessitating therapy.

Diagnosis in patients with extrapulmonary nocardiosis tends to be more straightforward. Isolation of *Nocardia* from a sterile source is diagnostic of nocardiosis. Additionally, patients with signs of dissemination do not necessarily require diagnostic sampling at every site of clinical infection. For example, a patient diagnosed with pulmonary nocardiosis who has imaging suggestive of brain abscess does not require sampling of the abscess for diagnostic purposes unless there is diagnostic uncertainty or lack of expected response to treatment. However, invasive sampling for culture or other microbiologic testing is necessary when there are not more feasible sites to sample, such as isolated brain abscess. If initial microbiologic stains show organisms consistent with *Nocardia* species, a presumptive diagnosis of nocardiosis can be made pending confirmation with culture-based methods.

Finally, it is important to consider the possibility of concurrent pathogens, particularly among immunocompromised patients. Approximately 20%–25% of solid organ transplant recipients have coinfections at the time of *Nocardia* diagnosis [40, 41]. These are commonly a mix of other "typical" bacterial organisms, though invasive fungal infections and opportunistic viral infections such as cytomegalovirus may be present as well. NTM coinfections may complicate diagnosis among patients with chronic pulmonary disease, leading to difficulties discerning whether NTM, *Nocardia*, or both are causing the clinical and radiologic findings [42].

Microbiologic Evaluation

If *Nocardia* is clinically suspected, samples should be sent for targeted staining and cultures. On Gram stain, *Nocardia* species will appear as a filamentous gram-positive bacillus. *Nocardia* may be suspected on modified Kinyoun or Ziehl-Neelsen (ie, modified acid-fast) staining, where it will classically appear as partially acid-fast with beaded or branching morphology. It is useful to differentiate from other acid-fast bacteria. Many mycobacteria are "fully" acid-fast and would stain well with traditional acid-fast staining procedures. *Rhodococcus*, another partially acid-fast organism, typically has minimal or no branching morphology.

Nocardia species grow well in a variety of culture media and can be recovered in bacterial, fungal, and mycobacterial cultures. Mycobacterial cultures may produce better yield because they are held up to 6 weeks and should be pursued if *Nocardia* is clinically suspected (Figure 1). Once culture yields colony growth, most *Nocardia* species can be identified by matrix-assisted laser desorption/ionization–time of flight mass spectrometry. If unsuccessful, Sanger sequencing of a species-specific genetic sequence (commonly 16S rRNA, *gyrB*, *secA1*, *hsp65*, or *rpoB* genes) can be performed [43–45]. The Clinical and Laboratory Standards Institute has set standards for *Nocardia* antimicrobial susceptibility testing and interpretative criteria, though there are limited supportive clinical data for *Nocardia* antimicrobial breakpoints [46, 47]. The recommended susceptibility testing method for *Nocardia* is broth microdilution. Both *Nocardia* species identification and antimicrobial susceptibility testing should be attempted on all clinically relevant isolates.

Molecular diagnostics have been used clinically for more rapid *Nocardia* diagnosis than can be done with traditional culture-based methods. *Nocardia*-specific PCR detects and amplifies a 16S rRNA segment that is genus-specific; follow-up testing is required for species identification. Compared to culture-based methods, *Nocardia*-specific PCR has a specificity of 74% and sensitivity of 88% [48]. Another molecular approach currently used in clinical microbiology reference laboratories is broad-range bacterial 16S rRNA PCR coupled with sequence-based identification, which can detect and identify a wide range of bacteria, including *Nocardia* species [49]. Finally, metagenomic next-generation sequencing methods have been used to detect *Nocardia* species from plasma, tissue, and fluid specimens [50, 51]. While possibly useful adjuncts, molecular methods do not currently supplant culture-based methods as the gold standard for *Nocardia* diagnosis. Additionally, *Nocardia*-specific PCR is not widely available, and culture is still required for antimicrobial susceptibility testing. Molecular methods also do not differentiate between colonization and invasive infection and should be interpreted similarly to a culture growing *Nocardia* species [52].

Though traditionally considered a biomarker for invasive fungal infection, *Nocardia* species have been demonstrated to have detectable 1,3-β-D-glucan in vitro [53]. However, subsequent retrospective studies of transplant recipients have shown conflicting results [54, 55]. Ultimately, given the possibilities of cross-reactivity from noninfectious sources and fungal coinfection, 1,3-β-D-glucan has little utility for diagnosis of *Nocardia* infection.

Evaluation for Dissemination

Once a diagnosis of nocardiosis has been established, possible sites of disseminated infection should be considered. Patients who are immunocompromised or infected with *Nocardia farcinica* have the highest risk of dissemination [8]. A thorough skin examination should be performed to evaluate for nocardial skin lesions. If the first recognized site is not pulmonary, chest CT should be considered, particularly if there are respiratory symptoms. Up to half of immunocompromised patients with CNS nocardiosis do not have neurologic symptoms [22, 33]. Accordingly, all immunocompromised patients should undergo brain imaging to evaluate for CNS dissemination. Patients without clear predisposing conditions for nocardiosis should also undergo brain imaging, as these patients may have unrecognized immunodeficiency and have appreciable rates of CNS involvement [20]. Magnetic resonance imaging (MRI) is preferred over CT as CT may fail to identify smaller *Nocardia* lesions. However, CT (ideally with intravenous contrast) will likely still identify larger abscesses, which are more likely to undergo therapeutic intervention [56], and is an acceptable alternative among patients unable to undergo MRI. CNS involvement is uncommon among patients with pulmonary nocardiosis whose only predisposing condition is chronic pulmonary disease [6]. As such, CNS imaging is not mandatory for these patients, unless there are CNS symptoms or other signs to suggest CNS involvement.

THERAPEUTIC APPROACH

Nocardiosis is a complex disease and best managed through a multidisciplinary approach. Ideally, specialists with expertise in antimicrobial therapy, optimization of underlying comorbidities or predisposing conditions, and procedural management are involved.

Empiric Therapy

Initial empiric antibiotic selection depends on the severity and extent of nocardiosis. Although no validated grading system for *Nocardia* severity exists, patients with mild nocardiosis are often managed in the outpatient setting, have a chronic course leading to diagnosis, and have nondisseminated infection. In contrast, patients with severe nocardiosis are typically hospitalized and have a more rapid course from onset to diagnosis [6]. Traditionally, empiric therapy includes 1–3 individual antibiotic agents. The decision to use combination therapy versus monotherapy in nocardiosis is driven by the need to cover the wide spectrum of potential *Nocardia* species and their variable susceptibility profiles, as well as the clinical status of the

Table 2. Antimicrobial Susceptibility Profiles of Common *Nocardia* Species

	Susceptibility (%) of Indicated Species to:												
Nocardia Species	Amk	Amox-clav	Cefepime	Ceftriaxone	Cip	Clr	Doxy	Imp	Lzd	Min	Mxf	TMP-SMX	Tob
Nocardia nova complex	100	4	47	14	1	97	1	100	100	19	3	100	3
Nocardia cyriacigeorgica	99	8	24	64	0	1	11	99	100	14	1	100	99
Nocardia farcinica complex	100	96	1	3	49	0	2	83	100	7	76	99	1
Nocardia brasiliensis	100	99	0	2	0	0	5	8	100	16	40	100	100
Nocardia abscessus complex	100	61	69	93	3	38	87	64	100	94	13	100	100
Nocardia species	93	37	33	40	14	42	25	76	100	39	39	99	60
Nocardia transvalensis complex	26	89	27	64	49	2	10	9	100	31	72	88	0
Nocardia asteroides	99	26	51	49	21	51	29	88	100	43	25	100	58
Nocardia otitidiscaviarum	100	0	0	0	0	17	43	3	100	60	23	87	53
Nocardia pseudobrasiliensis	62	5	0	0	100	95	0	0	100	0	86	33	100
Nocardia brevicatena/Nocardia paucivorans	95	47	95	95	100	100	95	100	100	95	84	100	95

Adapted with permission from the American Society of Microbiology in a modified format (Hamdi et al [57]).

Abbreviations: Amk, amikacin; Amox-clav, amoxicillin-clavulanic acid; Cip, ciprofloxacin; Clr, clarithromycin; Doxy, doxycycline; Imp, imipenem; Lzd, linezolid; Min, minocycline; Mxf, moxifloxacin; TMP-SMX, trimethoprim-sulfamethoxazole; Tob, tobramycin.

patient. While data are overall limited, no study has conclusively demonstrated that combination antibiotic therapy improves outcomes compared to monotherapy [6, 40]. Instead, the primary goal of initial combination treatment is to minimize the risk of administering an inactive regimen while awaiting antimicrobial susceptibility testing. Other considerations are the safety profile and published effectiveness of individual antimicrobials. This is particularly crucial in severe forms of nocardiosis (eg, disseminated or progressive pulmonary infection), where 2 or 3 different agents are typically initiated empirically. Antibiotics that most *Nocardia* isolates demonstrate susceptibility to include amikacin, imipenem, linezolid, and trimethoprim-sulfamethoxazole (TMP-SMX) [57]. Conversely, those with mild infection can start with a single antibiotic that is highly likely to be an active agent. TMP-SMX is the most well-studied and preferred agent for monotherapy [58, 59]. Additionally, select immunocompetent patients with mild pulmonary nocardiosis (typically those with chronic pulmonary disease) can be closely monitored until susceptibility results are available.

Nocardia displays variable interspecies antimicrobial susceptibility, which can be at least partially predicted based on species identification (Table 2) [57, 60–62]. For example, *Nocardia nova* demonstrates high rates of susceptibility to amikacin, imipenem, and TMP-SMX, and is highly likely to be susceptible to at least 1 commonly used empiric antibiotic. Conversely, *Nocardia pseudobrasiliensis* is much less commonly susceptible to amikacin (62%), imipenem (0%), and TMP-SMX (33%) and is instead typically susceptible to fluoroquinolones and macrolides [57]. Species identification allows for timely adjustments to empiric antibiotic therapy as necessary to minimize the risk of ineffective treatment before susceptibility results are known. While *Nocardia* species are present worldwide, there are some regional differences in species prevalence that can be considered [1].

Definitive Therapy

Once *Nocardia* susceptibility is determined, antibiotic therapy can be further tailored. If combination therapy is started empirically, treatment can be narrowed to monotherapy, particularly if there are signs of clinical improvement. Common options for *Nocardia* therapy are listed in Table 3. Antibiotic options have been categorized as bacteriostatic and bactericidal; however, this distinction has not been linked to differences in outcomes [63]. Similarly, use of intravenous over orally administered antibiotics has not been associated with better therapeutic outcomes.

TMP-SMX is the most utilized and best-studied treatment for nocardiosis [40]. Despite this, uncertainties persist regarding optimal dosing. TMP-SMX is traditionally dosed 15 mg/kg/day of the trimethoprim component, divided into multiple daily doses. TMP-SMX dosing is adjusted based on kidney function, and higher doses are often used in those with CNS involvement. This dosing is extrapolated from *Pneumocystis* treatment, whose own TMP-SMX dosing has been questioned [64]. Few studies have compared different TMP-SMX dosing schemes for nocardiosis, though data suggest that patients who initially receive lower-dose treatment do not have worse outcomes [58]. TMP-SMX is also associated with a high rate of early discontinuation due to adverse effects, approximately 15%–30% [58, 59]. Patients initially receiving >10 mg/kg/day of TMP-SMX have significantly higher rates of early discontinuation and commonly require dose reductions due to tolerability issues.

We typically initiate TMP-SMX therapy at 10–15 mg/kg/day of the trimethoprim component in divided doses and monitor closely for signs of toxicity. If toxicity develops, TMP-SMX dosing can be decreased among patients with initial clinical improvement or more mild infection. Patients with TMP-SMX toxicity and yet-to-improve severe infection may be better served transitioning to alternative therapy, as patients with

Table 3. Description of Common Antibiotics Used for *Nocardia* Therapy

Antibiotic	Usual Dosing[a]	Comment
Amikacin[b]	10–15 mg/kg IV daily	TDM: trough <5 μg/mL; peak 35–45 μg/mL. Monitoring of renal and auditory function is critical.
Amoxicillin-clavulanic acid	875–125 mg PO twice daily	Susceptibility should be confirmed prior to use due to variable activity against *Nocardia* spp.
Azithromycin	500 mg IV or PO daily	Clarithromycin susceptibility can be used as a surrogate for azithromycin susceptibility. Improved tolerability and less frequent dosing and drug interactions compared to clarithromycin. Has been used successfully for secondary prophylaxis.
Ceftriaxone[b]	2 g IV every 12–24 h	Consider every 12-h frequency for cerebral disease.
Ciprofloxacin[b]	500–750 mg IV or PO twice daily	Susceptibility tends to be species specific.
Clarithromycin	500 mg PO twice daily	Higher rates of resistance, confirm susceptibility prior to use. Strong CYP3A4 inhibitor.
Doxycycline[b]	100–200 mg IV or PO twice daily	Secondary agent, confirm susceptibility prior to use. Potential use for CNS penetration.
Imipenem[b]	500–1000 mg IV every 6 h	Carbapenem of choice and common agent in empiric combination regimens.
Levofloxacin[b]	500–750 IV or PO mg daily	Ciprofloxacin susceptibility can be used as a surrogate for levofloxacin susceptibility.
Linezolid[b]	600 mg IV or PO twice daily	Highly active against most *Nocardia* spp and achieves excellent CNS concentrations. Monitor for myelosuppression and optic or peripheral neuropathy with long-term use.
Meropenem[b]	500–1000 mg IV every 6 h or 1–2 g IV every 8 h	Less in vitro activity than imipenem against *Nocardia* spp altogether, though some isolates may be more susceptible to meropenem.
Minocycline[b]	100–200 mg IV or PO twice daily	Higher dose of 200 mg twice daily should be used for CNS disease to achieve adequate intracerebral levels. Use should be guided by susceptibility testing.
Moxifloxacin	400 mg IV or PO daily	Generally, more active in vitro than ciprofloxacin against *Nocardia* spp. Achieves higher CNS concentration compared to ciprofloxacin or levofloxacin.
Sulfadiazine	1.5 g PO every 6 h	TMP-SMX is commonly used as a surrogate for sulfadiazine susceptibility. Historical mainstay of treatment prior to availability of TMP-SMX.
Tedizolid	200 mg IV or PO daily	Linezolid susceptibility can be used as a surrogate for tedizolid susceptibility. Alternative to linezolid for those experiencing myelosuppression.
Tobramycin	5–7 mg/kg IV daily	Generally less active than amikacin in vitro against *Nocardia* spp. Monitoring of renal and auditory function is critical.
TMP-SMX[b]	10–15 mg/kg IV or PO of trimethoprim component per day in 2–3 divided doses	The optimal dose is unknown and lower doses have been used effectively.

Abbreviations: CNS, central nervous system; IV, intravenous; PO, per os; TDM, therapeutic drug monitoring; TMP-SMX, trimethoprim-sulfamethoxazole.

[a]Dosing based on normal kidney function. Some antibiotics require dose adjustments for patients with impaired kidney function.

[b]Agents that are commonly used for and/or typically dosed higher for CNS infection.

severe nocardiosis are underrepresented in the available data [58]. Peak SMX concentrations have not been shown to correspond with effectiveness for *Pneumocystis* or *Nocardia*, though some studies suggest that elevated SMX concentrations may have correlation with toxicity and could be considered in assessing the risk of intolerance [58, 65].

Amikacin is often used in combination for severe nocardiosis, and therapeutic drug monitoring (TDM) is essential to optimize efficacy and minimize toxicity. While administering intravenous amikacin daily, TDM should aim for an extrapolated peak serum concentration of 35–45 μg/mL and a trough of <5 μg/mL. Some experts recommend utilizing higher doses to target peak concentrations of 60–80 μg/mL for patients with CNS nocardiosis, though clinical data supporting this higher dosing strategy are lacking. The peak concentration can be extrapolated with 2- and 6-hour postinfusion concentrations, allowing for serum-tissue drug equilibrium. If only 1 serum concentration can be obtained, a peak concentration drawn 1 hour postinfusion with a goal of 25–35 μg/mL is acceptable [38].

Linezolid is uniquely susceptible in vitro to essentially all *Nocardia* isolates [57, 60–62]. Tedizolid has been used as a potentially less myelosuppressive alternative, though clinical experience using this agent for *Nocardia* is limited [66]. Among the carbapenems, imipenem is generally the preferred empiric choice due to more consistent in vitro activity against *Nocardia* species [67]. However, there are interspecies differences and meropenem may be more active in some cases [68].

Duration of Therapy

Patients with localized pulmonary nocardiosis are traditionally treated for up to 6 months, while those with disseminated disease (particularly involving the CNS) are commonly treated for at least 12 months (Figure 2) [69]. Nondisseminated cutaneous

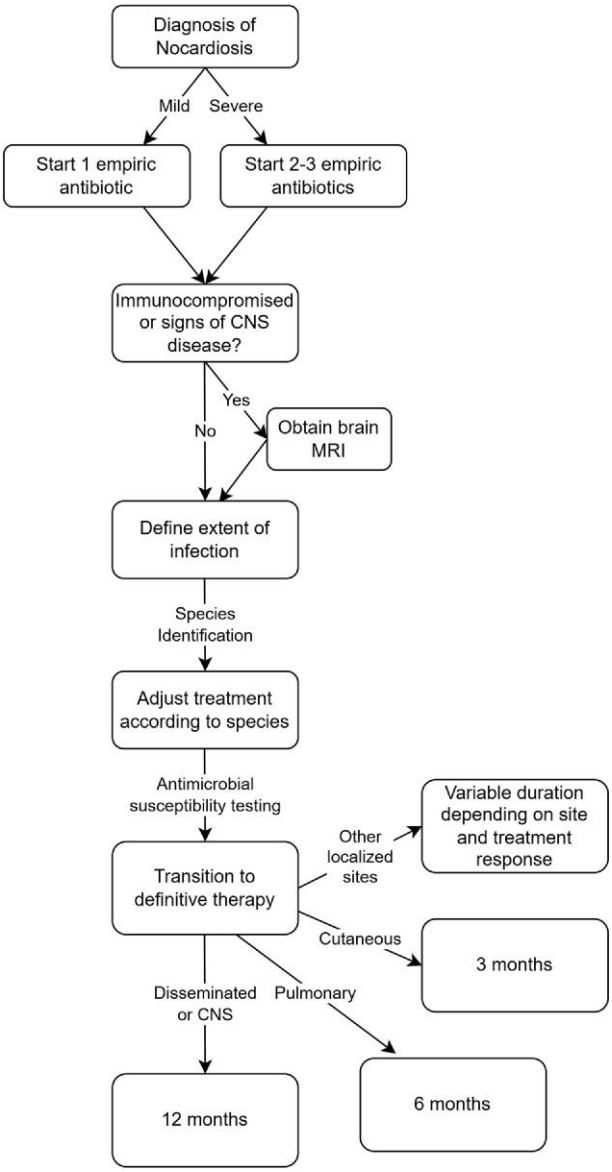

Figure 2. Proposed management scheme for patients with nocardiosis. Abbreviations: CNS, central nervous system; MRI, magnetic resonance imaging.

infection may be treated as short as 3 months, though mycetoma is usually treated for a much longer period [70, 71]. Optimal treatment durations for nondisseminated nocardiosis affecting sites other than the skin or lungs are unclear and may depend on procedural interventions and specific infection sites. For example, osteoarticular nocardiosis is often treated for more prolonged periods (≥6 months), though other forms such as keratitis have typically been treated for shorter durations (1–3 months) [72, 73].

However, it is important to understand the current uncertainty regarding optimal treatment durations for nocardiosis. There are no prospective, interventional studies examining any aspect of *Nocardia* treatment, including duration, number of antibiotics, or choice of specific antibiotic. Thus, treatment recommendations have consisted of expert opinion and retrospective studies. One small study of pulmonary nocardiosis found a longer duration of TMP-SMX treatment to be associated with a lower rate of recurrence or death within 2 years [74]. Another study found that patients with posttreatment recurrence tended to have shorter therapy durations, though this trend was primarily among patients with pulmonary nocardiosis [75]. Conversely, there are emerging data of treatment durations <120 days, even for disseminated disease. Outcomes have been generally favorable with short-course therapy, with low rates of death or recurrence. However, recurrences have occurred, and it is unclear who is the ideal candidate for short-course therapy [63, 75, 76].

Ultimately, clinical and radiographic response, as well as adverse effects, should be considered when determining the endpoint of therapy. The aforementioned treatment durations are generally used as initial goals, and the final duration is modified according to response and tolerance. Patients with pulmonary or CNS disease should undergo follow-up chest or brain imaging, respectively, to evaluate for response to treatment [30]. Pulmonary findings, such as nodules, may persist despite treatment. Patients with CNS involvement are commonly treated until radiographic resolution, though CNS lesions may not fully resolve and evidence supporting this practice is lacking [30]. Assuming appropriate therapeutic response, treatment may be abridged if toxicity or other complications motivate stopping early. In these cases, patients should be closely monitored for early signs of recurrence. Finally, treatment duration for uncommon forms of nocardiosis should be individualized on a case-by-case basis considering primary site, procedural approach, and response during therapy.

Procedural Intervention

Approximately 10%–20% of patients with nocardiosis undergo surgical intervention for nocardiosis, commonly soft tissue debridement or neurosurgical procedures [6, 7]. In CNS nocardiosis specifically, about half of patients undergo abscess debridement or stereotactic needle aspiration [30, 77]. Patients with larger cerebral abscesses may benefit from early neurosurgical intervention [56]. However, data are limited and subject to confounding by indication, where patients with more severe disease (and inherently higher risk for poor outcomes) are more likely to undergo surgery [77–79]. Patients with CNS nocardiosis may require surgery to establish a diagnosis, and ideally undergo as much concurrent aspiration or debridement as technically feasible and can be safely done [30, 77]. However, diagnosis is often ascertained through other sites of infection, leaving uncertainty as to who should undergo purely therapeutic procedures. This decision should be individualized, accounting for an individual's infection characteristics and their risk of complications from surgery. Patients who do not undergo therapeutic procedures should be

closely monitored for complications or failure of medical therapy, and surgical intervention can be reassessed if clinical progress stalls. There are even fewer data regarding interventions for other forms of nocardiosis, though patients with musculoskeletal or ocular nocardiosis typically undergo surgery [73, 80, 81].

Pulmonary Optimization

Patients with chronic lung disease benefit from optimizing their respiratory medications, including bronchopulmonary hygiene and other inhaled therapies. Non–cystic fibrosis bronchiectasis is the most common predisposing pulmonary condition for nocardiosis, likely due to impaired mucociliary clearance increasing the risk of infection [6, 82]. This can also lead to airway colonization with *Nocardia* species [83]. Therefore, these patients may benefit from airway clearance techniques and pulmonary rehabilitation. A typical airway clearance regimen consists of breathing techniques, nebulized bronchodilators and mucoactive agents (eg, albuterol and hypertonic saline, respectively), and airway oscillatory devices [84, 85].

While data are sparse for *Nocardia* specifically, patients with bronchiectasis, including those with NTM pulmonary disease, who receive airway clearance therapy have improvements in sputum clearance, decrease in respiratory symptoms and peripheral airway obstruction, improved exercise capacity, and even sputum culture conversion without antibiotic treatment [86]. Any association between inhaled corticosteroids and pulmonary nocardiosis is inconclusive [14]; however, guidelines recommend avoidance of inhaled corticosteroids in patients with bronchiectasis due to lack of clinical benefit and increased risk of complications, including pneumonia. Nonetheless, there remains a role for inhaled corticosteroids in patients with comorbid asthma and some patients with chronic obstructive pulmonary disease. Therefore inhaled medication regimens should be reviewed and optimized per underlying disease status.

Evaluation for Other Predisposing Conditions

Among patients without clear predisposing condition, undiagnosed immunodeficiency should be considered. The most common conditions that may present with an opportunistic infection such as *Nocardia* are chronic granulomatous disease, PAP, and anti-GM-CSF autoantibodies. Screening for undiagnosed HIV infection should be considered as well. These syndromes should be investigated in the correct clinical context, particularly as treatment of the underlying disorder may aid in nocardiosis management and prevention of future infectious complications [9, 87]. However, patients with an obvious predisposing condition such as immunosuppressing medications do not necessarily require evaluation for immunodeficiency and are specifically unlikely to have anti-GM-CSF autoantibodies [88].

Reduction in immunosuppression is often performed for severe disease, though evidence supporting this is limited [40]. Immunosuppression should be lowered or held if it can be done safely, recognizing the competing risks of rejection and graft-versus-host disease in transplant populations. Adjunctive interferon-gamma has been successfully used in a limited number of patients with severe nocardiosis refractory to standard medical therapy [89], though this treatment remains unproven outside of patients with chronic granulomatous disease.

PROPHYLAXIS

Primary Prophylaxis

The incidence of nocardiosis is relatively low, even among high-risk immunocompromised populations, making specific primary *Nocardia*-targeted prophylaxis uncommon practice. However, immunocompromised patients often receive TMP-SMX as *Pneumocystis* prophylaxis, which may incidentally reduce nocardiosis risk. Most data in solid organ transplant recipients are mixed [22, 41, 90–92], though a recent meta-analysis found a 70% reduction in odds of nocardiosis among solid organ transplant recipients receiving TMP-SMX prophylaxis [93]. Among hematopoietic stem cell transplant recipients, multiple studies have more clearly suggested a lower rate of nocardiosis with TMP-SMX prophylaxis [94–97]. However, patients in these studies received many different TMP-SMX doses and the studies often did not account for baseline kidney function, making the optimal *Nocardia* prophylaxis dose unclear.

Ultimately, risk factors for *Nocardia* overlap with those with *Pneumocystis*, and TMP-SMX prophylaxis can reduce the risk of these and other infections [92, 98, 99]. Thus, patients with indications for *Pneumocystis* prophylaxis should preferentially receive TMP-SMX. TMP-SMX prophylaxis is frequently discontinued after suspected adverse reactions; however, many patients can tolerate TMP-SMX upon rechallenge [100]. Additionally, most patients who use alternative prophylaxis and develop nocardiosis tolerate treatment-dose TMP-SMX, suggesting that TMP-SMX is often avoided unnecessarily in medical practice [101]. Patients with reported sulfa allergy should be evaluated for true allergy status, and desensitization or graded challenge should be considered when prophylaxis is indicated [92].

While TMP-SMX may reduce nocardiosis rates, it does not eliminate the risk of this infection. Patients who present with a compatible clinical syndrome should be evaluated for nocardiosis, irrespective of prophylaxis. In those who develop breakthrough nocardiosis, TMP-SMX resistance rates do not appear to be influenced by prior prophylaxis, and TMP-SMX remains a reasonable empiric treatment option in this setting [93].

Secondary Prophylaxis

Approximately 5% of patients who complete nocardiosis therapy develop a second episode [63, 75, 76]. These recurrences tend to occur either early after treatment completion (within

1 year, but often within several months) or after several years [75], likely reflecting relapse versus reinfection, respectively. These limited reported cases suggest that nonpulmonary (most notably CNS) nocardiosis is more likely to recur early, whereas pulmonary nocardiosis can recur at any point.

Secondary prophylaxis against *Nocardia* is frequently prescribed to prevent recurrence, but remains understudied [33, 63, 75, 94, 102]. Approximately 25% of patients are prescribed secondary prophylaxis, mostly among immunocompromised people [63, 75, 102]. Secondary prophylaxis is largely TMP-SMX, though other agents such as macrolides and fluoroquinolones have been used [102]. The choice of secondary prophylaxis typically considers the susceptibility pattern of the primary isolate. Few studies have evaluated the effectiveness of secondary prophylaxis, and none have demonstrated a clear benefit [75, 102]. However, given the rarity of recurrent nocardiosis, studies are underpowered and unable to discern if key populations may derive benefit from secondary prophylaxis.

All told, secondary prophylaxis could be considered in select cases of immunocompromised patients. Most do not experience recurrent nocardiosis and many patients are unlikely to benefit from prophylaxis. It is important to consider the consequences of recurrence, and most patients in current literature have favorable outcomes despite a second episode of nocardiosis [75]. However, several patient factors, including a higher burden of comorbidities, predispose to poor outcomes after nocardiosis [6]. Multiple measures of immunocompromise, including lymphopenia and higher immunosuppression exposure [22, 90, 94, 95], have been associated with developing a primary *Nocardia* episode. These have not been formally studied for recurrent nocardiosis but might be extrapolated to reinfection specifically. Factors that predict the risk for *Nocardia* recurrence and subsequent poor outcomes should be carefully considered and discussed to develop an individualized decision regarding secondary prophylaxis. Moreover, many patients at risk for reinfection also carry an indication for *Pneumocystis* prophylaxis as well, and TMP-SMX should be prioritized in this setting like primary prophylaxis.

PATIENT COUNSELING AND FOLLOW-UP CONSIDERATIONS

Patient education and establishment of a longitudinal care plan are essential for successful nocardiosis therapy. Patients should be followed closely, particularly early in therapy, for treatment response and signs of toxicity from antimicrobials. Patients should be counseled about common adverse effects from their antimicrobial therapy and contingencies should be established to mitigate these or transition therapy, as necessary. Continued management of underlying conditions or immunosuppression by pulmonologists, transplant practitioners, or rheumatologists is paramount and should be prioritized as well.

Total treatment lengths are based on low-quality evidence and should be treated as general guidance rather than rigid durations. The end date of treatment should be tailored to an individual patient's response to and tolerance of therapy and does not necessarily need to extend to the traditional 6–12 months. Additionally, there may be uncertainty regarding the pathogenicity of a *Nocardia* isolate in a respiratory culture, particularly since clinical and radiographic findings overlap with predisposing chronic pulmonary diseases. If appropriate treatment is initiated and clinical improvement is not seen, the initial diagnosis of pulmonary nocardiosis should be reassessed. If treatment is not initiated, patients should be followed closely to identify clinical or radiographic progression that suggests the need for nocardiosis therapy.

Once treatment has concluded, patients should be monitored for signs of recurrence and evaluated promptly if concern develops. Longitudinal, and often lifelong, follow-up by appropriate specialists is necessary to optimally treat underlying chronic conditions and prevent future episodes of nocardiosis or other infectious complications.

CONCLUSIONS

Nocardiosis is a challenging condition that primarily affects patients with chronic pulmonary disease and immunocompromising conditions. Diagnosis relies on modified acid-fast staining and culture-based methods, though molecular methods of diagnosis such as PCR are emerging. Treatment often consists of multiple empiric antibiotics, which can be adjusted based on species identification and later with antimicrobial susceptibility results. Treatment is often prolonged but should be personalized based on clinical and radiographic response, as well as tolerance of therapy. Finally, successful management requires a coordinated, multidisciplinary approach to provide effective and tolerable antimicrobial therapy and optimize associated predisposing conditions.

Notes

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