Current Infectious Disease Reports (2019) 21: 27
https://doi.org/10.1007/s11908-019-0684-7

SKIN, SOFT TISSUE, BONE AND JOINT INFECTIOUS DISEASE (N SAFDAR AND A POP-VICAS, SECTION EDITORS)

Updates on *Nocardia* Skin and Soft Tissue Infections in Solid Organ Transplantation

Marion Hemmersbach-Miller[1,2] · Jelena Catania[3,4] · Jennifer L. Saullo[1]

Published online: 21 June 2019

Abstract

Purpose of Review Due to their immunocompromised status, solid organ transplant (SOT) recipients are at risk for *Nocardia* infections. These infections often necessitate early invasive diagnostics alongside prolonged, often combination antimicrobial therapy. This review summarizes the importance of this pathogen in skin and soft tissue infections (SSTIs) in SOT recipients inclusive of recently reported cases in the literature and an update on the epidemiology, diagnostics, and management.

Recent Findings Six studies with 13 isolated SSTIs due to *Nocardia* have been published in the last 5 years in SOT recipients. The most common underlying type of transplant was kidney and time from transplantation to infection varied from 6 months to 16 years. Misdiagnosis was frequent. Available identified species included *N. brasiliensis* (2), *N. farcinica* (2), *N. flavorosea* (1), *N. abscessus* (1), *N. anaemiae* (1), *N. asteroides* (1), *N. nova* (1), and *N. vinacea* (1). Treatment choice and duration varied widely, and trimethoprim-sulfamethoxazole was utilized most often with no documented infection relapse.

Summary *Nocardia* SSTIs can occur both in isolation and as a component of a disseminated infection. Overall, isolated *Nocardia* SSTIs are uncommon in SOT recipients and are often initially misdiagnosed. They present multiple challenges to the clinician including evaluation for potential co-pathogens and/or non-infectious processes and ruling out the presence of disseminated infection. While trimethoprim-sulfamethoxazole remains the agent of choice for management of most isolated SSTIs, therapy must be tailored to the individual patient based on species-specific susceptibility patterns and formal susceptibility testing, site(s) of infection, and patient tolerability.

Keywords *Nocardia* · Skin and soft tissue infections · Organ transplantation · Immunocompromised host · Transplant recipients

This article is part of the Topical Collection on *Skin, Soft Tissue, Bone and Joint Infectious Diseases*

✉ Marion Hemmersbach-Miller
marion.hemmersbach@duke.edu

Jelena Catania
jelena.catania@gmail.com

Jennifer L. Saullo
jennifer.horan@duke.edu

[1] Infectious Diseases Division, Duke University Medical Center, Durham, NC, USA

[2] Duke Clinical Research Institute, Durham, NC, USA

[3] Infectious Disease Section, Orlando Veterans Affairs Medical Center, Orlando, FL, USA

[4] Department of Internal Medicine, University of Central Florida College of Medicine, Orlando, FL, USA

Introduction

Nocardia species are ubiquitous aerobic gram-positive, catalase-positive, partially acid-fast filamentous branching bacteria. They are found in soil and decaying plant matter and belong in the order Actinomycetales [1]. Although *Nocardia* can be found worldwide, geographic distribution of the differing species varies. Transmission most commonly occurs via inhalation; other potential routes include penetrating injuries, iatrogenic procedures, or ingestion [1, 2]. The genus *Nocardia* consists of over 80 different species although not all are clinically significant in humans [3]. Species identification is important as the spectrum of disease and antimicrobial susceptibility patterns vary by species of *Nocardia*. Recent changes in *Nocardia* taxonomy have resulted in a reclassification of some species making comparisons of epidemiologic trends across time more complex. This reclassification has been largely driven by the availability of more sophisticated diagnostics

including gene sequencing and matrix-assisted laser desorption ionization-time of flight mass spectrometry (MALDI-TOF MS) which have replaced previously utilized biochemical techniques [2, 4]. However, *Nocardia* species identification continues to be a challenge in clinical laboratories [3].

Nocardia impacts both immunocompetent and immunocompromised hosts though infections in the latter group predominate. Risks for infection include comorbidities such as diabetes, chronic lung disease, and alcoholism as well as other immunocompromising conditions including active cancer, hematopoietic cell, and solid organ transplantation and associated immunosuppressive therapies [5–15]. This review will focus on *Nocardia* skin and soft tissue infections (SSTIs) in solid organ transplant (SOT) recipients inclusive of the available published literature on this topic over the last 5 years.

Epidemiology and Significance of Nocardiosis in SOT Recipients

Nocardia can result in life-threatening infections in the SOT recipient particularly when disseminated disease is encountered [11, 16–26]. It is considered an opportunistic infection and typically presents in the late post-transplant period though the onset varies from 1 month to many years post-transplant [16, 18, 27, 28].

The overall incidence of *Nocardia* appears to be increasing and is likely due to improved identification in the clinical laboratory as well as an expansion of the at-risk population [11, 12, 29, 30]. The reported incidence of *Nocardia* in the SOT population ranges from 0.4 to 2.65% [12, 30, 31]. Recent studies demonstrate an increase, as well as overall higher rates of infection, in the lung transplant population [11, 12, 16, 19, 30, 31]. Likely, contributions to this include an increase in this transplant type over time, high levels of immunosuppression applied alongside the unique risk of direct exposure of the allograft to the outside environment in the context of an organism most commonly acquired via inhalation. The lowest rates of infection have been reported in the liver and kidney transplant populations [6, 11, 18, 32]. In the SOT population, specific risk factors identified include high calcineurin inhibitor levels, cytomegalovirus disease, and use of high-dose steroids [12, 29].

Nocardiosis most often presents as pneumonia in the SOT recipient, and disseminated infection is common. Extrapulmonary sites of infection include the skin and soft tissue, central nervous system (CNS), and bloodstream. Although isolated SSTIs occur frequently in the immunocompetent host, this is less common in the SOT population. For example, in a multicenter study including 117 cases of nocardiosis in SOT recipients, 37/117 (31.6%) demonstrated skin and soft tissue involvement with only 8/37 (21.6%) representing localized SSTIs [18]. This aspect is important to consider when managing isolated SSTIs in SOT recipients as extrapolation of the incidence and mortality for nocardiosis reported in this population overall may not be entirely illustrative. Large cohorts and more contemporary series report overall mortality rates of 16 to 32% [16, 19, 29–31] in SOT recipients with *Nocardia*. In the multicenter European case-control study inclusive of 117 SOT recipients with *Nocardia* infection, the 1-year all-cause mortality was more than 10 times higher in SOT recipients with nocardiosis than matched controls [19]. Additionally, it is well-known that *Nocardia* often presents with other opportunistic infections, such as fungal or mycobacterial infections and/or viral reactivation, specifically cytomegalovirus, which can also carry significant morbidity and mortality [12, 28, 29, 33].

Depending on the series, the most common species of *Nocardia* identified are *N. nova* complex [12, 16, 31], *N. farcinica* [31], *N. cyriacigeorgica* [6, 18, 32], *N. abscessus* complex [34], and *N. brasiliensis* [34]. However, overall epidemiology depends at least in part upon the geographic location and host. In addition, species may have notable clinical characteristics, including a predilection to certain sites of infection. For instance, *N. farcinica* has been described as a more virulent pathogen with a tendency for disseminated infection inclusive of the CNS [3, 35]. Another example is *N. brasiliensis* which is most often associated with skin and soft tissue infections and seen more commonly in tropical and subtropical climates [1, 2]. Other species such as *N. pseudobrasiliensis*, *N. abscessus*, *N. anaemiae*, *N. asteroides*, *N. farcinica*, *N. flavorosea*, *N. nova* complex, *N. asiatica*, *N. mexicana*, *N. niigatensis*, *N. otidiscaviarum*, *N. neocaledoniensis*, *N. wallacei*, *N. veterana*, and *N. vinacea* have also been described in association with SSTIs [1, 3, 16, 18, 19, 26, 36–42].

Nocardia Skin and Soft Tissue Infections in SOT Recipients

Nocardia SSTIs occur through one of two mechanisms, either primary cutaneous nocardiosis due to trauma or other inoculation, including iatrogenic, *or* secondary cutaneous nocardiosis due to disseminated infection [43–45]. The clinical presentation of primary cutaneous nocardiosis typically includes one of three patterns: (1) lymphocutaneous, (2) mycetoma, and (3) superficial skin infection [1, 45, 46]. Lymphocutaneous infection typically presents as an ulcerated draining lesion at the site of injury accompanied by proximal lymphangitic spread with overlying subcutaneous nodules and often regional lymphadenopathy. This pattern has been readily misdiagnosed as sporotrichosis, a fungal infection caused by *Sporothrix schenckii* and is often referred to as sporotrichoid nocardiosis. However, it can be seen with a multitude of infectious pathogens including other bacteria

(e.g., *Staphylococcus aureus*, *Streptococcus pyogenes*, *Francisella tularensis*), fungi (e.g., endemic fungi such as *Coccidioides*, *Blastomyces*, and *Histoplasma*; molds such as *Aspergillus* and *Scedosporium*), mycobacteria (e.g., *Mycobacterium tuberculosis* and atypical mycobacteria, most notably *M. marinum*), and viral pathogens (e.g., Cowpox, herpes simplex virus) as well as non-infectious processes inclusive of malignancies (e.g., squamous cell carcinoma, lymphoma, melanoma, and keratoacanthoma) [45, 47, 48].

Mycetoma or "Madura foot" has been recognized by the World Health Organization in 2016 as one of the neglected diseases often affecting patients in remote areas with poor access to health care. It is most commonly caused by bacterial pathogens (actinomycetoma) including *Nocardia*, *Actinomyces*, and fungal pathogens (eumycetoma) including *Madurella mycetomatis*, *Fusarium*, *Cladosporium*, and *Exophiala* species [49]. Mycetoma is a chronic, slowly progressive infection that often starts as a small nodule at the site of traumatic entry of the pathogen, usually the foot. If left untreated, it can lead to mass-like lesions with destructive granulomata and fistula formation, affecting the underlying tissue and bone with significant disability [50, 51]. Mycetoma is uncommon in the SOT population with no reported cases in the literature over the preceding 5-year period.

Superficial SSTIs can have a quite variable appearance including ulcers, papules, pustules, plaques, nodules, diffuse erythema, and cellulitis as well as abscess and fistula formation. Rare cases of necrotizing fasciitis have been reported in the non-SOT population [52, 53]. This cutaneous presentation can mimic essentially any type of SSTI as well as non-infectious culprits including inflammatory conditions such as erythema nodosum and pyoderma gangrenosum [38, 54, 55]. Secondary cutaneous nocardiosis seen in disseminated *Nocardia* infections is essentially indistinguishable from a primary SSTI though multifocal skin lesions heighten the concern for a disseminated process.

As mentioned, *Nocardia* infections isolated to the skin and soft tissue are overall less frequent in the SOT recipient in comparison with other sites of involvement, inclusive of disseminated infection. In fact, in the last 5 years, very few cases of isolated SSTI due to *Nocardia* have been described. A summary of these infections is shown in Table 1. There have been six studies identified that include a total of 13 cases [16, 18, 19, 26, 36, 37, 39]. One European series included eight SOT recipients with SSTIs as a component of a larger series of *Nocardia* infections; hence, full details regarding these cases were not available [18, 19]. The remaining five cases reported in the literature occurred in renal transplant recipients. Cutaneous lesions in this group were discovered between 6 months to 16 years following SOT with the superficial SSTI pattern predominating, saving one case of sporotrichoid nocardiosis [36]. No cases of mycetoma were reported in SOT recipients during this period. Identification of the *Nocardia* species was made by partial 16S rRNA sequencing in three cases [26, 36, 37]. Susceptibility testing was performed in four of the five cases and treatment duration ranged from three to 12 months with all cases achieving clinical cure and no reported relapse of infection during the variable periods of follow-up evaluation. Ayoade et al. [36] described a case of sporotrichoid nocardosis with *N. brasiliensis* alongside an extensive review of published SSTIs with this pathogen in SOT recipients. In total, they described five patients with SSTIs with three (two renal and one liver transplant recipients) representing isolated SSTIs without dissemination. Clinical cure was achieved in all three patients with reported treatment durations ranging from 8 weeks to 6 months. Khadka et al. [39] described a Nepali health care worker who underwent renal transplantation and developed cutaneous nocardiosis at the surgical site. The infection was initially thought to represent a typical bacterial SSTI but was not responding to standard antibiotic treatment and was then misdiagnosed further as *M. tuberculosis*. After 2 months of *M. tuberculosis*–directed therapy, the lesions continued to progress and eventually histopathology and culture revealed *Nocardia asteroides* further illustrating the potential delay in diagnosing *Nocardia* infections and the importance of maintaining a high index of suspicion for this pathogen.

Diagnostics

Nocardiosis requires early and sometimes invasive diagnostics including biopsy, culture, and radiographic imaging to establish both the presence and extent of infection. Ideally, the diagnosis of *Nocardia* is made via isolation of the organism in culture; hence, submitting a timely specimen from the site of infection to the microbiology laboratory cannot be overemphasized. It is also important for microbiology colleagues to be alerted to the clinical suspicion of this pathogen to ensure optimal incubation conditions and allow sufficient time for growth. Specimens submitted to the microbiology lab should be sent for routine bacterial, fungal, and mycobacterial cultures not only to confirm the presence of *Nocardia* but for evaluation of co-infections with other pathogens [12, 28, 29, 33, 56]. While diagnostics should be tailored to the individual clinical scenario, *Nocardia* most commonly affects the lung and can disseminate to essentially any organ with a predilection for the CNS [57]. Therefore, in SOT recipients diagnosed with cutaneous *Nocardia* infection, further diagnostics are advised inclusive of blood cultures and imaging of the chest and brain. The latter should be at least considered even in the absence of overt clinical symptoms of CNS involvement given the management implications for disease at this site.

Nocardia are able to grow on many non-selective media under strictly aerobic conditions, including chocolate agar, 5% sheep blood agar, automated blood culture broth media, and

Table 1 Summary of cases of isolated skin and soft tissue infections with *Nocardia*

Reference	SOT	Pattern	Age (years)	Onset post-transplant (months)	Site of infection	Geographic location	*Nocardia* species	Antibacterial treatment	Treatment duration	Outcome
Ayoade et al., Diseases 2018 [36]	Kidney ($n = 1$)	Sporotrichoid SSTI	53	192	Arm	USA	*N. brasiliensis*	Amox/clav	6 months	Cure No relapse at 6 months f/u No 2nd ppx
Chikowski et al. Clin Exp Dermatol 2014 [37]	Kidney ($n = 1$)	Superficial SSTI (erythematous nodule)	61	N/A	Arm	USA	*N. vinacea*	Lack of response on TMP-SMX, linezolid and clarithromycin; ultimate treatment with ceftriaxone followed by minocycline	12+ months	Cure No data on f/u or use of 2nd ppx
Coussement et al., CID 2016 [18]; Lebeaux et al., CID 2017 [19]	Type N/A ($n = 5$)[a]	N/A	Median 67; range 32–80	N/A	N/A	Europe	*N. farcinica* (2) *N. flavorosea* (1) *N. abscessus* (1) *N. anaemiae* (1)	N/A	Median 90 days; range 56–102 days	Cure No relapse at median 49 months f/u (range 6–86 months) 2/5 received 2nd ppx
Hemmersbach-Miller et al., Transpl Infect Dis 2018 [16]	Kidney ($n = 1$)[b]	Superficial SSTI (with abscess formation)	41	29	Leg	USA	*N. brasiliensis*	TMP-SMX	6 months	Cure No relapse at 14 years f/u No 2nd ppx
Khadka et al., BMC Clin Pathol 2018 [39]	Kidney ($n = 1$)	Superficial SSTI (erythematous papules with erosions and crusting)	62	6	Abdomen, around surgical scar	Nepal	*N. asteroides*	TMP-SMX	3 months	Cure No relapse at 2 months f/u No data on 2nd ppx
Kim et al., J Med Microbiol 2014 [26]	Kidney ($n = 1$)	Superficial SSTI (abscess formation)	51	48	Leg	Korea	*N. nova*	TMP-SMX	4 months	Cure No data on f/u or use of 2nd ppx

Review of primary, isolated SSTIs (e.g., without evidence of disseminated *Nocardia* infection) based on review of available literature in the preceding 5-year period

Amox/clav, amoxicillin/clavulanate; *f/u*, follow-up; *N/A*, not available; *2nd ppx*, secondary prophylaxis; *SOT*, solid organ transplant; *SSTI*, skin and soft tissue infection; *TMP-SMX*, trimethoprim-sulfamethoxazole

[a] Eight of the 117 cases (6.8%) reported in this reference were isolated SSTIs. The data represented within the table reflects five of these eight cases

[b] Isolated SSTI was reported in 1/37 (2.7%) of the total cases reported in this reference

others. They can also grow on a variety of selective fungal and mycobacterial media if they survive the initial digestion procedure used in processing specimens from non-sterile sites prior to culturing. Although they can be inhibited by certain antibiotics, such as penicillin and streptomycin, they readily grow on some selective media, such as colistin-nalidixic acid, modified Thayer-Martin agar (used for isolation of *Neisseria gonorrhoeae*), and selective buffered charcoal yeast extract agar used for isolation of *Legionella* species. This strategy can be used when trying to isolate *Nocardia* from contaminated specimens, such as sputum and wounds. Growth can be achieved at a variety of temperatures from 25 to 45 °C, enhanced by incubation in 10% CO_2. Typically, *Nocardia* can be recovered in culture between 2 to 7 days, but may take up to as long as 4 weeks, especially if grown on selective, mycobacterial media [58]. Typical colonies are dry and chalky, although they can also display shades of yellow, orange, and pink, usually with a pungent, musty odor of dirt. Gram stain shows beaded, branching gram-positive filaments that are partially acid fast, which can be used to differentiate *Nocardia* from *Streptomyces* species, another aerobic actinomycete that can have similar colony and gram stain appearance [58].

Historically, *Nocardia* species were differentiated phenotypically, based on their ability to hydrolyze or decompose adenine, casein, tyrosine, xanthine, and hypoxanthine [59]. Over the years, with increased use of molecular technologies, especially gene sequencing, and identification of more *Nocardia* species, it has become apparent that biochemical methods are not sufficiently sensitive to discriminate between the species [4]. Conville and colleagues recently proposed an identification methodology pathway for accurate identification of *Nocardia* clinical isolates [4]. This algorithm recommends primary use of MALDI-TOF MS systems that are validated for the most common *Nocardia* species. Mechanical disruption and protein extraction are necessary initial processing steps, but still lead to fairly rapid differentiation between most common *Nocardia* species including those in the *N. abscessus*, *N. nova*, *N. transvalensis*, *N. cyriacigeorgica*, and *N. farcinica* complexes. Two recent multicenter studies report 76% correct identification to species, with additional 14% identification to complex level, as well as 86% agreement of isolate identification between centers [60, 61]. If MALDI-TOF MS identification is not successful or further identification from complex, group, or taxa to species level is clinically necessary, Conville et al. recommend using 16S rRNA gene sequencing as the next step [4]. Although considered the gold standard for bacterial identification, this technology may not be able to reliably distinguish between all *Nocardia* species. For this reason, multi-locus sequence analysis (MLSA) using sequencing of 4 to 5 housekeeping genes, such as 16S rRNA, hsp65, rpoB, and others, can be pursued. This technology is only performed in a handful of reference laboratories and may also fall short of identification in certain instances, especially as additional new *Nocardia* species are identified.

Susceptibility testing of *Nocardia* species should be pursued on clinically relevant isolates. Standardization for susceptibility testing is published by the Clinical and Laboratory Standards Institute (CLSI), including broth microdilution testing, with updated clinical breakpoint interpretation [62, 63]. It is of utmost importance that susceptibility testing be performed at an experienced reference laboratory as several antimicrobials have been shown to give inconsistent results, including false resistance of ceftriaxone, imipenem, and sulfonamides [64]. Clinical breakpoints for *Nocardia* species have been established for the following antimicrobials: amikacin, amoxicillin-clavulanate, ceftriaxone, ciprofloxacin, clarithromycin, doxycycline, imipenem, linezolid, minocycline, moxifloxacin, rifampin, trimethoprim-sulfamethoxazole (TMP-SMX), tobramycin, and vancomycin [62].

Treatment

The backbone of management of *Nocardia* infections in SOT is antibiotic therapy. However, management must be individualized as there is not a "one size fits all" approach and surgical debridement alongside reduction of immunosuppressive therapy may be required. Considerations when selecting antibiotic therapy include the *Nocardia* species involved, site(s) of infection, presence of co-pathogens as well as adverse effects, intolerabilities, and drug interactions associated with candidate antibiotics. When managing infections in critically ill patients including those with severe pulmonary and/or disseminated infections, inclusive of the CNS, combination therapy is typically employed up-front with at least two and sometimes three agents [11]. However, empiric single-agent therapy is often utilized in the management of isolated SSTIs. The first-line antibiotic for consideration in this setting is TMP-SMX. This agent has excellent penetration into the skin, soft tissue, and bone, and high doses are typically employed (10–15 mg/kg/day of the TMP component) when treating *Nocardia* infections. Side effects of TMP-SMX include myelosuppression, nephrotoxicity, and gastrointestinal intolerance and can be notable barriers to use in the SOT population [65]. Further, not all *Nocardia* species are susceptible to this therapy. *N. brasiliensis*, the most common species associated with SSTIs, are generally quite susceptible to TMP-SMX but higher rates of resistance have been shown with particular species including *N. pseudobrasiliensis*, *N. transvalensis* complex, and *N. farcinica* [34]. Uhde and colleagues [66] retrospectively evaluated antibiotic susceptibility patterns over a 10-year period (1995 through 2004) for *Nocardia* isolates from United States (US) centers submitted to the Centers for Disease Control and Prevention and reported a 42% rate of resistance to TMP-SMX, highest among *N. farcinica* (80% resistant). This data would suggest that plan for empiric

monotherapy with TMP-SMX while awaiting susceptibility data may be flawed. However, much lower rates of TMP-SMX resistance have been reported by others both in the US and elsewhere [5, 31, 34, 67–69]. For example, Brown-Elliott and colleagues reviewed susceptibility results for 552 isolates of *Nocardia* from 2005 through 2011 from six major US laboratories utilizing CLSI-recommended broth microdilution methods and found only 3 isolates (0.5%) with TMP-SMX resistance [69]. They proposed that reported increased rates of TMP-SMX resistance were overstated and likely related to the difficulties in performing *Nocardia* susceptibility and lack of standardized proficiency testing. Our own center-specific data from an 18-year review of nocardiosis spanning 1996 to 2013 further supports the lack of emerging TMP-SMX resistance with identification in only 2 of 142 (1%) of *Nocardia* isolates [5].

Table 2 summarizes select susceptibility data for TMP-SMX and other antibiotics utilized in the treatment of *Nocardia* infections. While this information should by no means replace formal susceptibility testing, it can aid in defining an initial antimicrobial approach once the *Nocardia* complex and/or species has been identified and while awaiting the results of susceptibility testing. In patients intolerant of TMP-SMX, the use of alternative oral options for isolated SSTIs is appealing. However, the use of empiric monotherapy with oral agents such as amoxicillin/clavulanic acid, fluoroquinolones (ciprofloxacin, moxifloxacin), macrolides (azithromycin, clarithromycin), tetracyclines (minocycline), and oxazolidinones (linezolid, tedizolid) is limited as activity of these therapies depend on the *Nocardia* species and susceptibility patterns as demonstrated in Table 2. Therefore, in patients intolerant of TMP-SMX, combination therapy is often employed until susceptibility results are available. Of the available alternative oral agents, linezolid, the first-in-class oxazolidinone, appears to have the broadest in vitro activity across *Nocardia* species. Linezolid is a highly bioavailable oral therapy with good penetration into the skin and soft tissues, lungs, and central nervous system [71, 72]. Use of linezolid in *Nocardia* infections was first reported by Moylett et al. wherein it was successfully utilized as either mono- or combination therapy in 6 patients with isolated skin and soft tissue ($n = 1$), pulmonary ($n = 1$), and disseminated ($n = 4$) infections [73]. Additional data with linezolid specifically in the SOT population has emerged supporting its use as a component of up-front therapy while awaiting susceptibility data given its favorable pharmacokinetics and broad activity against *Nocardia* [74]. However, limitations to its use, particularly as long-term therapy, include associated side effects inclusive of myelosuppression, peripheral and optic neuropathy, and lactic acidosis as well as the potential for serotonin syndrome when taken with concomitant serotonergic medications often also applied in SOT recipients, including antidepressants in the selective serotonin reuptake inhibitor class [71, 72]. Tedizolid, a second-in-class oxazolidinone antibiotic, also appears to have excellent in vitro activity against *Nocardia* species [75]. With its ease of once daily dosing alongside overall lower reported risks of myelosuppresion and serotonin syndrome compared with linezolid, tedizolid represents an exciting addition to the *Nocardia* treatment armamentarium [75, 76].

The duration of treatment for nocardiosis in SOT depends on multiple factors including the degree of immunosuppression, site(s) of involvement, and overall severity of infection. In general, treatment is prolonged due to concerns for relapsed or recurrent infections with shorter treatment courses [77–79]. Guidelines put forth by the American Society of Transplantation (AST) recommend pulmonary infections be treated at least 6 months whereas disseminated infection, inclusive of the CNS, be treated a minimum of 12 months. The duration of therapy for isolated *Nocardia* SSTIs is least clear-cut, though a minimum 6-month course has also been recommended. As noted in the review of recent available literature,

Table 2 *Nocardia* antibiotic susceptibility patterns (composite data)

Species/complex	TMP-SMX	AMK	IMI	CTX	AM-CL	LZD	CLAR	MIN	CIP
N. abscessus/*N. abscessus* complex	+	+	±	+	±	+	–	±	–
N. brasiliensis	+	+	–	±	+	+	–	±	–
N. cyriacigeorgica	+	+	±	+	–	+	–	±	–
N. farcinica	+	+	±	–	±	+	–	±	±
N. nova/*N. nova* complex	+	+	+	±	–	+	+	±	–

Antibiotic class effect is NOT universally applicable. For example, susceptibility patterns among carbapenems (e.g., imipenem, meropenem, ertapenem) may vary within the same *Nocardi*a species or complex. List includes only select *Nocardia* species

AMK, amikacin; *AM-CL*, amoxicillin/clavulanate; *CIP*, ciprofloxacin; *CLAR*, clarithromycin; *CTX*, ceftriaxone; *IMI*, imipenem; *LZD*, linezolid; *MIN*, minocycline; *TMP-SMX*, trimethoprim-sulfamethoxazole. (+) indicates generally susceptible, (−) indicates generally resistance, and (±) indicates variable results from susceptibility testing. Composite data from the following references: [5, 34, 62, 70]

treatment duration is often quite variable with reported treatment duration ranging from 3 to 12 months. There is data suggesting shorter courses of therapy may be successfully applied in isolated SSTIs [29, 80]. For example, in a contemporary series of *Nocardia* infections in transplant recipients, five of the eight SOT recipients with isolated SSTIs with *N. farcinica* ($n = 2$), *N. flavorosea* ($n = 1$), *N. abscessus* ($n = 1$), and *N. anaemiae* ($n = 1$) received short-course therapy ranging from 56 to 102 days (median 90 days) with clinical cure and no evidence of infection relapse during a median follow-up of 49 months (range 6 to 86 months). Of note, two of the five patients (40%) also received secondary prophylaxis.

The application of secondary prophylaxis following of treatment of *Nocardia* infection is not well-established, though some consider this strategy in SOT recipients, particularly those with ongoing augmented immunosuppressive therapy [11, 16, 18]. Further, while historic data has suggested a role of TMP-SMX in primary prevention of *Nocardia*, breakthrough infections have been reported in upwards of 69% of patients receiving prophylactic TMP-SMX such that the role of prophylaxis and ideal agent and dose remain to be determined [12, 16, 18].

Conclusions

In conclusion, *Nocardia* SSTIs in the SOT recipient present multiple challenges to the clinician. These include sorting through a broad differential of potential pathogens, evaluation for possible co-pathogens, and/or non-infectious processes and ruling out the presence of disseminated infection. The identification of *Nocardia* from a skin and soft tissue site should prompt early and aggressive treatment. While TMP-SMX remains the empiric agent of choice, therapy should ultimately be guided by susceptibility results and take factors including drug interactions and medication-associated toxicities into account. Overall duration of therapy is dependent on multiple factors but is typically at least 6 months for isolated SSTI and 9 to 12 months for SSTI associated with disseminated infection. The role of both primary and secondary *Nocardia* prophylaxes needs to be further defined.

Funding This work was supported by the National Institute of Allergy and Infectious Diseases of the National Institutes of Health (grant number 5T32AI100851, MHM). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Compliance with Ethical Standards

Conflict of Interest Marion Hemmersbach-Miller reports grants from NIAID.

Jalena Catania has no conflict of interest.

Jennifer Saullo has no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

1. Lerner PI. Nocardiosis. Clinical Infect Dis: Off Publ Infect Dis Soc Am. 1996;22(6):891–903 **quiz 4-5**.
2. Brown-Elliott BA, Brown JM, Conville PS, Wallace RJ Jr. Clinical and laboratory features of the Nocardia spp. based on current molecular taxonomy. Clin Microbiol Rev. 2006;19(2):259–82. https://doi.org/10.1128/cmr.19.2.259-282.2006.
3. Brown-Elliott BACP, Wallace RJ. Current status of Nocardia taxonomy and recommended identification methods. Clin Microbiol Newsl. 2015;37(4):25–32.
4. Conville PS, Brown-Elliott BA, Smith T, Zelazny AM. The complexities of Nocardia taxonomy and identification. J Clin Microbiol. 2018;56(1). https://doi.org/10.1128/jcm.01419-17.
5. Woodworth MH, Saullo JL, Lantos PM, Cox GM, Stout JE. Increasing Nocardia incidence associated with bronchiectasis at a tertiary care center. Ann Am Thoracic Soc. 2017;14(3):347–54. https://doi.org/10.1513/AnnalsATS.201611-907OC.
6. Wang HL, Seo YH, LaSala PR, Tarrand JJ, Han XY. Nocardiosis in 132 patients with cancer: microbiological and clinical analyses. Am J Clin Pathol. 2014;142(4):513–23. https://doi.org/10.1309/ajcpw84aftuwmhyu.
7. Marciano BE, Spalding C, Fitzgerald A, Mann D, Brown T, Osgood S, et al. Common severe infections in chronic granulomatous disease. Clin Infect Dis: Off Publ Infect Dis Soc Am. 2015;60(8):1176–83. https://doi.org/10.1093/cid/ciu1154.
8. Rodriguez-Nava V, Durupt S, Chyderiotis S, Freydiere AM, Karsenty J, de Montclos M, et al. A French multicentric study and review of pulmonary Nocardia spp. in cystic fibrosis patients. Med Microbiol Immunol. 2015;204(4):493–504. https://doi.org/10.1007/s00430-014-0360-3.
9. Rosen LB, Rocha Pereira N, Figueiredo C, Fiske LC, Ressner RA, Hong JC, et al. Nocardia-induced granulocyte macrophage colony-stimulating factor is neutralized by autoantibodies in disseminated/extrapulmonary nocardiosis. Clin Infect Dis: Off Publ Infect Dis Soc Am. 2015;60(7):1017–25. https://doi.org/10.1093/cid/ciu968.
10. Peleg AY, Husain S, Kwak EJ, Silveira FP, Ndirangu M, Tran J, et al. Opportunistic infections in 547 organ transplant recipients receiving alemtuzumab, a humanized monoclonal CD-52 antibody. Clin Infect Dis: Off Publ Infect Dis Soc Am. 2007;44(2):204–12. https://doi.org/10.1086/510388.
11. Restrepo A, Clark NM. Nocardia infections in solid organ transplantation: Guidelines from the Infectious Diseases Community of Practice of the American Society of Transplantation. Clin Transpl 2019:e13509. doi:https://doi.org/10.1111/ctr.13509.
12. Peleg AY, Husain S, Qureshi ZA, Silveira FP, Sarumi M, Shutt KA, et al. Risk factors, clinical characteristics, and outcome of Nocardia infection in organ transplant recipients: a matched case-control study. Clin Infect Dis:Off Publ Infect Dis Soc Am. 2007;44(10):1307–14. https://doi.org/10.1086/514340.
13. Steinbrink J, Leavens J, Kauffman CA, Miceli MH. Manifestations and outcomes of nocardia infections: comparison of immunocompromised and nonimmunocompromised adult patients. Medicine. 2018;97(40):e12436. https://doi.org/10.1097/md.0000000000012436.

14. Paige EK, Spelman D. Nocardiosis: 7-year experience at an Australian tertiary hospital. Intern Med J. 2019;49(3):373–9. https://doi.org/10.1111/imj.14068.
15. McGuinness SL, Whiting SE, Baird R, Currie BJ, Ralph AP, Anstey NM, et al. Nocardiosis in the tropical northern territory of Australia, 1997-2014. Open Forum Infectious Diseases. 2016;3(4): ofw208–ofw. https://doi.org/10.1093/ofid/ofw208.
16. Hemmersbach-Miller M, Stout JE, Woodworth MH, Cox GM, Saullo JL. Nocardia infections in the transplanted host. Transpl Infect Dis: Off J Transpl Soc. 2018;20(4):e12902. https://doi.org/10.1111/tid.12902.
17. Haussaire D, Fournier PE, Djiguiba K, Moal V, Legris T, Purgus R, et al. Nocardiosis in the south of France during the last ten years. Int J Infect Dis : IJID : Off Publ Int Soc Infect Dis. 2017;57:13–20. https://doi.org/10.1016/j.ijid.2017.01.005.
18. Coussement J, Lebeaux D, van Delden C, Guillot H, Freund R, Marbus S, et al. Nocardia infection in solid organ transplant recipients: a multicenter European case-control study. Clin Infect Dis: Off Publ Infect Dis Soc Am. 2016;63(3):338–45. https://doi.org/10.1093/cid/ciw241.
19. Lebeaux D, Freund R, van Delden C, Guillot H, Marbus SD, Matignon M, et al. Outcome and treatment of nocardiosis after solid organ transplantation: new insights from a European study. Clin Infect Dis: Off Publ Infect Dis Soc Am. 2017;64(10):1396–405. https://doi.org/10.1093/cid/cix124.
20. Le Coustumier EM, Denes E, Martin C, Weinbreck P. Nocardiosis: a retrospective case series of 19 patients. Rev Med Interne. 2017;38(2):81–9. https://doi.org/10.1016/j.revmed.2016.08.015.
21. Shrestha S, Kanellis J, Korman T, Polkinghorne KR, Brown F, Yii M, et al. Different faces of Nocardia infection in renal transplant recipients. Nephrology (Carlton, Vic). 2016;21(3):254–60. https://doi.org/10.1111/nep.12585.
22. Kim YK, Sung H, Jung J, Yu SN, Lee JY, Kim SH, et al. Impact of immune status on the clinical characteristics and treatment outcomes of nocardiosis. Diagn Microbiol Infect Dis. 2016;85(4): 482–7. https://doi.org/10.1016/j.diagmicrobio.2016.05.004.
23. Koerner MM, El-Banayosy A, Schulz U, Zeriouh M, Koerfer R, Tenderich G, et al. Nocardiosis in heart transplant recipients. The Heart Surgery Forum. 2015;18(6):E250–2. https://doi.org/10.1532/hsf.1372.
24. Herzog AL, Wanner C, Lopau K. Successful short-term intravenous treatment of disseminated Nocardia farcinica infection with severe hyponatremia after kidney transplantation: a case report. Transplant Proc. 2016;48(9):3115–9. https://doi.org/10.1016/j.transproceed.2016.04.004.
25. Arze S, Arze L, Abecia C. Post-transplantation infections in Bolivia. Transplant Proc. 2016;48(2):646–53. https://doi.org/10.1016/j.transproceed.2016.02.049.
26. Kim YK, Oh JR, Choi HK, Kim HY, Park SD, Uh Y. Primary cutaneous nocardiosis caused by Nocardia nova in a kidney transplant recipient. J Med Microbiol. 2014;63(**Pt 1**:140–3. https://doi.org/10.1099/jmm.0.054239-0.
27. Fishman JA. Infection in solid-organ transplant recipients. N Engl J Med. 2007;357(25):2601–14. https://doi.org/10.1056/NEJMra064928.
28. Roberts SA, Franklin JC, Mijch A, Spelman D. Nocardia infection in heart-lung transplant recipients at Alfred Hospital, Melbourne, Australia, 1989-1998. Clin Infect Dis: Off Publ Infect Dis Soc Am. 2000;31(4):968–72. https://doi.org/10.1086/318150.
29. Lebeaux D, Morelon E, Suarez F, Lanternier F, Scemla A, Frange P, et al. Nocardiosis in transplant recipients. Eur J Clin Microbiol Infect Dis : Off Publ Eur Soc Clin Microbiol. 2014;33(5):689–702. https://doi.org/10.1007/s10096-013-2015-5.
30. Santos M, Gil-Brusola A, Morales P. Infection by Nocardia in solid organ transplantation: thirty years of experience. Transplant Proc. 2011;43(6):2141–4. https://doi.org/10.1016/j.transproceed.2011.06.065.
31. Majeed A, Beatty N, Iftikhar A, Mushtaq A, Fisher J, Gaynor P, et al. A 20-year experience with nocardiosis in solid organ transplant (SOT) recipients in the southwestern United States: a single-center study. Transpl Infect Dis : Off J Transpl Soc. 2018;20(4): e12904. https://doi.org/10.1111/tid.12904.
32. Valdezate S, Garrido N, Carrasco G, Medina-Pascual MJ, Villalon P, Navarro AM, et al. Epidemiology and susceptibility to antimicrobial agents of the main Nocardia species in Spain. J Antimicrob Chemother. 2017;72(3):754–61. https://doi.org/10.1093/jac/dkw489.
33. Poonyagariyagorn HK, Gershman A, Avery R, Minai O, Blazey H, Asamoto K, et al. Challenges in the diagnosis and management of Nocardia infections in lung transplant recipients. Transpl Infect Dis :Off J Transpl Soc. 2008;10(6):403–8. https://doi.org/10.1111/j.1399-3062.2008.00338.x.
34. Schlaberg R, Fisher MA, Hanson KE. Susceptibility profiles of Nocardia isolates based on current taxonomy. Antimicrob Agents Chemother. 2014;58(2):795–800. https://doi.org/10.1128/aac.01531-13.
35. Wallace RJ Jr, Tsukamura M, Brown BA, Brown J, Steingrube VA, Zhang YS, et al. Cefotaxime-resistant Nocardia asteroides strains are isolates of the controversial species Nocardia farcinica. J Clin Microbiol. 1990;28(12):2726–32.
36. Ayoade F, Mada P, Joel Chandranesan AS, Alam M. Sporotrichoid skin infection caused by Nocardia brasiliensis in a kidney transplant patient. Diseases (Basel, Switzerland). 2018;6(3). https://doi.org/10.3390/diseases6030068.
37. Chikowski RE, Sprigle AM, Krishna SM, Nunley JR. Primary cutaneous Nocardia vinacea in a renal transplant recipient: report of a rare case and review of the literature. Clin Exp Dermatol. 2014;39(4):534–6. https://doi.org/10.1111/ced.12303.
38. Atzori LPA, Pau M. Cutaneous nocardiosis. SOJ Microbiol Infect Dis. 2014;2(1). https://doi.org/10.15226/sojmid.2014.00110.
39. Khadka P, Shah DS. Primary cutaneous nocardiosis: a diagnosis of consideration in a renal transplant recipient. BMC Clin Pathol. 2018;18:8. https://doi.org/10.1186/s12907-018-0075-2.
40. McGhie T, Fader R, Carpenter J, Brown-Elliott BA, Vasireddy R, Wallace RJ, Jr. Nocardia neocaledoniensis [corrected] as a cause of skin and soft tissue infection. J Clin Microbiol 2012;50(9):3139–3140. doi:https://doi.org/10.1128/jcm.00559-12.
41. Welsh O, Salinas-Carmona MC, Brown-Elliott BA, Smith T, Cardenas-De La Garza JA, Wallace RJ Jr. Disseminated actinomycetoma due to Nocardia wallacei. Int J Dermatol. 2018;57(5):580–2. https://doi.org/10.1111/ijd.13909.
42. Dua J, Clayton R. First case report of Nocardia veterana causing nodular lymphangitis in an immunocompromised host. Australas J Dermatol. 2014;55(3):e48–50. https://doi.org/10.1111/ajd.12043.
43. Escudero-Jimenez A, Saez-Nieto JA, Turowicz M, Bartolome-Alvarez J. Skin infection after infiltration by Nocardia cerradoensis. Enferm Infecc Microbiol Clin. 2016;34(5):325–6. https://doi.org/10.1016/j.eimc.2015.07.015.
44. Baek JO, Kim JS, Lee SK, Jeong JH, Lee MJ, Seo IH. Two cases of primary cutaneous nocardiosis caused by intralesional injection. Dermatol Ther. 2019;32(1):e12775. https://doi.org/10.1111/dth.12775.
45. Kalb RE, Kaplan MH, Grossman ME. Cutaneous nocardiosis. Case reports and review. J Am Acad Dermatol. 1985;13(1):125–33.
46. Naldi L, Venturuzzo A, Invernizzi P. Dermatological complications after solid organ transplantation. Clin Rev Allergy Immunol. 2018;54(1):185–212. https://doi.org/10.1007/s12016-017-8657-9.
47. Smego RA, Castiglia M, Asperilla MO. Lymphocutaneous syndrome - a review of non-sporothrix causes. Medicine. 1999;78(1): 38–63. https://doi.org/10.1097/00005792-199901000-00004.

48. Abudu B, Cohen PR. Sporotrichoid keratoacanthomas: case report and review of neoplasms presenting in a sporotrichoid pattern. Cureus. 2018;10(8). https://doi.org/10.7759/cureus.3196.
49. van de Sande WW. Global burden of human mycetoma: a systematic review and meta-analysis. PLoS Negl Trop Dis. 2013;7(11): e2550. https://doi.org/10.1371/journal.pntd.0002550.
50. Verma P, Jha A. Mycetoma: reviewing a neglected disease. Clin Exp Dermatol. 2019;44(2):123–9. https://doi.org/10.1111/ced.13642.
51. McNeil MM, Brown JM. The medically important aerobic actinomycetes: epidemiology and microbiology. Clin Microbiol Rev. 1994;7(3):357–417.
52. Ricci JA, Weil AA, Eberlin KR. Necrotizing cutaneous nocardiosis of the hand: a case report and review of the literature. J Hand Microsurg. 2015;7(1):224–7. https://doi.org/10.1007/s12593-015-0173-7.
53. Lin YC, Huang ZY, Sun JR, Yu CM, Wang CH. First case report of Nocardia brasiliensis infection causing necrotizing fasciitis in an immunocompetent patient. J Microbiol Immunol Infect. 2016;49(5):824–5. https://doi.org/10.1016/j.jmii.2016.03.007.
54. George SJ, Rivera AM, Hsu S. Disseminated cutaneous nocardiosis mimicking cellulitis and erythema nodosum. Dermatol Online J. 2006;12(7):13.
55. Desai M, Imran M, Irum A, Magadan J 3rd. Primary cutaneous nocardiosis in a patient taking adalimumab therapy for Crohn's disease. Kans J Med. 2017;10(1):20–1.
56. Burke VE, Lopez FA. Approach to skin and soft tissue infections in non-HIV immunocompromised hosts. Curr Opin Infect Dis. 2017;30(4):354–63. https://doi.org/10.1097/qco.0000000000000378.
57. Anagnostou T, Arvanitis M, Kourkoumpetis TK, Desalermos A, Carneiro HA, Mylonakis E. Nocardiosis of the central nervous system: experience from a general hospital and review of 84 cases from the literature. Medicine. 2014;93(1):19–32. https://doi.org/10.1097/md.0000000000000012.
58. Procop GWCD, Hall GS, Janda WM, Koneman EW, Schreckenberger PC, Woods GL. Color atlas and textbook of diagnostic microbiology. 7th ed; 2017.
59. Mishra SK, Gordon RE, Barnett DA. Identification of nocardiae and streptomycetes of medical importance. J Clin Microbiol. 1980;11(6):728–36.
60. Body BA, Beard MA, Slechta ES, Hanson KE, Barker AP, Babady NE, et al. Evaluation of the Vitek MS v3.0 matrix-assisted laser desorption ionization-time of flight mass spectrometry system for identification of Mycobacterium and Nocardia species. J Clin Microbiol. 2018;56(6):e00237–18. https://doi.org/10.1128/jcm.00237-18.
61. Blosser SJ, Drake SK, Andrasko JL, Henderson CM, Kamboj K, Antonara S, et al. Multicenter matrix-assisted laser desorption ionization-time of flight mass spectrometry study for identification of clinically relevant Nocardia spp. J Clin Microbiol. 2016;54(5): 1251–8. https://doi.org/10.1128/jcm.02942-15.
62. Wayne P. CLSI. Performance standards for susceptibility testing of mycobacteria, Nocardia spp., and other aerobic actinomyces. **1st Edition2018**.
63. Wayne P. CLSI. Susceptibility testing of mycobacteria, Nocardia spp., and other aerobic actinomyces. **3rd Edition2018**.
64. Conville PS, Brown-Elliott BA, Wallace RJ Jr, Witebsky FG, Koziol D, Hall GS, et al. Multisite reproducibility of the broth microdilution method for susceptibility testing of Nocardia species. J Clin Microbiol. 2012;50(4):1270–80. https://doi.org/10.1128/jcm.00994-11.
65. Ho JMW, Juurlink DN. Considerations when prescribing trimethoprim-sulfamethoxazole. CMAJ : Canad Med Assoc J = J l'Assoc Med Canad. 2011;183(16):1851–8. https://doi.org/10.1503/cmaj.111152.
66. Uhde KB, Pathak S, McCullum I Jr, Jannat-Khah DP, Shadomy SV, Dykewicz CA, et al. Antimicrobial-resistant Nocardia isolates, United States, 1995-2004. Clin Infect Dis: Off Publ Infect Dis Soc Am. 2010;51(12):1445–8. https://doi.org/10.1086/657399.
67. Lai CC, Liu WL, Ko WC, Chen YH, Tang HJ, Huang YT, et al. Antimicrobial-resistant Nocardia isolates, Taiwan, 1998-2009. Clin Infect Dis: Off Publ Infect Dis Soc Am. 2011;52(6):833–5. https://doi.org/10.1093/cid/ciq255.
68. Larruskain J, Idigoras P, Marimon JM, Perez-Trallero E. Susceptibility of 186 Nocardia sp. isolates to 20 antimicrobial agents. Antimicrob Agents Chemother. 2011;55(6):2995–8. https://doi.org/10.1128/aac.01279-10.
69. Brown-Elliott BA, Biehle J, Conville PS, Cohen S, Saubolle M, Sussland D, et al. Sulfonamide resistance in isolates of Nocardia spp. from a US multicenter survey. J Clin Microbiol. 2012;50(3): 670–2. https://doi.org/10.1128/jcm.06243-11.
70. Brown-Elliott BA, Killingley J, Vasireddy S, Bridge L, Wallace RJ Jr. In vitro comparison of ertapenem, meropenem, and imipenem against isolates of rapidly growing mycobacteria and Nocardia by use of broth microdilution and etest. J Clin Microbiol. 2016;54(6): 1586–92. https://doi.org/10.1128/jcm.00298-16.
71. Diekema DJ, Jones RN. Oxazolidinone antibiotics. Lancet (London, England). 2001;358(9297):1975–82. https://doi.org/10.1016/s0140-6736(01)06964-1.
72. Pfizer Inc. Zyvox package insert. New York: Pfizer Inc.; 2013.
73. Moylett EH, Pacheco SE, Brown-Elliott BA, Perry TR, Buescher ES, Birmingham MC, et al. Clinical experience with linezolid for the treatment of Nocardia infection. Clin Infect Dis: Off Publ Infect Dis Soc Am. 2003;36(3):313–8. https://doi.org/10.1086/345907.
74. De La Cruz O, Minces LR, Silveira FP. Experience with linezolid for the treatment of nocardiosis in organ transplant recipients. The Journal of infection. 2015;70(1):44–51. https://doi.org/10.1016/j.jinf.2014.08.010.
75. Brown-Elliott BA, Wallace RJ Jr. In vitro susceptibility testing of tedizolid against isolates of Nocardia. Antimicrob Agents Chemother. 2017;61(12). https://doi.org/10.1128/aac.01537-17.
76. Roger C, Roberts JA, Muller L. Clinical pharmacokinetics and pharmacodynamics of oxazolidinones. Clin Pharmacokinet. 2018;57(5):559–75. https://doi.org/10.1007/s40262-017-0601-x.
77. King CT, Chapman SW, Butkus DE. Recurrent nocardiosis in a renal transplant recipient. South Med J. 1993;86(2):225–8.
78. Palmer DL, Harvey RL, Wheeler JK. Diagnostic and therapeutic considerations in Nocardia asteroides infection. Medicine. 1974;53(5):391–401.
79. Wallace RJ Jr, Septimus EJ, Williams TW Jr, Conklin RH, Satterwhite TK, Bushby MB, et al. Use of trimethoprim-sulfamethoxazole for treatment of infections due to Nocardia. Rev Infect Dis. 1982;4(2):315–25.
80. Ambrosioni J, Lew D, Garbino J. Nocardiosis: updated clinical review and experience at a tertiary center. Infection. 2010;38(2): 89–97. https://doi.org/10.1007/s15010-009-9193-9.