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Sulfonamides without trimethoprim in the treatment of *Nocardia* infections: A case report and literature review

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Abstract

Sulfonamides are recommended as part of first-line therapy for most *Nocardia* infections, with trimethoprim-sulfamethoxazole (TMP-SMX) considered the drug of choice for susceptible isolates. However, in the case of central nervous system, disseminated disease, and other serious *Nocardia* infections, TMP-SMX should not be used as monotherapy. The preferred treatment for a patient unable to take TMP-SMX because of allergy or intolerance remains uncertain. Prior to the availability of TMP-SMX in 1973, other sulfonamides were mainstays of treatment. We describe a *Nocardia* infection successfully treated with sulfadiazine in a lung transplant recipient who could not tolerate TMP-SMX. A review of similar cases reported in the literature provides insight into the successful treatment of *Nocardia* infections with sulfonamide regimens not containing trimethoprim in transplant recipients and other immunocompromised hosts.

KEYWORDS

immunocompromised, *Nocardia*, sulfadiazine, sulfisoxazole, sulfonamide, transplant, trimethoprim

1 | INTRODUCTION

Sulfonamides are recommended as part of first-line therapy for most *Nocardia* infections, with trimethoprim-sulfamethoxazole (TMP-SMX) considered the drug of choice for susceptible isolates. *Nocardia* infections are uncommon, but infections in immunocompromised hosts can be severe. The preferred treatment for a patient unable to take TMP-SMX because of an allergy or intolerance remains uncertain. Prior to the availability of TMP-SMX in 1973, other sulfonamides such as sulfadiazine and sulfisoxazole were mainstays of treatment,[1] and some older case reports describe successful treatment of *Nocardia* infections with sulfonamides without trimethoprim.[2–7] Here we present a case of severe disseminated *Nocardia* infection in a lung transplant recipient who could not tolerate TMP-SMX, developed progressive infection on alternative-class agents, and was eventually treated successfully with sulfadiazine. We then present a review of other similar cases reported in the literature to provide insight into the successful treatment of *Nocardia* infections with sulfonamides without trimethoprim regimens in transplant recipients and other immunocompromised hosts.

2 | CASE REPORT

A 67-year-old man with a history of bilateral orthotopic lung transplant in 2013 for idiopathic pulmonary fibrosis presented in the fall of 2018 with a several week history of headaches, fatigue, dry cough and intermittent fevers. The post-lung transplantation course prior to presentation had been complicated by a single episode of acute cellular rejection treated with thymoglobulin in 2014. He had since maintained stable pulmonary function on an anti-rejection regimen consisting of azathioprine, prednisone and tacrolimus. Infection prophylaxis at time of admission included valganciclovir for history of recurrent cytomegalovirus reactivation and inhaled pentamidine for *Pneumocystis* prophylaxis. Additional past medical history included steroids-related diabetes mellitus controlled on insulin and

supraventricular cardiac arrythmias on anticoagulation and other anti-arrythmia medications. Moreover, the first-year post-transplant, the patient had experienced chronic nausea and vomiting in setting of known gastroparesis limiting use of multiple drugs with known nausea side effects, including TMP-SMX and mycophenolate.

Upon initial presentation, a chest x-ray and computer tomography scan (CT) of the chest demonstrated a new left upper lobe lung mass. Bronchoscopy with bronchoalveolar lavage cultures revealed gram-positive branching rods that were modified acid fast stain positive suggestive of *Nocardia* spp. The patient was empirically started on oral TMP-SMX and imipenem/cilistatin. Magnetic resonance imaging (MRI) of the brain did not show evidence for intracerebral *Nocardia* infection. Final identification of the isolate revealed *Nocardia transvalensis complex*. Oral TMP-SMX was continued and imipenem/cilistatin was changed to oral ciprofloxacin based on published susceptibility patterns for this complex. Antimicrobial susceptibility testing of the isolate confirmed susceptibility to TMP-SMX and ciprofloxacin as well as ceftriaxone, linezolid, and moxifloxacin. The isolate was intermediate to amoxicillin/clavulanate, doxycycline, and minocycline; and resistance to amikacin, cefepime, clarithromycin, imipenem, and tobramycin.

Less than a week after discharge, the patient developed severe nausea. Oral TMP-SMX was changed to tedizolid, and ciprofloxacin was continued. Two months later the patient developed severe left leg pain, and hamstring tendonitis was suspected on MRI. Ciprofloxacin was discontinued, but pain persisted. Three weeks later, tedizolid was also discontinued for the possibility of tedizolid-induced neuropathy.

Four days after stopping tedizolid and 29 days after stopping ciprofloxacin (3.5 months after the index presentation), the patient was readmitted with multiple right leg skin nodules as well as worsening left leg pain and weakness that had progressed to the point that he could not walk without a walking assistance device. Repeat chest CT showed progression of the left upper lobe lung mass, and repeat brain MRI showed multiple new small abscesses in the left frontal, left parietal, bilateral occipital lobes and in the left cerebellum. Left lower extremity MRI showed findings in the mid left femur consistent with osteomyelitis and adjacent abscess. Right leg skin biopsy and left leg aspirate cultures confirmed relapse of disseminated *Nocardia transvalensis complex* infection. Blood cultures were negative and transthoracic echocardiogram was without evidence of vegetations.

Despite one week of combination therapy with intravenous (IV) TMP-SMX and ceftriaxone, left lower leg pain progressed. Repeat left lower extremity MRI revealed progression of osteomyelitis of mid left femur and persistent adjacent abscess. A left femur corticotomy, incision, and drainage with drain placement was performed. Given severe multi-organ nocardiosis, linezolid was added while awaiting antimicrobial susceptibility testing. On repeat susceptibility testing, the isolate demonstrated the same susceptibility profile with the exception of amoxicillin/clavulanate and doxycycline reported as susceptible rather than intermediate. After clinical improvement, the TMP-SMX was transitioned from IV to oral route, and linezolid and ceftriaxone were continued. The patient was discharged three weeks after admission.

Because of severe nausea and vomiting from oral TMP-SMX and new pancytopenia, the patient was readmitted a week later. A brain MRI showed overall improvement in abscesses. Linezolid and TMP-SMX were stopped because of adverse effects, but ceftriaxone was continued. Doxycycline and moxifloxacin were added, and the patient was subsequently discharged six days after admission.

Despite initial improvement after discontinuation of TMP-SMX and linezolid, nausea and vomiting and progressive left leg pain recurred three weeks later (approximately five months after the index hospitalization) prompting another re-admission. The patient was found to have gangrenous cholecystitis and underwent a laparoscopic cholecystectomy. Bile drain cultures were negative. Surveillance CT chest imaging revealed improvement in lung involvement. However, MRI revealed persistent left lower extremity osteomyelitis despite a decrease in the size of the associated soft tissue abscess, and there was enlargement of the previously identified brain abscesses. Given concern for inadequate treatment response on ceftriaxone, moxifloxacin, and doxycycline, the IV TMP-SMX and linezolid-combination regimen was resumed with moxifloxacin as the third agent. Less than 2 weeks into this regimen, the patient re-experienced nausea that was unresponsive to anti-emetics, hyponatremia, and decreasing blood cell counts. In the setting of repeated intractable nausea and laboratory abnormalities during every course of TMP-SMX and the patient's desire to leave the hospital, it was decided to eliminate the trimethoprim component of the regimen. IV TMP-SMX was substituted for oral sulfadiazine 25-50mg/kg/day divided into four doses with goal dose of 50mg/kg/day if tolerated. Moxifloxacin was continued. Given persistent cytopenias, he was unable to tolerate either linezolid or tedizolid. The patient was discharged on sulfadiazine and moxifloxacin three weeks after admission. Doxycycline was added as a third agent one month later.

After 3 months of sulfadiazine, moxifloxacin and doxycycline therapy, left leg pain had resolved. CT of the chest showed resolution of the lung mass, and MRI of the brain showed marked improvement in the brain abscesses. Moxifloxacin was discontinued, and the patient continued on dual therapy with sulfadiazine and doxycycline. Approximately 4.5 months later, there was no evidence of recurrence. Sulfadiazine and doxycycline were continued indefinitely. Figure 1 illustrates the timeline of his various antibiotic regimens.

Unfortunately, despite clinical improvement in disseminated nocardiosis, new onset of persistent left flank pain and rising Ebstein-Barr virus viral load prompted further investigations which revealed post-transplant lymphoproliferative disorder. He is currently undergoing treatment for this disease while being continued on his *Nocardia* treatment.

3 | LITERATURE REVIEW

We searched PubMed for articles related to *Nocardia* infections and sulfadiazine. We included articles that were published

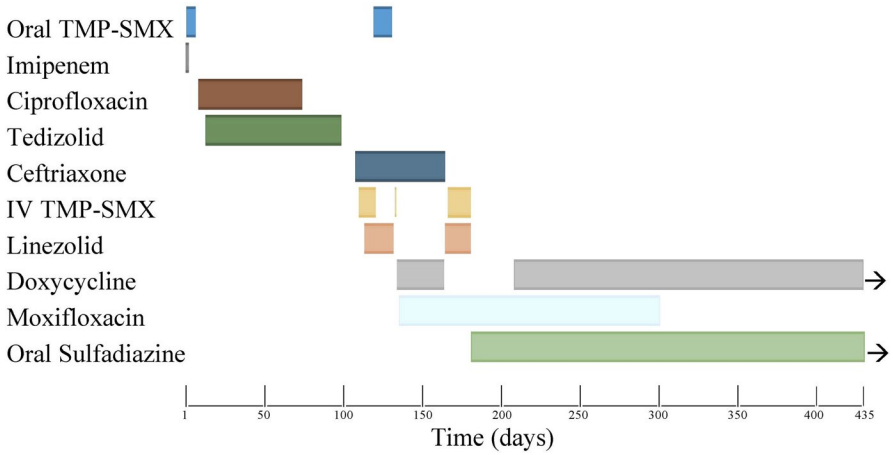

FIGURE 1 Timeline of antibiotic regimens for the presented case. Abbreviations: TMP-SMX, trimethoprim-sulfamethoxazole; imipenem, imipenem/cilistain; iv, intravenous

between database inception and April 22, 2020. To identify such articles, we used the following search terms: PubMed: ("*Nocardia* infections"[mesh] OR *Nocardia*[mesh] OR nocard*[tiab]) AND (sulfadiazine*[tiab] OR sulfadiazine[mesh]). We reviewed the full text of articles written in English that were accessible through the University of North Carolina Health Sciences Library that reported usage of a sulfonamide without trimethoprim for *Nocardia* infections in transplant recipients or patients with a hematologic malignancy. Cases reporting the usage of a sulfonamide without trimethoprim for *Nocardia* infections in non-transplant recipients or patients without hematologic malignancies were not included in this review.

In addition to the case presented here, one case in a renal transplant recipient and nine cases in patients with an underlying hematologic malignancy with *Nocardia* infections treated successfully with a sulfonamide without trimethoprim regimen were identified. Table 1[8–11] summarizes the sulfonamide treatment regimens, underlying immunocompromising conditions, disease locations, and outcomes. Sulfonamides that were used include sulfadiazine, sulfisoxazole and a triple sulfa combination not otherwise defined. The dosing of sulfonamides ranged from 2.8-8.0 grams per day with durations ranging from at least one month to as long as one year. Underlying hematologic malignancy conditions include Hodgkin disease, acute lymphocytic leukemia, and lymphosarcoma. Most patients had pulmonary involvement – two of which also had skin and soft tissue involvement. Other sites involved include the central nervous system, skeletal muscle, and larynx. All 10 cases responded to therapy. Table 2[12,13] summarizes the properties and evidence of sulfadiazine.

4 | DISCUSSION

Most *Nocardia* spp. are susceptible to TMP-SMX and other sulfonamides.[14,15] In a retrospective cohort of 51 patients with nocardiosis after solid organ transplant (SOT) or hematopoietic cell transplant (HCT) between 1996-2013, 98% (n = 12) and 100% (n = 29) of HCT and SOT recipients, respectively, had *Nocardia* infections that were susceptible to TMP-SMX.[16] Sulfonamides (most commonly in the form of TMP-SMX) are often part of first-line therapy for *Nocardia* infections given the high rate of susceptibly to sulfonamides. However, it remains unknown whether sulfonamides alone as an alternative to TMP-SMX can be used especially in a setting where a patient cannot tolerate TMP-SMX. Thus, we conducted a literature review on case reports and case series of *Nocardia* infections treated with sulfonamides alone as described and illustrated above. Additionally, we reviewed the literature for information about *Nocardia* susceptibility to TMP and sulfonamides.

Both sulfonamides and TMP inhibit the folate synthesis pathway. Sulfonamides are structurally related to paraaminobenzoic acid (PABA) and act by inhibiting dihydropteroate synthetase and preventing the conversion of PABA to dihydropteroate. Trimethoprim acts at a following stage of folate synthesis by inhibiting dihydrofolate reductase, the enzyme that converts dihydrofolic acid to tetrahydrofolic acid. Tetrahydrofolic acid is a cofactor for the synthesis of bacterial purine and pyrimidine necessary for the biosynthesis of nucleic acids and proteins.

The combination of TMP-SMX has synergistic activity against many species of *Nocardia* in vitro, although the clinical relevance of this in vivo remains unknown.[1,17] In general, synergy between SMX and TMP was previously thought to be because of the ability of SMX to potentiate the action of TMP by diminishing the accumulation of dihydrofolic acid, enhancing the interaction between TMP and its target dihydrofolic acid reductase.[18,19] However, a more recent study has demonstrated the two drugs together disrupt a metabolic feedback loop resulting in depletion of tetrahydrofolate acid through mutual synergistic effects.[20] TMP acts synergistically with sulfonamides by blocking sequential steps in the folate synthesis pathway. The few studies dating back to the early 1980s that have evaluated the susceptibly of *Nocardia* to TMP alone have shown varying degrees of susceptibility.[1,21,22]

In a review of published cases between 1955 and 1987, sulfonamides were used in 55 patients being treated for *Nocardia* infection. Of these, 15 patients were treated with TMP-SMX alone, 10 were treated with TMP-SMX in combination with other agents, seven were treated with a sulfonamide alone, and 23 patients received

TABLE 1 Reports of *Nocardia* infections treated with sulfonamides in transplant recipients and hematological malignancy

Case Number (year published)	Sulfonamide Regimen	Additional anti-*Nocardia* drugs	Immunocompromising Condition	Sites of Disease	Outcome
Present Case (2018)	Sulfadiazine 25-50 mg/kg/d divided into 4 doses; goal of 50 mg/kg/d	As per case report above	Lung transplant recipient	Lung, muscle, bone, skin/ soft tissue, brain	Resolved
Case 1 (1993)[8]	Sulfadiazine for 6 months	None	Renal transplant recipient	Lung	Resolved
Case 2 (1976)[9]	Sulfadiazine 6 g/d for at least 4 weeks	None	Hodgkin disease	Skin/soft tissue confirmed; lung presumed	Resolved - required incision and drainage of multiple skin lesions
Case 3 (1975)[10]	Sulfadiazine 6 g/d for 120 days	Streptomycin 1 g/d for 23 days followed by 2 grams 3 times per week for 56 days	Hodgkin disease	Skeletal muscle	Resolved – no histologic or cultural evidence of disease at autopsy 5 months after cessation of therapy
Case 4 (1975)[10]	Sulfisoxazole 4 g/d for 114 days	None	Acute lymphocytic leukemia	Lung	Resolved – no disease in follow up in 7-9 months post-treatment
Case 5 (1975)[10]	"Triple sulfa" 4 g/d for 43 days	None	Acute lymphocytic leukemia	Larynx	Resolved – no disease in follow up in 7-9 months post-treatment
Case 6 (1975)[10]	Sulfisoxazole 4 g/d for 52 days	None	Hodgkin disease	Lung	Resolved – no histologic or cultural evidence of disease at autopsy 4 days after cessation of therapy
Case 7 (1975)[10]	Sulfisoxazole 2.8 g/d for 60 days	None	Acute lymphocytic leukemia	Lung	Resolved – had persistent pulmonary cysts 2 months post treatment but no evidence of infection
Case 8 (1975)[10]	Sulfisoxazole 6 g/d for 104 days	None	Hodgkin disease	Lung	Resolved – had persistent pulmonary cysts at end of therapy but no evidence of infection
Case 9 (1971)[11]	Sulfonamides in average daily doses of 6-8 grams IV for 1 month followed by oral sulfonamides 4-6 g/d	± tetracycline in average daily doses of 1 g/d	Hodgkin disease	Lung	Resolved
Case 10 (1971[11]	Sulfadiazine 8 g/d IV followed by sulfisoxazole 8 g/d for 6 weeks followed by 4 g/d for 3 months	None	Lymphosarcoma	Lung	Resolved

Abbreviations: g/d, grams/day; IV, intravenously; mg/kg/d, milligrams per kilogram per day.

TABLE 2 Sulfadiazine properties and evidence[12,13]

Recommended Use	Dosing	Renal Adjustment
FDA approved dosing	2-4 grams by mouth initially, followed by 4-8 grams by mouth daily divided in 3-6 doses	Use with caution; no specific recommendations provided
Guidelines for the Prevention and Treatment Opportunistic Infections in Adults and Adolescents with HIV	1-1.5 grams by mouth every 6 hours (1.5 grams if > 60 kilograms)	Creatinine clearance of 10-50 mL/min: 1-1.5 grams orally every 12 hours Creatinine clearance of < 10 mL/min or hemodialysis: 1-1.5 grams orally every 24 hours, give dose after dialysis on dialysis days

Abbreviations: FDA, food and drug administration; HIV, human immunodeficiency virus; mL/min, milliliter/minute.

sulfonamide combination therapies without TMP. Overall, survival was 82% among patients who received a sulfa drug, and there were no differences in outcomes among the different regimens.[23] Although the numbers were small, this review illustrated that those treated with sulfonamide only regimens without TMP for the treatment of *Nocardia* infections had good outcomes.

Unfortunately, the adverse effects associated with TMP-SMX often preclude the use of this drug. The more common adverse reactions to TMP-SMX involve the gastrointestinal tract (nausea, vomiting) and skin (rash and pruritus).[24,25] Although uncommon, TMP-SMX may also cause nephrotoxicity. However, it is important to distinguish nephrotoxicity from decreased tubular secretion of creatinine from competing TMP, which can lead to an increase in serum creatinine that is not reflective of a true reduction in glomerular filtration rate.[25]

Although sulfonamide in the form of TMP-SMX is commonly the drug of choice as part of many first-line regimens for *Nocardia* infections, the literature supports use of sulfonamides without TMP as an alternative to TMP-SMX. Our case highlights the importance of considering this alternative therapy, especially in a setting where the patient is not tolerating TMP-SMX, as this patient showed good clinical response to sulfadiazine without adverse effects. Further studies are required to investigate whether sulfonamides without TMP are just as effective and thus an equivalent alternative therapy to TMP-SMX for *Nocardia* infections.

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AUTHORS' CONTRIBUTION

Heather Root: Data curation, investigation, methodology, project administration, resources, visualization, writing - original draft, and writing - review and editing. Lindsay Daniels: Data curation, investigation, methodology, resources, supervision, writing - original draft, and writing - review and editing. Ashley Marx: data curation, investigation supervision, validation, and writing - review and editing. Luther Bartelt: supervision, validation, and writing - review and editing. Anne Lachiewicz: supervision, validation, visualization, and writing - review and editing. David van Duin: conceptualization, methodology, supervision, validation, and writing - review and editing.

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