

Nocardiosis in Immunocompromised Patients on Alternative *Pneumocystis* Prophylaxis

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Prophylactic trimethoprim/sulfamethoxazole (TMP/SMX) prevents *Pneumocystis jirovecii* pneumonia and nocardiosis in immunocompromised patients but sometimes is avoided because of purported allergies or side effects. Of 25 immunocompromised patients receiving alternative prophylaxis in whom nocardiosis developed, 16 subsequently tolerated TMP/SMX treatment. Clinicians should consider TMP/SMX allergy evaluation and rechallenging to assess patient tolerance.

Trimethoprim/sulfamethoxazole (TMP/SMX) is the drug of choice for *Pneumocystis jirovecii* pneumonia (PJP) prophylaxis in immunocompromised patients (1). Second-line prophylactic agents include atovaquone, dapsone, pentamidine, and clindamycin with pyrimethamine. Alternative agents can be less effective than TMP/SMX at preventing PJP and opportunistic infections caused by *Listeria monocytogenes*, *Toxoplasma gondii*, and *Nocardia* spp. Prophylactic TMP/SMX is sometimes avoided because of a prior adverse drug reaction or when patients are receiving drugs that have potentially overlapping toxicities. Nonetheless, second-line PJP prophylaxis regimens can increase the risk for opportunistic infections, such as nocardiosis (2). Most nocardiosis occurs in patients with impaired cell-mediated immunity; TMP/SMX is the cornerstone of standard therapy (3). We describe a series of nocardiosis cases in immunocompromised patients who were receiving alternative or no PJP prophylaxis because of TMP/SMX avoidance. We provide the reasons for TMP/SMX avoidance and proportion of patients who subsequently tolerated TMP/SMX.

We conducted a retrospective chart review at Stanford Hospital (Stanford, CA, USA) for patients with nocardiosis diagnosed during January 1, 1998–January 28, 2020. We included patients

avoiding TMP/SMX for PJP prophylaxis in whom nocardiosis was identified on culture or by molecular techniques, such as 16S rRNA PCR-based assay. We used Stanford Hospital's protocols for defining immunocompromised status requiring PJP prophylaxis. We collected baseline demographic, clinical, microbiological, and outcome information, including immunocompromising condition, PJP prophylaxis indication and agent, reason for TMP/SMX avoidance, and TMP/SMX rechallenge outcome, if performed. This study was approved by Stanford University's Institutional Review Board (approval no. 54959).

During the study period, nocardiosis developed among 25 immunocompromised patients deliberately avoiding TMP/SMX. Most (68%) patients were female; median age of patients was 55 years. Among the 25 patients, 7 (28%) were lung transplant recipients, 6 (24%) had undergone allogeneic hematopoietic cell transplantation (HCT), 5 (20%) were heart transplant recipients, and 7 (28%) had other immunocompromising conditions (Appendix Table, <https://wwwnc.cdc.gov/EID/article/27/10/21-0620.App1.pdf>). At diagnosis, 15 (60%) patients were taking atovaquone, 4 (16%) inhaled pentamidine, 3 (12%) dapsone, and 3 (12%) no antimicrobial drug prophylaxis.

Thirteen (52%) patients were not taking TMP/SMX because of a reported history of allergy, 6 because of concern for cytopenia (24%), and 3 because of elevated creatinine (12%). TMP/SMX was avoided in 1 patient for elevated transaminases, 1 for gastrointestinal intolerance, and 1 for unstated reasons. Among 10 patients with a TMP/SMX allergy label who attempted challenge or desensitization, 7 (70%) tolerated the drug; nonsevere rash developed in the other 3 patients. Among 10 patients avoiding TMP/SMX prophylaxis for nonallergy reasons, 9 (90%) tolerated TMP/SMX when rechallenged. Overall, TMP/SMX introduction was attempted in 20/25 patients; 80% successfully tolerated the drug, and 20% had mild, reversible adverse effects (Figure).

In this retrospective case series, 16/25 (64%) patients who had nocardiosis while deliberately avoiding TMP/SMX prophylaxis ultimately were treated with TMP/SMX. Immunocompromised patients often are prescribed alternative drugs to TMP/SMX prophylaxis because of concerns over side effects or allergic reactions (4). However, desensitization or rechallenge could enable a substantial proportion of patients to safely take TMP/SMX for prophylaxis. In our study, 70% of patients with a history of TMP/

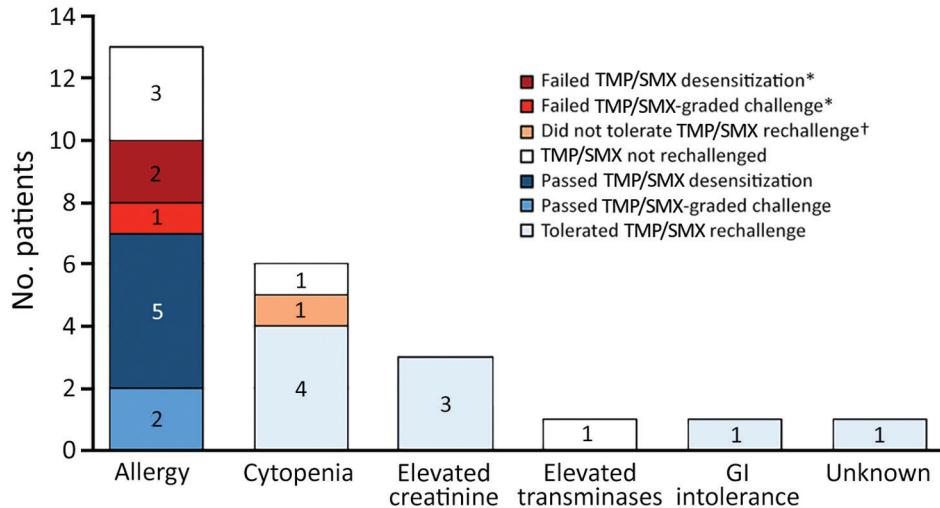


Figure. Reasons for TMP/SMX avoidance and TMP/SMX rechallenge outcomes among immunocompromised patients in whom TMP/SMX prophylaxis for *Pneumocystis jirovecii* pneumonia prophylaxis was avoided, Stanford, California, USA. *Failed TMP/SMX introduction because of rash or GI symptoms that were not severe. †Developed intractable nausea and vomiting after TMP/SMX was introduced and did not tolerate rechallenge. GI, gastrointestinal; TMP/SMX, trimethoprim/sulfamethoxazole

SMX allergy tolerated a TMP/SMX graded challenge or desensitization when attempted, and 90% of patients avoiding TMP/SMX prophylaxis for non-allergy reasons tolerated TMP/SMX when rechallenged. Our results concur with findings from a study that showed 74% of kidney transplant recipients who underwent TMP/SMX rechallenge had no recurrence of adverse drug reactions (5).

TMP/SMX prophylaxis might decrease the incidence of nocardiosis in immunocompromised patients. In a retrospective review of HCT recipients with nocardiosis, most (12/15) cases occurred in patients receiving alternate PJP prophylaxis (2). Other studies have questioned the efficacy of TMP/SMX prophylaxis in preventing nocardiosis in HCT or solid organ transplant recipients (6–8).

Taken together, these findings suggest that rates of this highly pathological infection might be reduced by systematically reevaluating TMP/SMX avoidance and reconsidering prophylactic TMP/SMX. Consulting with an allergist can detect contraindications, such as severe cutaneous adverse reactions, and opportunities for challenge or desensitization. Patients with a history of maculopapular rash, cytopenia, or increased creatinine with TMP/SMX might tolerate reintroduction. Electronic medical records can be designed to prompt revisiting whether TMP/SMX avoidance is appropriate (9).

The first limitation of our study is that we only included immunocompromised patients from a single healthcare system; our findings might not be generalizable to other settings. Second, some immunocompromised patients with nocardiosis possibly were not included in our cohort; although defining the incidence of nocardiosis would be informative, the intent of our study was to describe consequences

of unnecessary TMP/SMX avoidance. Third, specifics of desensitization or graded challenge protocols were not consistently documented and thus might not be uniform.

Despite these limitations, our study shows that most patients in whom nocardiosis developed while avoiding TMP/SMX prophylaxis later tolerated TMP/SMX treatment. Future research should prospectively evaluate the risks and benefits of TMP/SMX reintroduction in immunocompromised patients who have had a prior adverse reaction. In conclusion, our findings suggest that revisiting TMP/SMX avoidance could prevent nocardiosis cases.

A.G.P. developed the research question, designed the data collection, compiled and analyzed the data, contributed to writing the manuscript, developed the figure, revised the manuscript; A.Y.L. developed the research question, designed the study, supervised data collection and cleaning, contributed to data analysis and manuscript preparation; D.J.E., N.B., and A.K.S reviewed the manuscript and provided expert input; all authors approved the final version of the manuscript to be published.

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Dr. Puig is an infectious diseases specialist at City of Hope National Medical Center. His main research interests center on evaluating the impact of infections following solid organ and hematopoietic stem cell transplantation, and the efficacy of anti-infective prophylaxis protocols.

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Autochthonous Case of *Rickettsia slovaca* Infection in Russia

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We describe an autochthonous case of *Rickettsia slovaca* infection in a man 35 years of age from Russia who had tickborne lymphadenopathy. We used ELISA and quantitative PCR testing to further identify DNA and confirm diagnosis. Physicians in Russia should consider similar diseases in differential diagnoses after tick bites.

Rickettsia slovaca was isolated in *Dermacentor marginatus* ticks in 1968 in Slovakia and recognized as a *Rickettsia* species with unknown pathogenicity. In 1997, a study described the first laboratory-confirmed case of *Rickettsia slovaca* infection in a human (1). *R. slovaca* has been detected in ticks in many countries in Europe, including the Mediterranean region. Human cases of syndromes that can be caused by *R. slovaca*, including tickborne lymphadenopathy (TIBOLA), *Dermacentor*-borne necrosis-erythema-lymphadenopathy (DEBONEL), and scalp eschar and neck lymphadenopathy after tick bite (SENLAT) have been reported (2,3). *R. slovaca* has been detected in ticks in 4 of 85 regions of Russia (Figure), and 1 imported case of *R. slovaca* infection was reported (4–7). The aim of our study was to describe an autochthonous case of *R. slovaca* infection in a man in Russia.

In May 2019, a 35-year-old male resident of Russia with an unremarkable medical history sought treatment for eschar on the skin of his right shin, painful and enlarged inguinal lymph nodes, rash, pain in his right knee, and severe fatigue. Before onset, he was in a rural village in the Voronezh region of Russia for 8 days, where he had contact with domestic animals and later noticed an insect bite near the location of the eschar. He reported no history of foreign travel in the previous 6 months.

Nocardiosis in Immunocompromised Patients Receiving Alternative *Pneumocystis* Prophylaxis

Appendix

Appendix Table. Clinical characteristics of nocardiosis and TMP/SMX avoidance among patients treated with alternative prophylactic agents against *Pneumocystis jirovecii* pneumonia*

ID	Age, y/sex	Underlying conditions	Organism	Infection type	Prophylactic agent	Reason TMP/SMX avoided	Allergy testing outcome	Treatment (duration)	Outcome
1	35/F	Dermatomyositis on high-dose systemic steroids	<i>Nocardia spp</i>	Pulmonary	Dapsone	Allergy, swollen lips	Did not test or challenge	MIN (6 mo)	S
2	46/M	Anaplastic large cell lymphoma s/p allogeneic HCT	<i>N. asteroides</i>	Disseminated (lung and paraspinal)	Inhaled pentamidine	Allergy, rash	Failed desensitization†	CRO (3 mo)	S
3	63/F	COPD s/p lung transplant	<i>N. farcinica</i>	Pulmonary	Atovaquone	Cytopenia	Tolerated regular dose reintroduction	TMP/SMX+LZD+MXF (6 mo)	S
4	17/M	Congenital heart disease s/p heart transplant	<i>N. cyriacigeorgica</i>	Pulmonary	Atovaquone	Cytopenia	Tolerated regular dose reintroduction	TMP/SMX+CRO+AMK; TMP/SMX+CD (6 mo)	D
5	43/F	LAM s/p lung transplant	<i>Nocardia spp</i>	Pulmonary	Atovaquone	Allergy, rash	Failed desensitization†	IPM+LZD; CRO+LZD; LZD; Inh AMK (Unknown)	D
6	51/F	Bronchiolitis obliterans s/p lung transplant	<i>N. farcinica</i>	Disseminated (lung and brain)	Inhaled pentamidine	Allergy, rash	Did not test or challenge	MEM+AMC; AMC+CLR; AMC+MIN; DOX+AMC (12 mo)	D
7	55/F	Pulmonary fibrosis s/p lung transplant	<i>N. cyriacigeorgica</i>	Pulmonary	Dapsone	Cytopenia	Did not tolerate rechallenge‡	IPM+CIP; MIN (12 mo)	S
8	67/F	COPD s/p lung transplant	<i>N. cyriacigeorgica</i>	Pulmonary	Atovaquone	Allergy, itchiness	Passed desensitization	TMP/SMX+MEM (Unknown)	S
9	51/F	Acute myeloid leukemia s/p allogeneic HCT	<i>N. cyriacigeorgica</i>	Disseminated (blood, lung, and brain)	Dapsone	Allergy, rash	Passed desensitization	MEM+AMC; MEM; CRO+TMP/SMX; CRO (Unknown)	S
10	79/F	Autoimmune hepatitis on high-dose systemic steroids	<i>Nocardia spp</i>	Bacteremia	None	GI intolerance	Tolerated regular dose reintroduction	TMP/SMX (1 wk)	D
11	11/M	Pre-B acute lymphoblastic leukemia s/p allogeneic HCT	<i>N. cyriacigeorgica</i>	Mediastinal	Inhaled pentamidine	Allergy, rash	Passed graded challenge	IPM+CRO; MEM+CRO (2 mo)	D

ID	Age, y/sex	Underlying conditions	Organism	Infection type	Prophylactic agent	Reason TMP/SMX avoided	Allergy testing outcome	Treatment (duration)	Outcome
12	17/F	Dilated cardiomyopathy s/p heart transplant	<i>N. farcinica</i>	Pulmonary	Inhaled pentamidine	Allergy, rash	Failed graded challenge†	AMC+MIN; MEM+MXF; LZD+MEM; CIP+LZD; CIP+AMC; AMC (10 mo) AMC+MIN (Unknown)	S
13	58/M	Dermatomyositis on high-dose systemic steroids	<i>N. paucivorans</i>	Pulmonary	Atovaquone	Elevated transaminases	Did not test or challenge		S
14	55/F	Adriamycin-induced cardiomyopathy s/p heart transplant	<i>N. veterana</i>	Pulmonary	Atovaquone	Cytopenia	Tolerated regular dose reintroduction	TMP/SMX; AMC+MIN; AMC (7 mo)	S
15	63/M	Ischemic cardiomyopathy s/p heart transplant	<i>N. cyriacigeorgica</i>	Pulmonary	Atovaquone	Serum creatinine elevation	Tolerated regular dose reintroduction	TMP/SMX; LZD; MEM; ETP+MIN; ETP+MXF;ETP (8 mo)	S
16	59/F	Primary ciliary dyskinesia s/p lung transplant	<i>N. nova</i>	Cerebral	Atovaquone	Allergy: desquamating rash	Passed desensitization	IPM+LZD; MEM+LZD+TMP/SMX; MEM+TMP/SMX (3 mo) IPM; TMP/SMX (12 mo)	S
17	57/M	HIV/AIDS	<i>N. farcinica</i>	Pulmonary	None	Allergy: unclear	Passed graded challenge		S
18	56/M	B cell acute lymphoblastic leukemia s/p allogeneic HCT	<i>N. asiatica</i>	Pulmonary	Atovaquone	Cytopenia	Tolerated regular dose reintroduction	TMP/SMX (12 mo)	S
19	61/F	Interstitial lung disease s/p lung transplant	<i>Nocardia spp</i>	Pulmonary	Atovaquone	Allergy: unclear	Passed desensitization	TMP/SMX; TMP/SMX+MEM; TMP/SMX (6 mo)	S
20	85/M	Non-small-cell lung carcinoma with brain metastases on high-dose systemic steroids	<i>N. cyriacigeorgica</i>	Pulmonary	None	None	Tolerated regular dose reintroduction	IPM+TMP/SMX (1 wk)	D
21	30/F	Relapsed Hodgkin lymphoma status post allogeneic HCT	<i>N. nova</i>	Pulmonary	Atovaquone	Serum creatinine elevation	Tolerated regular dose reintroduction	TMP/SMX+MEM; TMP/SMX; MEM; TMP/SMX (12 mo)	S
22	44/M	Chronic myelogenous leukemia status post allogeneic HSCT	<i>N. nova</i>	Pulmonary	Atovaquone	Serum creatinine elevation	Tolerated regular dose reintroduction	TMP/SMX+IPM; TMP/SMX+CRO (1 wk)	D
23	69/F	Stage IVB follicular lymphoma on high-dose systemic steroids	<i>N. farcinica</i>	Disseminated (lung and brain)	Atovaquone	Allergy, drug-induced hypersensitivity syndrome	Did not test or challenge	MEM; IPM+LZD+MXF; MEM+MXF; MEM (10 mo)	D
24	73/F	COPD on high-dose systemic steroids	<i>N. cyriacigeorgica</i>	Pulmonary	Atovaquone	Allergy, rash	Passed desensitization	CRO+TMP/SMX; TMP/SMX (Unknown)	S
25	53/F	Transposition of the great arteries, post heart transplant	<i>N. farcinica</i>	Pulmonary	Atovaquone	Cytopenia	Did not test or challenge	MXF+LZD+IPM; MXF+IPM; MXF (12 mo)	S

*AMC, amoxicillin/clavulanate; AMK, amikacin; CDN, cefdinir; CIP, ciprofloxacin; CLR, clarithromycin; COPD, chronic obstructive pulmonary disease; CRO, ceftriaxone; D, died; DOX, doxycycline; ETP, ertapenem; GI, gastrointestinal; HCT, hematopoietic stem cell transplantation; inh, inhaled; IPM, imipenem; LAM, lymphangioliomyomatosis; LZD, linezolid; MEM, meropenem; MIN, minocycline; MXF, moxifloxacin; S, survived.

†Failed TMP/SMX introduction due to rash or GI symptoms that were not severe.

‡Developed intractable nausea and vomiting after TMP/SMX was introduced.