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Systematic review

Trimethoprim-sulfamethoxazole significantly reduces the risk of nocardiosis in solid organ transplant recipients: systematic review and individual patient data meta-analysis

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ABSTRACT

Background: Whether trimethoprim-sulfamethoxazole (TMP-SMX) prophylaxis prevents nocardiosis in solid organ transplant (SOT) recipients is controversial.
Objectives: To assess the effect of TMP-SMX in the prevention of nocardiosis after SOT, its dose-response relationship, its effect on preventing disseminated nocardiosis, and the risk of TMP-SMX resistance in case of breakthrough infection.
Methods: A systematic review and individual patient data meta-analysis.
Data sources: MEDLINE, Embase, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, Web of Science Core Collection, and Scopus up to 19 September 2023.
Study eligibility criteria: (a) Risk of nocardiosis between SOT recipients with and without TMP-SMX prophylaxis, or (b) sufficient details to determine the rate of TMP-SMX resistance in breakthrough nocardiosis.
Participants: SOT recipients.
Intervention: TMP-SMX prophylaxis versus no prophylaxis.
Assessment of risk of bias: Risk Of Bias In Non-randomized Studies-of Exposure (ROBINS-E) for comparative studies; dedicated tool for non-comparative studies.
Methods of data synthesis: For our primary outcome (i.e. to determine the effect of TMP-SMX on the risk of nocardiosis), a one-step mixed-effects regression model was used to estimate the association between the outcome and the exposure. Univariate and multivariable unconditional regression models were used to adjust for the potential confounding effects. Certainty of evidence was assessed using Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach.
Results: Individual data from three case-control studies were obtained (260 SOT recipients with nocardiosis and 519 uninfected controls). TMP-SMX prophylaxis was independently associated with a significantly decreased risk of nocardiosis (adjusted OR = 0.3, 95% CI 0.18–0.52, moderate certainty of evidence). Variables independently associated with an increased risk of nocardiosis were older age, current use of corticosteroids, high calcineurin inhibitor concentration, recent acute rejection, lower lymphocyte count, and heart transplant. Breakthrough infections (66/260, 25%) were generally susceptible to TMP-SMX (pooled proportion 98%, 95% CI 92–100).

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Conclusions: In SOT recipients, TMP-SMX prophylaxis likely reduces the risk of nocardiosis. Resistance appears uncommon in case of breakthrough infection. **Matteo Passerini, Clin Microbiol Infect 2023;▪:1**

Introduction

Immunosuppressive therapy required to prevent allograft rejection places solid organ transplant (SOT) recipients at a higher risk of opportunistic infections. Prophylaxis with trimethoprim-sulfamethoxazole (TMP-SMX) is recommended in SOT recipients without contraindications, to prevent *Pneumocystis jirovecii* pneumonia (PJP) [1,2]. Notably, TMP-SMX is also active against other pathogens possibly encountered in SOT recipients, such as *Nocardia* [3]. *Nocardia* species are ubiquitous in the environment and may cause clinical infection in up to 3.5% of SOT recipients [4]. *Nocardia* infection has been associated with increased mortality among SOT recipients, which may exceed 30% in case of dissemination to the central nervous system [5]. Although the effectiveness of TMP-SMX prophylaxis for PJP is well established, there are limited data assessing its role for prevention of nocardiosis. This evidence has been mixed, with some studies indicating a protective effect and others suggesting no effectiveness [4]. The limited sizes of available studies limited their ability to comprehensively determine the effect of TMP-SMX prophylaxis and its dosing on the development of nocardiosis [4], extrapulmonary dissemination, and TMP-SMX resistance in case of breakthrough nocardiosis. We, therefore, performed a systematic review and meta-analysis of individual patient-level data (IPD) to determine the effect of TMP-SMX prophylaxis in the prevention of nocardiosis in SOT recipients. Moreover, we assessed the dose-response relationship of TMP-SMX, its effectiveness in preventing dissemination, and the proportion of TMP-SMX resistance in case of breakthrough nocardiosis.

Methods

Data sources and search strategies

A comprehensive search of several databases was performed on 15 August 2022 and updated on 10 August 2023. The search was re-run on 19 September 2023 with no language restrictions. Animal studies were excluded. No date limits were applied to the search strategy. Databases searched were Ovid MEDLINE(R) 1946 to Present and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily, Ovid Embase (1974+), Ovid Cochrane Central Register of Controlled Trials (1991+), Ovid Cochrane Database of Systematic Reviews (2005+), Web of Science Core Collection via Clarivate Analytics (1975+), and Scopus via Elsevier (1788+).

The search strategies were designed and conducted by a medical librarian with input from the study investigators. Controlled vocabulary supplemented with keywords was used. The actual search strategy is available in Table S1. The protocol of this systematic review was prospectively registered in PROSPERO (No. CRD42022353078). We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines for systematic review. We received a waiver for Institutional review board (IRB) from our Ethical Committee to perform the systematic review; moreover, we established a Data Share Agreement according to the local protocol for obtaining the de-identifiable IPD.

Study selection, data extraction, and quality assessment

We included individual studies which either (a) compared the risk of *Nocardia* infection between SOT recipients with and without TMP-SMX prophylaxis, or (b) provided sufficient details to determine the rate of TMP-SMX resistance in breakthrough *Nocardia* infection (in this case also the total number of SOT should be provided). Two reviewers (MP and ZY) screened all titles and abstracts independently. Studies included at this level by either reviewer were included for full-text screening by the same reviewer pair. Extracted data included study design, year, time of patient inclusion, country, transplanted organ, definition of Nocardia diagnosis, number of patients with Nocardia, number of patients on TMP-SMX, number of breakthrough infections, TMP-SMX susceptibility data, and information on TMP-SMX dosage. Risk of bias assessment was performed using the ROBINS-E tool for comparative observational studies [6], and a dedicated tool for single-arm non-comparative studies [7]. Potential disagreements were resolved through discussion.

Type of outcome measure

The primary outcome was to assess the effect of TMP-SMX prophylaxis on the risk of nocardiosis in SOT recipients. The secondary outcomes were to assess the dose-response relationship of TMP-SMX in *Nocardia* prevention, the effect of TMP-SMX on the risk of disseminated nocardiosis, and the proportion of breakthrough infections that are resistant to TMP-SMX. Last, we compared the risk of death at 6 months between infected patients and control SOT recipients.

Study-level meta-analysis

We first conducted a study-level meta-analysis (aggregate data meta-analysis). We used the restricted maximum likelihood random-effects model because heterogeneity of patients' characteristics and study settings was anticipated. For our primary outcome, we first used raw numbers of cases and controls to determine OR and associated 95% CIs. A sensitivity analysis was also conducted, using matched unadjusted ORs and 95% CIs (determined using conditional logistic regression for matched case-control studies). To determine the proportion of breakthrough *Nocardia* infections caused by a TMP-SMX-resistant isolate, results of the non-comparative series were pooled using the Freedman-Turkey transformation [8].

IPD meta-analysis

Authors of all eligible comparative studies were contacted through e-mail address to request individual-level data. At least three attempts to contact study authors were made, before possible study exclusion. To allow comparison of data from different studies, we used the following definitions: (a) disseminated *Nocardia* infection: infection in at least two non-contiguous organs or any central nervous system infection; (b) high calcineurin inhibitors (CNI) trough concentration: >10 ng/mL for tacrolimus and >300 ng/mL for cyclosporine. Data for continuous variables are described as mean or median (and standard deviation or interquartile range,

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respectively) and categorical variables as frequencies and percentages. Independent t-test, Mann-Whitney, and Chi-square test were used to compare cases and controls, as appropriate. A $p < 0.05$ was considered statistically significant. For our primary outcome, a one-step mixed-effects regression model was first used to estimate the association between the outcome and the exposure. Univariate and multivariable unconditional regression models were used to adjust for the potential confounding effects of several clinically important variables: recipient's age, sex, diabetes status at time of diagnosis (TOD) of nocardiosis, transplanted organ(s), type of induction, high CNI trough level at TOD, current use of azathioprine or mycophenolate mofetil, current use of steroids, acute rejection (AR) in 6 months before diagnosis of nocardiosis, cytomegalovirus (CMV) infection (defined as CMV viral replication with or without symptoms [9]) in 6 months before diagnosis of nocardiosis, and the last measurement of lymphocyte count prior the onset of symptoms of nocardiosis. *A priori* planned sensitivity analyses were conducted to test the robustness of the results, including (a) a multivariable mixed-effects unconditional regression model adjusting for the same variables of the full model except those with a high amount of missing data (i.e. type of induction and lymphocytes count), and (b) a two-step approach in which estimates of individual studies were derived first, and then pooled together after a restricted maximum likelihood random-effects model. We used the I^2 statistic to measure heterogeneity across the studies, with I^2 >50% considered substantial. A priori planned subgroup analyses were performed to explore the association between *Nocardia* infection and TMP-SMX dosage (<1600 mg and <2400 mg of sulfamethoxazole weekly versus the relative higher dosage) adjusting for estimated glomerular filtration rate at TOD. Data were analysed using R version 4.3.0 [10]. Certainty of evidence (CoE) was assessed using the GRADE approach [11].

Results

Systematic review

A total of 13 studies were included in the systematic review (Fig. 1), including five observational comparative studies satisfying the criteria for comparison of the risk of Nocardia infection between SOT recipients with and without TMP-SMX prophylaxis [4,12–15], and eight non-comparative studies. Eleven observational studies (including 3/5 above mentioned) had sufficient details to calculate the prevalence of TMP-SMX resistance in breakthrough Nocardia infections [12–14,16–23]. Characteristics of included studies are detailed in Tables S2a–S2c.

Assessment of risk of bias

The methodological quality of the included studies is summarized in Tables S3 and S4. Regarding the five comparative studies, three were judged to be at low risk of bias [4,12,14], one left some concerns because it only included lung transplant patients [13], and the remaining study was considered to be at very high risk of bias [15] because patients with and without nocardiosis were not matched. Two of three studies included in the IPD meta-analysis were those considered to be at low risk of bias, and the remaining one showed some concerns [12–14]. Regarding the eight non-comparative studies, six were considered low risk [17–20,22,23], one unclear risk [16], and one high risk [21].

Study-level meta-analysis

A study-level meta-analysis of the five comparative studies detected a significant protective effect of TMP-SMX on the risk of

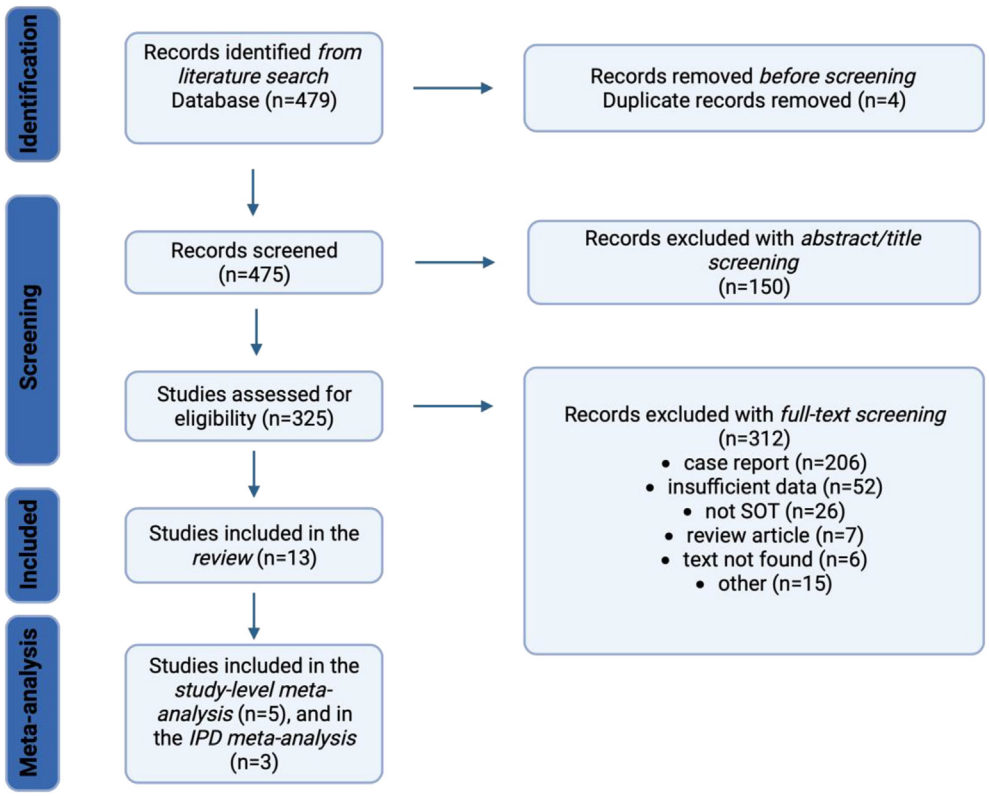

Fig. 1. PRISMA flow diagram of studies included in the meta-analysis of study-level data and in the meta-analysis of individual participant data. SOT, solid organ transplant; IPD, individual patient data.

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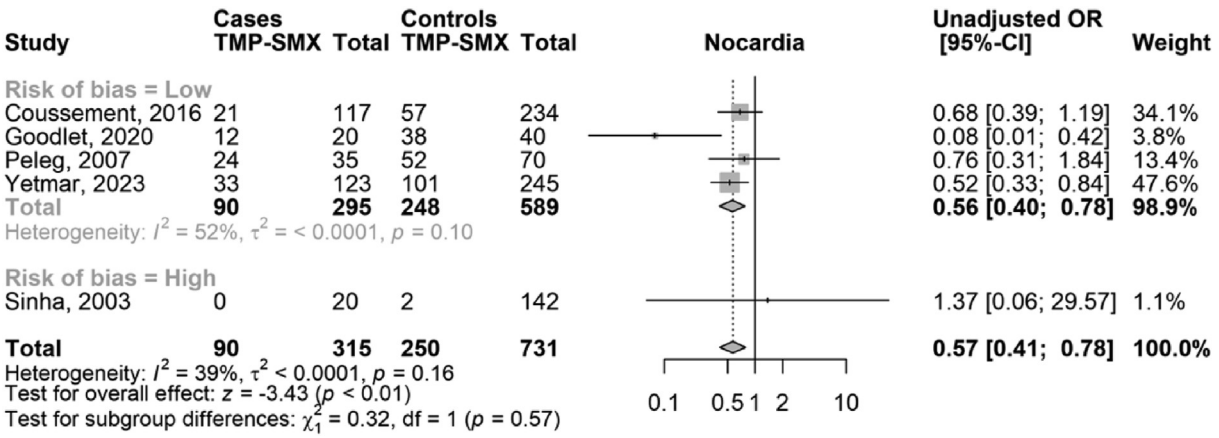

Fig. 2. Study-level data meta-analysis evaluating the effect of TMP-SMX on the risk of nocardiosis among SOT recipients (comparison of SOT recipients with nocardiosis [cases] and matched control SOT recipients who did not develop nocardiosis [controls]). SOT, solid organ transplant; TMP-SMX, trimethoprim-sulfamethoxazole.

Nocardia infection (unmatched unadjusted OR 0.57, 95% CI 0.41–0.78; Fig. 2). The significant effect of TMP-SMX was confirmed after excluding the only study considered to be at high risk of bias (OR 0.56, 95% CI 0.4–0.78), as well as in the planned sensitivity analysis taking into account matching of cases and controls (unadjusted OR 0.38, 95% CI 0.25–0.59, Fig. S1). Among breakthrough infections, the pooled proportion of *Nocardia* isolates susceptible to TMP-SMX was 98% (95% CI 92–100; Fig. 3).

IPD meta-analysis

Individual data were obtained for three of the five comparative studies [12–14], representing 86% of all published patients (779/906). All three studies were 1:2 matched case-control studies. Overall, 260 SOT recipients with nocardiosis were compared with 519 uninfected control SOT recipients. Among case patients, the mean age was 57 ± 12 years, 25% were receiving TMP-SMX when nocardiosis occurred (66/260), and the most common transplant types were kidney (47%), lung (19%), and heart (18%). Microbiologically, *N. farcinica*, *N. nova complex,* and *N. cyriacigeorgica* were the most frequently identified *Nocardia* species, causing 28.4% (74/260), 23.5% (61/260), and 11.2% (29/260) of the episodes of nocardiosis, respectively (Table S5).

Effect of TMP-SMX and other factors on the risk of nocardiosis, and TMP-SMX dose-response relationship

In univariate analysis, SOT recipients who developed nocardiosis were significantly less likely to be on TMP-SMX prophylaxis than the counterparts who did not develop nocardiosis (25% [66/260] versus 38% [196/518], p < 0.001). In contrast, cases were significantly more often on steroids and had diabetes, high CNI trough concentration, and a recent AR episode or CMV infection. Moreover, patients with nocardiosis were older and had significantly lower lymphocyte counts than did the controls (Tables 1 and 2).

Multivariable unconditional logistic regression was performed, using all variables included in the univariate analysis (Table 2). This multivariable analysis confirmed that current use of TMP-SMX was significantly associated with a decreased risk of nocardiosis, after adjustment for potential confounders (unmatched adjusted OR: 0.3, 95% CI: 0.18–0.52, p < 0.0001, Table 2). In contrast, factors independently associated with a significantly higher risk of nocardiosis were older age, lower lymphocyte count, current use of steroid, AR in the prior 6 months, high CNI trough level, and heart transplant. The protective effect of TMP-SMX was confirmed in the two planned sensitivity analyses (Tables S6 and S7).

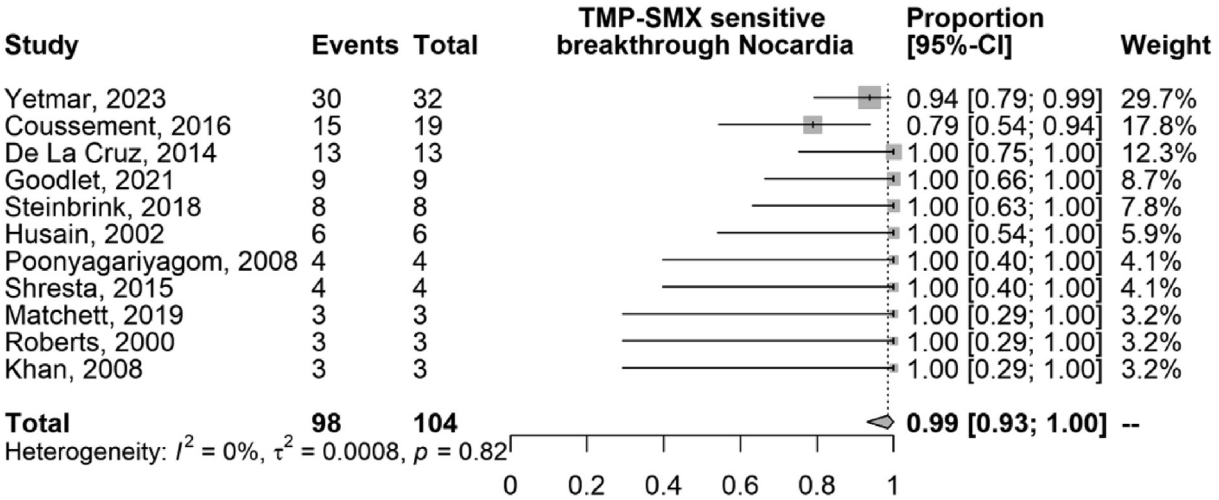

Fig. 3. Proportion of patients with breakthrough *Nocardia* infection caused by a TMP-SMX-susceptible isolate. TMP-SMX, trimethoprim-sulfamethoxazole.

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Table 1
Characteristics of cases and control SOT recipients up to the diagnosis of nocardiosis

	SOT recipients with nocardiosis (cases) (n = 260)	Matched control SOT recipients (n = 519)
Studies, *n* (%)		
Coussement et al., 2016 [12]	117 (45)	234 (45)
Yetmar et al., 2023 [14]	123 (47)	245 (47)
Goodlet et al., 2020 [13]	20 (7.7)	40 (7.7)
Age at TOD years, mean (SD)	57.4 (12.3)	53.6 (13.3)
Male, *n* (%)	166 (64)	334 (64)
Organ(s) transplanted, *n* (%)		
Kidney	123 (47)	244 (47)
Lung	49 (19)	100 (19)
Heart	46 (18)	94 (18)
Liver	15 (5.8)	30 (5.8)
Kidney + pancreas	14 (5.4)	33 (6.4)
Kidney + liver	4 (1.5)	6 (1.2)
Pancreas	4 (1.5)	6 (1.2)
Heart + kidney	2 (0.8)	4 (0.8)
Heart + lung	2 (0.8)	0 (0)
Combined (not specified)	1 (0.4)	2 (0.4)
Site(s) of *Nocardia* infection, *n* (%) (*n* = 260)		
Lung and/or pleural	227 (87.3)	—
Skin and/or soft tissue	68 (26.1)	—
Central nervous system	49 (18.8)	—
Blood	24 (9.2)	—
Bone and/or joint	6 (2.3)	—
Other	8 (3.1)	—
Disseminated infection	92 (35.4)	
Diabetes at TOD, *n* (%), *n* = 778	107 (41)	171 (33)
Lymphocyte count at TOD, ×1000/mm^3, median (IQR), *n* = 734	0.52 (0.29–0.90)	1.10 (0.67–1.60)
Current use of corticosteroids at TOD, *n* (%)	249 (96)	429 (83)
Type of inductions, *n* (%), *n* = 717		
ATG	131 (51)	232 (50)
Anti-CD25	64 (25)	145 (31)
Alemtuzumab	29 (11)	53 (11)
OKT3	1 (0.4)	3 (0.7)
Other	10 (3.9)	9 (2.0)
Current use of AZA or MMF, *n* (%), *n* = 778	223 (86)	447 (86)
High CNI at TOD, *n* (%), *n* = 777	89 (34)	125 (24)
Acute rejection in prior 6 mo, *n* (%)	55 (21)	44 (8.5)
CMV infection in prior 6 mo, *n* (%), *n* = 778	34 (13)	37 (7.1)
Current use of TMP-SMX, *n* (%), *n* = 778	66 (25)	196 (38)
Median time from transplant to diagnosis of nocardiosis, mo (IQR)[a]	15.7 (6.1–47.4)	—
Mean weekly dose of sulfamethoxazole, mg (SD), *n* = 262[b]	1864 (894)	2177 (1047)

ATG, anti-thymocyte globulin; AZA, azathioprine; CMV, cytomegalovirus; CNI, calcineurin inhibitor; IQR, interquartile range 1–3; MMF, mycophenolate mofetil; OKT3, muromonab-CD3; SD, standard deviation; SOT, solid organ transplant; TMP-SMX, trimethoprim-sulfamethoxazole; TOD, time of diagnosis.

[a] The median time from transplant to diagnosis of nocardiosis was 17.5 mo (IQR: 6.9–47.4), 9.8 (6–17.8), and 13.3 (5.1–49) for Coussement et al., 2016 [12], Goodlet et al., 2020 [13], and Yetmar et al., 2023 [14], respectively.

[b] Among case patients, the mean weekly dose of sulfamethoxazole was 1819 mg (SD: 668), 1400 mg (644), and 2061 mg (1040) for Coussement et al., 2016 [12], Goodlet et al., 2020 [13], and Yetmar et al., 2023 [14], respectively. Among controls, the mean weekly dose of sulfamethoxazole was 2161 mg (958), 1958 mg (587), and 2271 mg (1216) for Coussement et al., 2016 [12], Goodlet et al., 2020 [13], and Yetmar et al., 2023 [14], respectively.

We did not identify any significant effect of TMP-SMX dosing in the two planned subgroup analyses and in an a posteriori subgroup analysis of patients with heart and/or lung transplant, considered to be at higher risk of nocardiosis (Tables S8, S9, and S9a).

Outcomes of SOT recipients with and without nocardiosis

Six-month all-cause mortality was significantly higher among SOT recipients with nocardiosis than among matched control SOT recipients (11.5% [30/260] versus 1.3% [7/519], p < 0.0001). Among those with nocardiosis, the mortality was not statistically different among those receiving and not receiving TMP-SMX prophylaxis when nocardiosis occurred (10.6% [7/66] versus 11.8% [23/194], p 0.07).

Effect of TMP-SMX and other factors on the risk of presenting with disseminated infection among SOT recipients with nocardiosis

Ninety-two (35.4%) infected patients presented with disseminated nocardiosis. Dissemination was significantly associated with identification of *N. farcinica*, which was isolated in 43.5% of disseminated infections (40/92) versus 20.3% of non-disseminated infections (34/168, p < 0.001). Among 260 SOT recipients with nocardiosis, dissemination was more frequent in patients without prophylaxis (78/194 [40.2%] versus 14/66 [21.1%] patients on prophylaxis). However, in multivariable unconditional analysis, there was no significant effect of TMP-SMX on the risk of dissemination (adjusted OR: 0.61, 95% CI: 0.26–1.46, p 0.27); the only identified risk factor for dissemination was alemtuzumab induction (Table S10). Six-month mortality rate did not significantly differ between SOT recipients with and without disseminated nocardiosis (14/92 [15.2%] versus 16/168 [9.5%], p 0.17).

Effect of TMP-SMX on the risk of in vitro resistance to TMP-SMX among SOT recipients with nocardiosis

Among 252 of 260 (96.9%) cases of nocardiosis with susceptibility testing results available, 23 (9.1%) had *in vitro* resistance to TMP-SMX. Among 66 episodes of breakthrough nocardiosis, 61 had susceptibility testing results available, of whom 6 of 61 (9.8%) were

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Table 2
Factors associated with risk of nocardiosis in SOT recipients (univariate and multivariable analysis of individual participant data)

Variable	Level	Univariate		Multivariable ($n = 635$)	
		OR (95% CI)	p	OR (95% CI)	p
Age at TOD, y	Per 1 y increase in age	1.02 (1.01–1.04)	<0.001	1.04 (1.02–1.06)	<0.0001
Sex	Male	0.98 (0.72–1.33)	0.889	0.97 (0.63–1.5)	0.889
Diabetes at TOD	Diabetes	1.42 (1.04–1.93)	<0.05	1.01 (0.64–1.6)	0.963
Organ(s)	Kidney	1 (Reference)	—	1 (Reference)	—
	Lung	0.97 (0.65–1.46)	0.891	0.66 (0.31–1.4)	0.283
	Heart	0.97 (0.64–1.47)	0.888	0.49 (0.27–0.89)	<0.05
	Liver	0.99 (0.51–1.91)	0.981	2.05 (0.54–7.79)	0.294
	Kidney + pancreas	0.84 (0.43–1.63)	0.609	0.99 (0.4–2.47)	0.987
	Kidney + liver	1.32 (0.37–4.77)	0.67	0.85 (0.18–3.98)	0.832
	Pancreas	1.32 (0.37–4.77)	0.67	0.38 (0.08–1.82)	0.227
	Heart + kidney	0.99 (0.18–5.49)	0.993	0.73 (0.08–6.57)	0.782
	Heart + lung	Inf (0–Inf)	1	Inf (0–Inf)	0.964
	Combined (not specified)	0.99 (0.09–11)	0.995	0.29 (0.02–3.9)	0.352
Type of induction	ATG	1 (Reference)	—	1 (Reference)	—
	Anti-CD25	0.78 (0.54–1.12)	0.185	0.83 (0.49–1.43)	0.506
	Alemtuzumab	0.97 (0.59–1.6)	0.902	1 (0.5–2.02)	0.996
	OKT3	0.59 (0.06–5.73)	0.65	0.61 (0.05–8.35)	0.714
	Other	1.97 (0.78–4.97)	0.152	3.3 (0.98–11.1)	0.054
High CNI at TOD	Yes	4.45 (3.19–6.22)	<0.0001	5.34 (3.3–8.64)	<0.0001
Current AZA or MMF	Yes	0.96 (0.62–1.47)	0.842	0.92 (0.48–1.77)	0.809
Current steroids	Yes	4.75 (2.49–9.05)	<0.0001	6.04 (2.39–15.3)	<0.001
Acute rejection in prior 6 mo	Yes	2.91 (1.9–4.47)	<0.0001	1.94 (1.08–3.51)	<0.05
CMV infection within 6 mo	Yes	1.96 (1.2–3.2)	<0.01	1.91 (0.98–3.73)	0.059
Current TMP-SMX	Yes	0.56 (0.4–0.78)	<0.001	0.3 (0.18–0.52)	<0.0001
Lymphocytes count at TOD ($\times 1000/mm^3$)	Per $1000/m^3$ decrease in lymphocytes	3.85 (2.78–5.26)	<0.0001	3.70 (2.56–5.56)	<0.0001

ATG, anti-thymocyte globulin; AZA, azathioprine; CMV, cytomegalovirus; CNI, calcineurin inhibitor; IQR, interquartile range 1–3; MMF, mycophenolate mofetil; OKT3, muromonab-CD3; SD, standard deviation; SOT, solid organ transplant; TMP-SMX, trimethoprim-sulfamethoxazole; TOD, time of diagnosis.

caused by an isolate found to be resistant to TMP-SMX. Three of these six patients were receiving <2400 mg weekly of sulfamethoxazole, despite estimated glomerular filtration rate >30 mL/minutes. There was no significant difference in the proportion of isolates resistant to TMP-SMX between SOT recipients receiving and not receiving TMP-SMX prophylaxis (9.1% [6/66] vs. 8.8% [17/194], p 0.93).

CoE

The CoE for the effect of TMP-SMX on the risk of post-transplant nocardiosis was assessed for the estimate derived from the IPD meta-analysis. Starting from low certainty because the studies were non-randomized, the quality of evidence was rated up to moderate certainty because a large effect (OR < 0.5) was identified [24]. Moreover, adjustment for potential confounders was done (Fig. S2).

Discussion

This IPD meta-analysis including over 700 SOT recipients found TMP-SMX prophylaxis to be associated with a significantly reduced risk of nocardiosis after adjustment for potential confounders. However, we did not detect a significant dosage of TMP-SMX considered protective, and TMP-SMX had uncertain effects on preventing disseminated nocardiosis. Most breakthrough episodes of nocardiosis were caused by isolates susceptible to TMP-SMX, ameliorating potential concerns regarding resistance development on prophylaxis. Our study additionally affirmed other risk factors previously associated with nocardiosis in SOT, mainly related to increased immunosuppression.

The incidence of nocardiosis in SOT recipients is variable depending on organ type and region, as low as <1% in some studies [25], which makes assessment and identification of risk factors difficult. Thus, previous studies exploring an association between TMP-SMX prophylaxis and nocardiosis showed conflicting results. One multicentre European study [12] and one US single-site [4] did not show a protective effect of TMP-SMX. Conversely, other US studies [13,14] detected a significant protective effect. There are several potential reasons for this discrepancy. First, in some studies, the number of included subjects did not permit adjustment for important confounders. Second, the heterogenous dosages of TMP-SMX could influence the effect of prophylaxis; in our systematic review, we found nine different regimens of TMP-SMX (Table S2a). Third, some studies included just lung transplant patients [13] for whom TMP-SMX prophylaxis is recommended for longer durations [2] and whose risk of nocardiosis acquisition may be higher [25]. In contrast, in studies including all types of SOT recipients [12,14], only a minority of patients were on TMP-SMX prophylaxis at time of evaluation. Fourth, the geographical distribution of the patients could influence the baseline risk of nocardiosis making it easier to detect a difference in the effect of TMP-SMX prophylaxis for some studies; thus, the two papers showing effectiveness of TMP-SMX prophylaxis [13,14] included patients in the Southwest United States, where arid and windy conditions could enhance *Nocardia* aerosolization [26,27]. However, consistent evidence of a higher incidence of nocardiosis in such areas is not available at the moment. In our IPD meta-analysis, the merged number of subjects was more than double of the largest study, and we had the opportunity to adjust for >10 potential confounders in a multivariable analysis.

When a prior allergy or adverse reaction to TMP-SMX is reported, a switch to alternative prophylaxis for PJP such as dapsone, atovaquone, or pentamidine is considered [2]. However, these drugs lack TMP-SMX's broader spectrum of activity, and therefore, potentially increase the risk of nocardiosis, and other post-transplant infections. Given that we found TMP-SMX to be associated with a significantly decreased risk of nocardiosis, and that SOT recipients with nocardiosis had a significantly increased risk of death as compared with uninfected SOT recipients (even if 6-month mortality may be a suboptimal outcome for *Nocardia* infections), we believe that efforts should be made to collect a detailed history to distinguish true allergic reactions and

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potentially offer eligible patients TMP-SMX desensitization, which was showed to be effective and safe in patients without HIV [28]. In addition, most immunocompromised patients who receive alternative PJP prophylaxis tolerate high-dose, therapeutic TMP-SMX [29].

Our primary findings of the protective effect of TMP-SMX prophylaxis was also confirmed in an a posteriori subgroup analysis looking at the effect of prophylaxis in heart and/or lung transplant recipients (which are generally considered to be at high risk of nocardiosis), as well as in other SOT recipients (Tables S9a and S9b). In contrast, TMP-SMX had uncertain effects on preventing disseminated nocardiosis specifically. Our ability to answer this research question was however limited by several factors including the relatively low number of patients with disseminated infection, and there was imprecision as illustrated by the wide confidence interval (adjusted OR: 0.61, 95% CI: 0.26−1.46), which was consistent with either strong protection against dissemination or no effect. Besides, we found a significant association between *N. farcinica* and disseminated nocardiosis, which has several clinical implications. For instance, because *N. farcinica* is both generally resistant to ceftriaxone and associated with dissemination of infection (including to the central nervous system), ceftriaxone should be used with caution in patients with possible or confirmed central nervous system (CNS) involvement [30].

The principal objective of this IPD meta-analysis was to assess the association of TMP-SMX prophylaxis with nocardiosis. However, because the three matched case-control studies included in our IPD meta-analysis explored the possible risk factors for *Nocardia*, we were also able to detect other significant associations. These were mainly indicators of the immune status of the subjects, which can be impaired by older age, recent AR, or concomitant immunosuppressive medications (corticosteroid use and high concentrations of CNI). Interestingly, we also found that lymphocytes count is negatively correlated with nocardiosis. Our findings support an association between lymphocytes count and opportunistic infections among SOT recipients, as seen for *Pneumocystis jiroveci* [31]. We hypothesize that TMP-SMX prophylaxis could be beneficial to prevent opportunistic infections in SOT recipients with sustained lymphopenia. However, this decision should also be based on the possible risk of pancytopenia because of TMP-SMX itself, even if this is limited with the prophylactic dosage.

Although our study indicates that TMP-SMX prophylaxis significantly protects against nocardiosis, it is also important to acknowledge that this effect is only partial and current TMP-SMX prophylaxis should not exclude nocardiosis as a potential diagnosis in patients presenting with signs and symptoms of an opportunistic infection. In fact, in our IPD meta-analysis, 66 of 260 (25.4%) of nocardiosis occurred while on TMP-SMX. The explanation for this data is challenging. It does not seem to be correlated with *Nocardia* species resistance to TMP-SMX. A possible explanation could be the dosage of TMP-SMX, given that half of these 66 were receiving <2400 mg of weekly TMP-SMX. However, the remaining half of the breakthrough infections were receiving a higher dose, and no dose threshold for effectiveness was able to be determined in this analysis. Another hypothesis is the high bacterial burden of *Nocardia* that can overcome the prophylactic level of TMP-SMX. Regrettably, we did not have data on environmental exposure, which should be examined in future studies on *Nocardia* infection.

We found that over 90% of breakthrough infections remained susceptible to TMP-SMX, with no significant difference in resistance compared with patients not on prophylaxis. Therefore, the use of TMP-SMX as a treatment option even in breakthrough infection is a valid option and current prophylaxis should not discourage its use.

Our study presents some limitations. First, some variables potentially associated with nocardiosis such as length of stay in intensive care unit [12], use of CD20-depleting therapy [32], and environmental exposure were not available in all studies, and we were, therefore, unable to adjust for their potential impact. Second, we were unable to follow a conditional approach to determine the effect of TMP-SMX on the risk of nocardiosis, because matching criteria varied between the three included studies. Third, TMP-SMX safety data were not available, despite their importance for individualized management. Fourth, our findings are based on individual data collected through chart review of retrospective data; therefore, the findings are exposed to the limitations of retrospective observational data. For example, the fact that a patient had an active prescription for TMP-SMX prophylaxis does not mean that the patient was actually receiving TMP-SMX, and non-adherence may have been an issue. Fifth, we obtained IPD for only three of five eligible studies, and this may have biased our findings. However, the two remaining studies represented only 14% of all published patients and were typically older and/or at higher risk of bias than the three included ones. Also, all five eligible studies were included in our study-level data meta-analysis which confirmed the protective effect of TMP-SMX.

In conclusion, TMP-SMX prophylaxis is associated with reduced odds of nocardiosis in SOT recipients based on observational data. Moreover, most isolates causing infections breaking through prophylaxis remain susceptible to TMP-SMX, supporting its role in the initial management of transplant recipients with nocardiosis. Our findings support the selection of TMP-SMX as the preferred agent for prophylaxis against infections after Solid Organ Transplantation (SOT), particularly in the presence of risk factors for nocardiosis.

Author contributions

The authors confirm contribution to the paper as follows: study conception and design: MP, TN, JC, AG, MM, and MHM; data acquisition: MP, ZAY, JC, KJG, and DL; data analysis: MP, TN, AG, and MHM; interpretation of results: MP, ZAY, JC, and MHM; draft manuscript preparation: MP, TN, ZAY, JC, KJG, DL, AG, MM, ZT, and MHM. All authors reviewed the results and approved the final version of the manuscript.

Transparency declaration

The authors declare that they have no conflicts of interest.
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Data availability

Data are available upon request.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cmi.2023.10.008.

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