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MAJOR ARTICLE

Intermittent Versus Daily Trimethoprim/Sulfamethoxazole Regimens for *Pneumocystis* Pneumonia Prophylaxis: A Systematic Review and Meta-analysis

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Background. In immunocompromised individuals, trimethoprim/sulfamethoxazole (TMP/SMX) for *Pneumocystis* pneumonia (PCP) prophylaxis has adverse events, and the optimal dosage is unclear. The objective of this study was to assess efficacy and safety of intermittent versus daily TMP/SMX for PCP prophylaxis.

Methods. This systematic review included randomized controlled trials (RCTs) indexed in the Cochrane Central Register of Controlled Trials, PubMed, Ichushi, or Embase databases, published from database inception to September 2023. The inclusion criteria were adults taking intermittent or daily TMP/SMX for PCP prophylaxis. Risk of bias was assessed using the Cochrane risk-of-bias tool. The primary outcomes were PCP incidence, PCP-related mortality, and adverse events requiring temporary or permanent TMP/SMX discontinuation.

Results. Four RCTs (N = 2808 patients) were included. PCP incidence did not differ significantly between the intermittent and daily regimen groups (risk ratio [RR], 1.17 [95% confidence interval {CI}, .89–1.53]; certainty: very low). There was no PCP-related mortality in the 3 RCTs reporting its outcome. Compared with the daily regimen group, the intermittent regimen group experienced significantly fewer adverse events requiring temporary or permanent TMP/SMX discontinuation (RR, 0.51 [95% CI, .42–.61]; certainty: low)

Conclusions. This systematic review and meta-analysis suggests that intermittent TMP/SMX regimens for PCP prophylaxis may be more tolerable than daily regimens and may have similar efficacy. Further RCTs are needed to apply this to current practice.

Clinical Trials Registration. PROSPERO (CRD42022359102).

Keywords. daily prophylaxis; intermittent prophylaxis; PCP; *Pneumocystis* pneumonia; trimethoprim/sulfamethoxazole.

Pneumocystis jirovecii is an opportunistic pathogen that causes severe pneumonia, primarily in immunocompromised patients, with mortality rates as high as 10%–20% in patients with human immunodeficiency virus (HIV) infection and 30%–60% in patients without HIV infection [1]. Prophylaxis using trimethoprim/sulfamethoxazole (TMP/SMX) reduces the incidence of *Pneumocystis* pneumonia (PCP) by up to 80%–85% in patients with and without HIV infection [2, 3], and therefore, is recommended as the first-line drug for PCP prevention in various high-risk groups such as people with HIV (PWH), patients with hematological malignancies, hematopoietic stem cell transplant recipients, chimeric antigen receptor T-cell therapy recipients, solid organ transplant recipients, and those using moderate-to-high doses of steroids [4, 5]. However, TMP/SMX is frequently associated with adverse effects such as gastrointestinal symptoms, skin rashes, cytopenia, hyperkalemia, and renal dysfunction [6]. Notably, the risk of most adverse events (AEs) associated with TMP/SMX is dose-dependent [7, 8]; that is, an increase in dose might increase the likelihood and severity of AEs. Therefore, establishing the optimal dose and frequency of TMP/SMX is crucial for balancing the efficacy and safety of TMP/SMX for PCP prophylaxis.

However, determining the optimal dose and frequency of TMP/SMX as PCP prophylaxis is challenging for clinicians treating immunocompromised patients. A single-strength (TMP/SMX 80 mg/400 mg) daily regimen and double-strength regimen (TMP/SMX 160 mg/800 mg) 3 times per week have been shown to have no significant differences in efficacy and cause fewer AEs compared to a double-strength daily regimen [9, 10].

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Using 1 of these 2 regimens is thus preferred to a double-strength daily regimen, although higher doses may be needed if prophylaxis against another pathogen, such as *Toxoplasma*, is required. Although few retrospective studies have reported their efficacy and safety, single-strength regimens 3 times per week, half-strength (TMP/SMX 40 mg/200 mg) daily regimens, and those with even further reduced doses have been used in clinical settings, mainly in older patients, patients with impaired renal function, and those who are intolerant to standard doses [11–13]. Retrospective cohort studies suggest a higher adherence and uptake with nondaily regimens [13, 14]. Furthermore, a 2014 Cochrane meta-analysis found no significant difference in efficacy and safety between daily and intermittent regimens [2]. However, the analysis included a limited sample (n = 205 patients) of adult patients without HIV, which limits the generalizability of the findings. Although these studies suggest the potential benefits of intermittent regimens, current recommendations predominantly favor daily regimens because of the lack of comprehensive evidence regarding the efficacy and safety of intermittent regimens [4]. To date, no large-scale meta-analyses have assessed the comparative efficacy and safety of intermittent regimens.

To address this knowledge gap, we conducted a systematic review and meta-analysis of randomized controlled trials (RCTs) including patients with and without HIV, to assess the efficacy and safety of intermittent TMP/SMX regimens as PCP prophylaxis.

METHODS

We searched 4 databases (Cochrane Central Register of Controlled Trials, PubMed, Ichushi, and Embase) from database inception to September 2023. The search design was prepared with the assistance of a librarian. The full search terms are included in Supplementary Data 1. This systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [15]. The systematic review was registered on PROSPERO on 22 December 2022 (registration number: CRD42022359102).

We included individual, cluster, and quasi-RCTs comparing intermittent and daily administration of TMP/SMX for primary or secondary PCP prophylaxis that reported documented PCP incidence, mortality, adverse effects, and other outcomes in immunocompromised hosts. "Daily regimen" was defined as TMP/SMX prescribed every day, and "intermittent regimen" was defined as those that were not. TMP/SMX dosage was not restricted. Pediatric studies were excluded. Three investigators assessed the full texts of the articles independently, and discrepancies were resolved by discussion.

The following major outcome was extracted from the included studies: documented PCP infection, PCP-related mortality, and AEs requiring temporary or permanent TMP/SMX discontinuation. Other outcomes—namely, any AEs, severe adverse effects requiring treatment discontinuation, skin rashes, leukopenia, anemia, thrombocytopenia, hepatic dysfunction, kidney dysfunction, gastrointestinal dysfunction, and infections other than PCP, including bacterial infections—were also analyzed.

Two investigators independently extracted the following data from the studies: year of publication, country, sample size, study design, and definition of AEs. Data were transferred to a data extraction sheet using Microsoft Excel (version 16.77.1) and Google Sheets (https://www.google.com/intl/ja/sheets/about/). The following data were then checked by the reviewer: study-related information (eg, publication country, study years, single-center, or multicenter study), participants' baseline characteristics (type of population, inclusion and exclusion criteria, and comorbidities), intervention-related information (dose or schedules of TMP/SMX prescription), information regarding the risk of bias (eg, randomization method, allocation concealment, blinding, discontinuation of the study, and incomplete outcome reporting), and information regarding outcomes. We preferentially extracted data using the intention-to-treat method, which included all individuals randomly assigned to study outcomes. For dichotomous outcomes, we recorded the number of participants manifesting the outcome in each group, as well as the number of participants evaluated. For continuous outcomes, we documented values and measures used to represent the data (including means with standard deviations and medians with interquartile ranges). We contacted the authors to request any missing information.

Two investigators assessed the risk of bias independently. Disagreements were resolved through discussion with a third investigator. The risk of bias was assessed using the Cochrane risk-of-bias tool [16] to evaluate 7 domains of bias: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessments, incomplete outcome data, selective reporting, and other bias. We assessed the effect of allocation concealment on the results based on the evidence of a strong association between poor allocation concealment and overestimation of the effect [17] as follows: low risk of bias, adequate allocation concealment; unclear bias, uncertainty regarding allocation concealment; and high risk of bias, inadequate allocation concealment.

The 2 reviewing authors independently recorded the methods of allocation generation, blinding, incomplete outcome data, selective reporting, the unit of randomization (patient or episode), and publication status, in addition to the adequacy of allocation concealment.

We analyzed dichotomous data by calculating the risk ratio (RR) for each study, with the uncertainty in each result presented as 95% confidence intervals (CIs). RRs and CIs were pooled using the Mantel-Haenszel method and random-effects models. Additionally, forest plots and funnel plots were visually inspected to assess heterogeneity and publication bias,

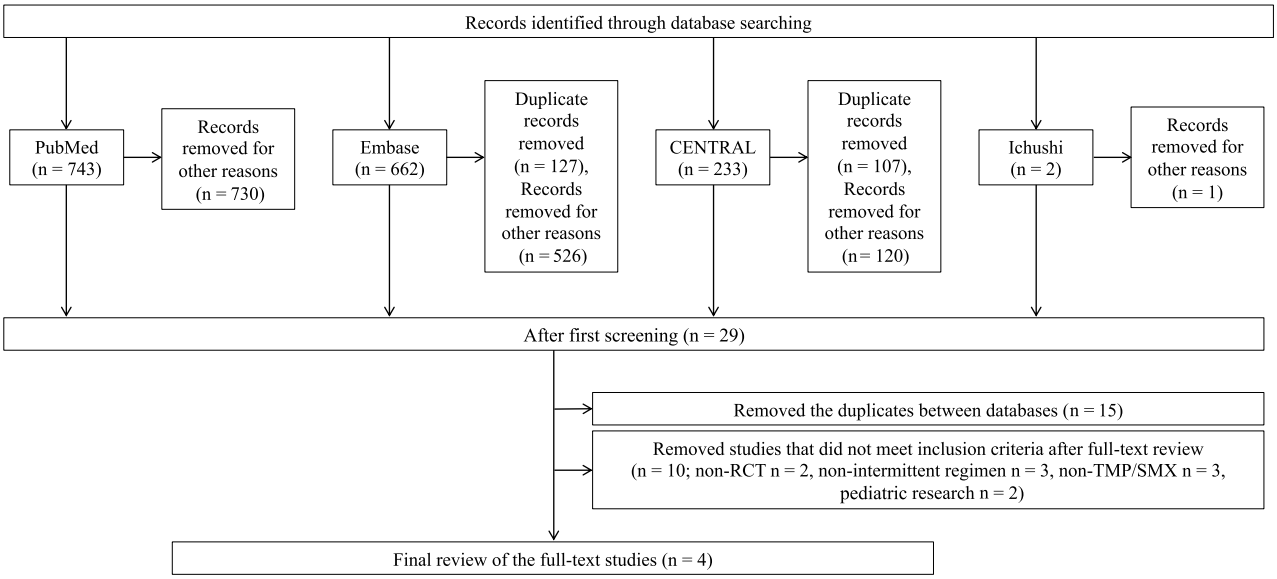

Figure 1. Flow diagram of the study selection process. Of the 1576 articles initially retrieved, 1572 were excluded because they did not meet the inclusion criteria. The 4 remaining articles were included in the final analysis. Abbreviations: CENTRAL, Cochrane Central Register of Controlled Trials; RCT, randomized controlled trial; TMP/SMX, trimethoprim/sulfamethoxazole.

respectively. Data analysis was conducted using Review Manager, version 5.4 (Cochrane Collaboration, 2020, London, United Kingdom).

We used the Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) approach to interpret the findings and rate the certainty of evidence [18]. Specifically, we graded the major outcomes, namely, documented PCP incidence, PCP-related mortality, and AEs requiring temporary or permanent TMP/SMX discontinuation. The certainty of evidence was evaluated using the GRADEpro guideline-development tool software (GRADEpro GDT, Evidence Prime Inc, Hamilton, Ontario, Canada; https://www.gradepro.org/), with study design, risk of bias, directness of outcomes, heterogeneity, precision within results, bias due to publication, estimated effect and dose relationship with response, and confounders as parameters. The GRADE analysis rated the certainty of the evidence as high, moderate, low, or very low. We took the GRADE analysis into account in formulating our conclusions.

RESULTS

The search identified 1640 articles. Following a thorough review, 1570 records were excluded (Figure 1). Four studies met the inclusion criteria and were included in the analyses [10, 19–21]. Study details are summarized in Table 1. Of the included studies, 3 were published in the 1990s [10, 19, 20] and 1 in the 2010s [21]. The total number of patients was 2808, but 1 large study [10] included 2625 patients. TMP/SMX doses and frequency varied between studies, but in all studies, the daily dose was the same in each group within the study, and the total weekly dose was lower in the intermittent TMP/SMX group than in the daily TMP/SMX group.

The risk-of-bias assessment data are shown in Figure 2. Risk of bias was not high in any of the 4 studies. All studies were individual RCTs.

The forest plots of the major outcomes are summarized in Figure 3. As PCP infection events were reported in 1 of the 4 RCTs, the pooled RR was calculated based on 1 large RCT (RR, 1.17 [95% CI, .89–1.53]). Three of the 4 RCTs reported on PCP-related mortality, but all studies reported no events. In all 4 RCTs, those receiving intermittent regimens were less likely to require temporary or permanent TMP/SMX discontinuation due to AEs than those receiving daily regimens (RR, 0.51 [95% CI, .42–.61]; heterogeneity: $\chi^2 = 1.55$, $P = .67$, $I^2 = 0\%$). The funnels plots showed no evidence of publication bias (Supplementary Figure 1). The incidence of other outcomes (any AEs, severe AEs requiring treatment discontinuation, skin rash, leukopenia, anemia, thrombocytopenia, hepatic dysfunction, kidney dysfunction, gastrointestinal dysfunction, and infections other than PCP, including bacterial infections) is shown in Supplementary Figure 2. The GRADE analysis of documented PCP incidence, PCP-related mortality, and AEs requiring temporary or permanent TMP/SMX discontinuation used in the RCTs rated the certainty of the evidence as very low, not available, and low, respectively (Table 2).

DISCUSSION

In this meta-analysis, which included 4 RCTs and a total of 2808 participants, the incidence of PCP in the intermittent

Table 1. Characteristics of the Randomized Controlled Trials Included in the Review

Reference, Publication Year	Country of Publication	Study Design	Patient Characteristics	Intervention	Comparison
Yamamoto et al [21], 2014	Japan	Individual RCT	Systemic autoimmune diseases receiving medium- to high-dose glucocorticoid therapy	TMP/SMX (80 mg/400 mg) once a day, twice per week	TMP/SMX (80 mg/400 mg) once a day, every day
El-Sadr et al [10], 1999	USA	Individual RCT	HIV	TMP/SMX (160 mg/800 mg) once a day, thrice per week	TMP/SMX (160 mg/800 mg) once a day, every day
Bozzette et al [20], 1995	USA	Individual RCT	HIV, CD4 <200 cells/μL	TMP/SMX (80 mg/400 mg) twice a day, thrice per week	TMP/SMX (80 mg/400 mg) twice a day, every day
Olsen et al [19], 1993	USA	Individual RCT	Cardiac transplant recipients	TMP/SMX (160 mg/800 mg) twice a day, thrice per week	TMP/SMX (160 mg/800 mg) twice a day, every day

Abbreviations: HIV, human immunodeficiency virus; RCT, randomized controlled trial; TMP/SMX, trimethoprim/sulfamethoxazole.

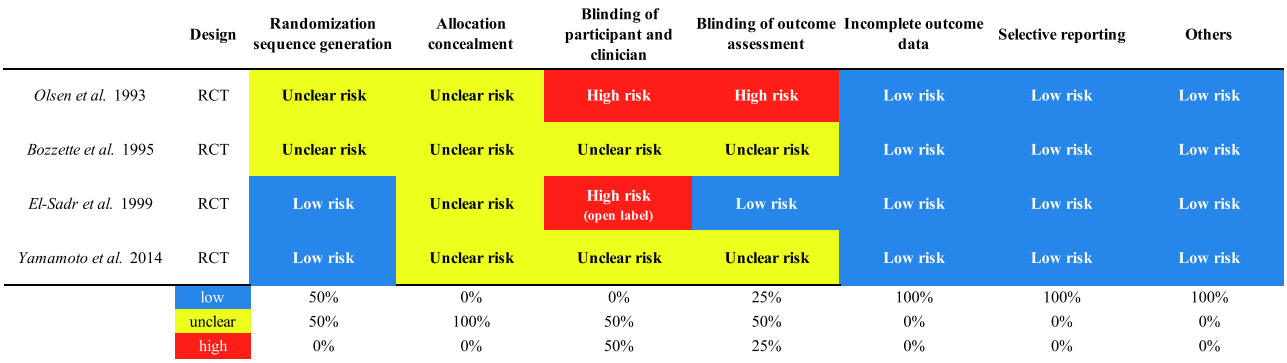

Figure 2. Evaluations of the risk of bias, presented as percentages across all included studies. The risk of bias included randomization sequence, concealment, blinding of participants and clinicians, incomplete outcome data, selective reporting, and others in RCTs. Blue: low risk of bias; yellow: unclear risk of bias; red: high risk of bias. Abbreviation: RCT, randomized controlled trial.

TMP/SMX dosing regimen groups did not differ significantly from that of the daily regimen groups (very low evidence), and no PCP-related deaths were recorded in either the intermittent or daily dosing groups. Fewer adverse effects were observed in the intermittent groups (low evidence) than in the daily dosing groups. Although concerns regarding risk of bias, imprecision, and low certainty persist, the evidence suggests that intermittent dosing regimens reduce the risk of adverse effects without reducing efficacy compared with daily dosing regimens.

Few meta-analyses have addressed the distinctions between intermittent and daily TMP/SMX regimens as PCP prophylaxis. This analysis contributes to the topic by comprehensively aggregating studies. The 2014 Cochrane Review on PCP prophylaxis in adult patients without HIV incorporated a subanalysis comparing daily and intermittent TMP/SMX regimens [2], which included 2 studies that were also included in our review. The 2014 review reported comparable PCP incidence and PCP-related mortality within the regimen but found no difference in the AE rates. Although the authors of the 2014 review concluded that "there is no superiority for daily prophylaxis over thrice-weekly prophylaxis with TMP/SMX," this statement was based on a limited sample size of 205 patients from 2 studies. Attempting to build on the foundation laid by previous research, our study expanded this scope and confirmed that intermittent regimens of TMP/SMX may be useful.

The common adverse effects associated with TMP/SMX include gastrointestinal toxicity, skin rashes, anemia, thrombocytopenia, neutropenia, hyperkalemia, and renal dysfunction [22]. Between 17% and 61% of patients receiving TMP/SMX discontinue prophylaxis on a temporary or permanent basis owing to AEs according to select studies, which indicates that adverse effects are a major obstacle in the use of TMP/SMX for PCP prophylaxis. Despite its AEs, because of its established efficacy, TMP/SMX is a clinically important regimen, recommended by guidelines. The adverse effects are dose-dependent [23, 24], corroborating the observation that fewer AEs leading to discontinuation occurred in the intermittent group with reduced total doses than in the daily regimen group. It is also unclear whether the decreased incidence of AEs was due to the lower doses, the intermittent nature of the dosing, or a combination of both. This study suggests a clinically significant 45% reduction in AEs with intermittent dosing. However, the inclusion of several older studies that used higher doses of

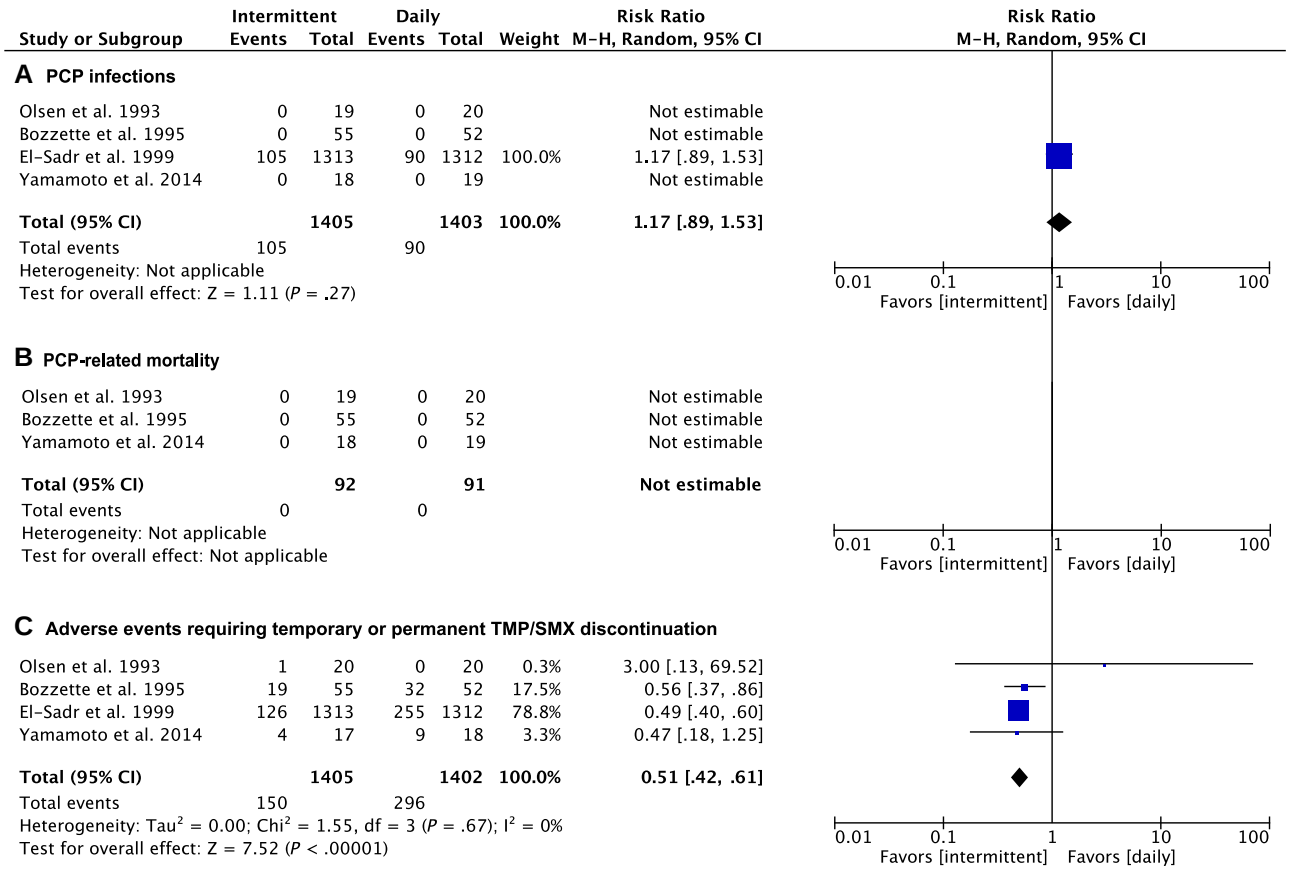

Figure 3. Forest plots of (A) PCP events, (B) PCP-related mortality, and (C) adverse events in intermittent vs daily administration of trimethoprim/sulfamethoxazole in randomized controlled trials. These forest plots illustrate the risk ratios (RRs) and confidence intervals (CIs) for the major outcomes assessed in the 4 studies included in the meta-analysis. Each row represents a study with the RRs and 95% CIs indicated by square and horizontal lines, respectively. The diamonds at the bottom represent the pooled RR and its 95% CI. The sizes of the boxes are proportional to the inverse variance. Abbreviations: CI, confidence interval; M-H, Mantel-Haenszel; PCP, *Pneumocystis* pneumonia; TMP/SMX, trimethoprim/sulfamethoxazole.

Table 2. Summary of Findings—Comparison of Intermittent and Daily Regimens as *Pneumocystis* Pneumonia Prophylaxis in Our Systematic Review and Meta-analysis

Outcomes	No. of Patients: Intermittent Regimen	No. of Patients: Daily Regimen	Effect: Relative (95% CI)	Effect: Absolute (95% CI)	No. of Participants (Studies)	Certainty of the Evidence (GRADE)	Comments
Documented PCP	105/1402 (7.5%)	90/1406 (6.4%)	RR, 1.18 (.88–1.58)	10 more per 1000 (from 7 fewer to 33 more)	2808 (4 RCTs)	⊕◯◯◯ Very low[a,b,c] Due to risk of bias, imprecision, and indirectness	Only 1 RCT reported events
PCP-related mortality	Not pooled	Not pooled	Not pooled	…	183 (3 RCTs)	See comment	No event was reported in these studies
Adverse events: requiring temporary or permanent TMP/SMX discontinuation	150/1405 (10.7%)	296/1402 (21.1%)	RR, 0.54 (.45–.64)	97 fewer per 1000 (from 116 fewer to 76 fewer)	2807 (4 RCTs)	⊕⊕◯◯ Low[a,c] Due to risk of bias and indirectness	…

Abbreviations: CI, confidence interval; Grading of Recommendations, Assessment, Development, and Evaluations; PCP, *Pneumocystis* pneumonia; RCT, randomized controlled trial; RR, risk ratio; TMP/SMX, trimethoprim/sulfamethoxazole.

[a]Allocation concealment, blinding of participant and clinician, and blinding of outcome assessment were unclear or high risk in most studies.

[b]Effect estimate demonstrating no significant impact, as evidenced by a wide CI that overlaps with no effect.

[c]The largest study, conducted before 2000 in people with human immunodeficiency virus, was downgraded 1 level for indirectness, owing to the limited use of antiretroviral therapy at the time and notable differences in its patient population compared with current patient profiles.

TMP/SMX (eg, 160 mg/800 mg twice daily) than those currently used precludes a definitive interpretation of our results.

Other than intermittent dosing, several strategies aim to enhance low-dose TMP/SMX tolerability for PCP prevention. For example, 1 retrospective study investigated varying TMP/SMX ratios in patients with rheumatoid arthritis receiving moderate-to-high doses of steroids [12]. An RCT compared 3 groups, namely full-dose TMP/SMX (80 mg/400 mg daily), half-dose TMP/SMX (40 mg/200 mg daily), and escalating dose (starting at TMP/SMX 8 mg/40 mg and gradually increasing to TMP/SMX 40 mg/200 mg), and found a consistent preventive efficacy, with the incidence of AEs being lower in the half-dose group than in the full-dose group. Furthermore, a retrospective analysis evaluated TMP/SMX (20 mg/100 mg) for PCP prophylaxis and reported similar outcomes [13]. Owing to the dose-related adverse effects of TMP/SMX, reduced doses and intermittent dosing are promising future strategies. Although this systematic review focused exclusively on RCTs, retrospective studies on the subject have also been conducted. One such study compared TMP/SMX prophylaxis in standard-dose (≥6 single-strength [80 mg/400 mg] TMP/SMX tablets/week) and low-dose groups (<6 single-strength tablets/week) in patients without HIV undergoing dialysis. No cases of PCP were reported in either group, and the incidence of AEs was lower in the low-dose group than in the standard-dose group [25]. These results are consistent with the integrated results of RCTs.

The indirectness of older studies poses a significant concern in this study. Particularly, the study by El-Sadr et al [10] included in our review, which is the largest RCT on PCP prophylaxis in PWH, markedly influenced the results. As the study included mainly young men, the efficacy and tolerability of TMP/SMX prophylaxis has not been well studied in older people who may be more susceptible to toxicity, or users of nephrotoxic drugs, which may be more toxic. The 7%–8% incidence of PCP in the study by El-Sadr et al [10] is also considerably higher than that in other RCTs and observational studies. These results may indicate the severe immunodeficiency status of PWH before effective HIV drugs were developed and may not be directly applicable to current immunocompromised patients. Modern medicine has increased the diversity of immunodeficiency conditions, mainly due to the development of drug treatment, and strategies for the prophylaxis of PCP need to be adapted as medical practice evolves. In conditions of relatively mild immunocompromised states with a low incidence of PCP under TMP/SMX prophylaxis, the reduction in AEs may provide greater benefits to patients. The lower incidence of AEs in the intermittent group identified in this study, as well as the lack of RCTs on the dosage and administration of TMP/SMX in contemporary immunocompromised patients, highlights the need for further research.

CONCLUSIONS

This systematic review and meta-analysis suggests that intermittent TMP/SMX regimens for PCP prophylaxis are more tolerable than daily regimens and may have similar efficacy. However, the variability in populations and dosing highlights the need for further prospective research in current situations and comparisons of standard-dose TMP/SMX with low-dose TMP/SMX regimens.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Author contributions. T. M., K. I., T. F., and R. K. conceived and designed the study. T. M., K. I., T. F., R. K., and F. K. designed and performed the search strategy. T. M., K. I., and T. F. screened and selected the articles. T. M., K. I., and E. O. extracted the data and assessed the risk of bias. T. M. analyzed the data. K. I., E. O., and S. M. supervised the data analysis. T. M., K. I., and E. O. rated the certainty of evidence. T. M. and K. I. interpreted the data. T. M. and K. I. drafted the manuscript. T. F., R. K., F. K., E. O., and S. M. reviewed and revised the manuscript. All authors read and approved the final version of the manuscript.

Patient consent. This study does not include factors necessitating patient consent.

Potential conflicts of interest. The authors: No reported conflicts of interest.

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