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ORIGINAL RESEARCH

Low-Dose Sulfamethoxazole-Trimethoprim Could Prevent *Pneumocystis jiroveci* Pneumonia in Kidney Transplant Recipients: A Retrospective, Observational Study

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Objective: Emerging evidence suggests that low doses of sulfamethoxazole-trimethoprim (TMP-SMX) may offer protection against *Pneumocystis jiroveci* pneumonia (PJP) in kidney transplant recipients. However, cases of PJP following the withdrawal of prophylaxis have been documented. This study aimed to investigate the relationship between the occurrence of PJP and different regimes of low-dose TMP-SMX prophylaxis.

Methods: This retrospective observational study was conducted in the First Affiliated Hospital of Zhejiang University in China. Recipients diagnosed with PJP were included, and four controls were matched for each case based on transplantation time, age, and sex. Multivariate conditional logistic regression was employed to compare the odds of PJP occurrence among different TMP-SMX regimens.

Results: From January 1, 2017, to December 31, 2020, 1763 patients underwent kidney transplantation at our center. Thirty-one patients developed PJP post-transplantation, and 124 patients without PJP were included as controls. One patient developed PJP during the prophylaxis period, and the others occurred after TMP-SMX discontinuation, resulting in a PJP incidence rate of 1.36% over the follow-up period. Compared to controls, the PJP group received a significantly lower cumulative TMP-SMX dose (median: 57 single-strength dose [SSD] tablets *vs* 100 tablets; $p = 0.001$) and had a shorter prophylaxis duration (median: 6.00 months *vs* 10.00 months; $p = 0.004$). They also exhibited higher CMV infection rates (29.0% vs 4.8%, $p < 0.001$), elevated serum creatinine levels at discharge (174.80μmol/L vs 134.58 μmol/L, $p = 0.018$), and reduced CD 4^+ cell counts (354.12/L vs 542.58/L, $p = 0.05$). Multivariate analysis revealed that a higher cumulative TMP-SMX dose was significantly associated with a lower risk of PJP ($p = 0.005$). Subgroup analysis indicated that at least 6 months of TMP-SMX prophylaxis is necessary for PJP prevention in recipients on quarter-strength daily (SMX/TMP 100/20 mg, $p = 0.022$) or half-single strength daily (SMX/TMP 200/40 to 400/80 mg, $p = 0.005$) regimens.

Conclusion: An adequate prophylactic duration of either quarter-strength daily TMP-SMX or half-single strength daily TMP-SMX may protect kidney transplant recipients from PJP.

Keywords: *Pneumocystis jiroveci* pneumonia, low dose, sulfamethoxazole-trimethoprim, kidney transplant, anti-*Pneumocystis* prophylaxis

Introduction

Pneumocystis jiroveci pneumonia (PJP) continues to pose a significant threat to kidney transplant recipients.[1–3] The incidence of PJP can reach up to 5%–15% in solid organ transplant recipients in the absence of universal prophylaxis, carrying a high mortality rate of 10% to 50%.[4] As a first-line anti-*Pneumocystis* prophylaxis, trimethoprim-

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sulfamethoxazole (TMP-SMX)[5,6] is also recommended for kidney transplantation recipients.[4,7,8] Advances in prophylactic strategies and immunosuppressive regimens have reduced the incidence of PJP in transplant recipients to 0.3%–2.5%.[7]

The standard dosage of prophylactic TMP-SMX for adult transplant recipients is 80 mg of TMP/400 mg of SMX daily (single-strength dose, SSD) or 160 mg of TMP/800 mg of SMX (double-strength dose, DSD) three times per week.[8] A comprehensive meta-analysis[9] compared different anti-*Pneumocystis* prophylactic regimens and concluded that TMP-SMX was the most efficacious, despite its severe side effects that lead to a high discontinuation rate. The DSD of TMP-SMX three times per week presents lower risks than daily administration but still carries a 14.5% likelihood of discontinuation within year.[9]

TMP-SMX is associated with concerning adverse reactions, including bone marrow suppression, hepatitis, and hyperkalemia.[4] Furthermore, it may impair renal function by inhibiting creatinine secretion, inducing crystalline nephropathies, and causing interstitial nephritis.[10,11] Differentiating between drug-related renal injury and renal rejection once these effects occur is challenging. Consequently, clinical centers often resort to lower doses of TMP-SMZ than those recommended by guidelines to reduce these risk factors.[12,13]

Current guidelines recommend standard-dose TMP-SMX prophylaxis over 6 months for PJP prevention in immunocompromised patients.[4] However, some recent published clinical observations challenge this recommendation. In kidney transplant recipients, a retrospective study demonstrated that dose reduction of TMP-SMX due to frequent adverse reactions did not result in any PJP cases, supporting the efficacy of lower-dose regimens for PJP prophylaxis.[14] Among heart transplant recipients, a 5-year observational study further established that thrice-weekly SSD TMP-SMX administered for one year effectively prevented PJP, with zero breakthrough infections observed during a median follow-up.[15] These findings suggest that reduced-dose TMP-SMX exhibits comparable efficacy to standard dosing in clinical practice. Nevertheless, controversies still persist: a pediatric solid organ transplant cohort study utilizing a low-dose TMP-SMX regimen (TMP 2.5 mg/kg/dose, thrice weekly) reported no confirmed breakthrough PJP infections among 234 patients; however, 2.6% (n = 6) required empirical transitioned to therapeutic dosing due to clinical suspicion of PJP. While reduced-dose TMP-SMX regimens demonstrate substantial advantages in safety and tolerability, critical questions regarding potential suboptimal protection from insufficient dosing and optimal treatment duration remain unresolved.

In our prior study, we discovered that a quarter- to half-strength daily dose of TMP-SMX offered protection to kidney transplant recipients against PJP during the prophylaxis period, aligning with a recently published study.[13] However, some recipients still developed PJP after the prophylactic drug withdrawal. The relationship between the occurrence of PJP and the duration or dosage of TMP-SMX prophylaxis remains unexplored. Consequently, a case–control study was conducted at our center to compare the odds of PJP across different TMP-SMX regimens.[16–18]

Method

Study Design and Participants

This retrospective observational study was conducted at the First Affiliated Hospital of Zhejiang University (FAHZJ) in China. The inclusion criteria were: (1) patients who underwent kidney transplantation between January 1, 2017, and December 31, 2020; (2) patients diagnosed with PJP after kidney transplantation were included as infected cases. Four controls were selected for each infected case by matching for transplantation time, age, and sex; (3) complete follow-up data were available.

The study adhered to the principles outlined in the Helsinki Declaration of 1975 and the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement.[19] The FAHZJ-authorized ethics committee granted ethical approval for this study. The ethics committee exempted informed consent due to the anonymity of the data and the absence of patient identification information. All organs were voluntarily donated with written informed consent and followed the Declaration of Istanbul.

Definitions and Diagnosis

A matched index date was allocated to each control according to the time of PJP in the matched patients.

The single-strength dose (SSD) of TMP-SMX is 80 mg TMP/400 mg SMX; the half-strength dose (HSD) of TMP-SMX is 40mg TMP/200 mg SMX; the quarter-strength dose (QSD) of TMP-SMX is 20mg TMP/100 mg SMX.

The diagnosis methods were consistent with those reported in previous study.[12] PJP was definitively established either through the detection of pneumocystis cysts or trophozoites in bronchoalveolar lavage fluid, or by utilizing a combination of methods including next-generation sequencing analysis (NGS) of bronchoalveolar lavage fluid or blood samples, along with radiographic confirmation via computed tomography (CT) scans. Additionally, measurements of blood beta-D-glucan levels were incorporated into the comprehensive diagnostic workflow to ensure accurate diagnosis. CMV infection was defined as detecting CMV DNA in blood or other tissue, regardless of symptoms.[20]

Data Collection

Electronic medical records and follow-up data were reviewed to collect necessary information, including age, body mass index (BMI), sex, donor source, primary renal disease, preoperative dialysis duration, immunosuppression regimens, CMV infection history, creatinine at discharge, $CD4^+$ and $CD8^+$ T lymphocyte count a week post-surgery, acute rejection history, TMP-SMX dose, and TMP-SMX duration.

TMP-SMX Dose

TMP-SMX is routinely used to prevent PJP in recipients with creatinine clearance below 150 μmol/L after kidney transplantation. The main initial dose was HSD of TMP-SMX daily, and the maintenance dose would be adjusted to a QSD of TMP-SMX daily if the serum creatinine increased by 10% or other adverse reactions related to TMP-SMX occurred. If further reduction is deemed necessary, stop entirely.

Statistical Analysis

The count data is expressed as n (%), and the measurement data is presented as means (standard deviation [SD]) or medians (interquartile range [IQR]), as appropriate. Student's t-tests or the Mann–Whitney *U*-test were performed as appropriate to compare quantitative data between different groups; Pearson χ^2 or Fisher exact test was used to compare categorized parameters. Multivariate conditional logistic regression was used to compare the risk factors for PJP. Demographic data, laboratory test indicators, graft types, immunosuppressive therapy, CMV infections, rejections pre-PJP, serum creatinine levels, dialysis course pre-transplant, total number of lymphocytes, absolute $CD4^+$ and $CD8^+$ T lymphocyte counts, TMP-SMX dose, and TMP-SMX duration were investigated. Factors with a univariate *p*-value of ≤ 0.05 were entered into the multivariate logistic regression analysis.[21,22] A two-tailed *p*-value <0.05 was considered statistically significant. The R software (R Core Team, www.r-project.org) was used for analysis.

Sample Size Calculation

According the reported exposure rates[23] of TMP-SMX prophylaxis <6 months and the data from our previous PJP cohort[12] (40% in cases vs 15% in controls, OR of 3.8), we used standard formulas[24] with $\alpha=0.05$ (two-tailed), 80% power, 0.2 correlation coefficient for exposure and 1:4 case–control matching, the calculated minimum required sample size was 28 cases and 112 controls to detect an OR of 3.8.

Results

Characteristics of Included Patients

From January 1, 2017, to December 31, 2020, 1763 recipients underwent renal transplantation in our center, with 24 cases (1.4%) developing PJP during the follow-up. Seven recipients who underwent renal transplantation in other centers but received treatments in our center were also enrolled in the PJP group (Figure 1). In total, 155 recipients were included, with 31 cases in the PJP group and 124 cases without PJP in the control group (Figure 1). The median follow-up duration of the study cohort was 28.0 (IQR:21.5–40.4) months. All patients enrolled in this study were successfully followed up until the completion of the study. Ninety-six patients were male, with a mean age of 37.94 (SD 11.70). The median time from PJP or matched index date after transplantation was 16.40 (IQR: 6.60–21.65) months at inclusion, and

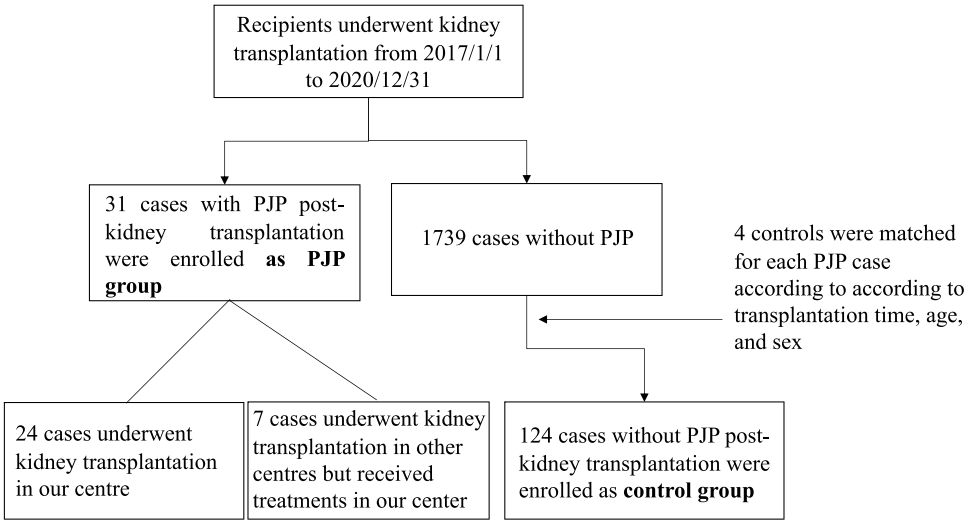

Figure 1 Study flow diagram.

the primary renal disease included primary glomerulonephritis in 88 patients, polycystic kidney disease in five patients, hypertensive nephropathy in three patients, diabetes nephropathy in two patients, and other diseases in 57 patients. Ninety-six patients received grafts from donors after death and 59 from living donors. Among the 31 PJP patients, 19 were definitively diagnosed through NGS or Gomori's methenamine silver staining (GMS) staining, while 12 received clinical diagnoses based on characteristic pulmonary CT findings combined with elevated blood β-D-glucan levels. Compared to the control group, patients with PJP had a higher incidence of CMV infections (29.0% vs 4.8%, $p < 0.001$), higher levels of serum creatinine at discharge (174.80 μmol/L vs 134.58 μmol/L, $p < 0.018$), and lower CD 4^+ T lymphocyte counts (354.12/L vs 542.58/L, $p = 0.05$). The duration of PJP from transplantation or the matched index date after transplantation, age, and gender ratio were similar between the two groups. Characteristics of included patients are shown in Table 1 and Supplement Table 1 (excluding recipients in other centers).

Characteristics of PJP in RT Recipients

The median time to develop PJP after renal transplantation was 16.40 (IQR 7.30–20.80) months in 31 patients with PJP, 6.23 (IQR 4.70–15.30) months in recipients did not use TMP-SMX, 18.05 (IQR 9.03–20.78) months in recipients used QSD daily TMP-SMX, and 15.90 (IQR 10.88–19.78) months in recipients used HSD&SSD daily TMP-SMX. Of these, one patient developed a breakthrough infection during prophylaxis with QSD daily TMP-SMX, and others occurred after the discontinuation of TMP-SMX. The median time between infections and the discontinuation of TMP-SMX was 6.83 months in recipients who used QSD daily TMP-SMX (IQR 5.00–11.80 months), and 6.88 months in recipients who used HSD&SSD daily TMP-SMX (IQR6.19–9.43 months).

Prophylaxis Against PJP

As prophylaxis against PJP, two (1.3%) patients used SSD daily TMP-SMX, 50 (32.3%) used HSD daily TMP-SMX, 91 (58.7%) used QSD daily TMP-SMX, and 12 (7.7%) did not use TMP-SMX. There is a significant difference in the prophylaxis therapy between the two groups ($p < 0.001$, Table 1). In the PJP group, 22.6% of recipients did not use prophylaxis, which was higher compared with 4.0% in the control group. Recipients in the PJP group took fewer cumulative TMP-SMX doses than those in the PJP group (Table 2, $p = 0.001$). The prophylactic regimens for PJP in subgroup cohort (excluding recipients from other centers and their corresponding matches) are presented in Supplemental Table 2.

The median TMP-SMX duration was 6.00 (IQR: 0.30–12.00) months in the PJP group, which was significantly shorter than 10.00 (IQR: 6.00–12.00) months in the control group ($p = 0.004$, Table 2). In the control group, 94.4% (QSD daily TMP-SMX) and 83.3% (HSD&SSD daily TMP-SMX) of recipients used TMP-SMX more than six months, which

Table 1 Characteristics of the Patients at Baseline

Characteristic	Total	PJP Group	Control Group	*P*
N	155	31	124	
Sex, n (%)				0.772
Male	96 (61.9%)	18 (58.1%)	78 (62.9%)	
Female	59 (38.1%)	13 (41.9%)	46 (37.1%)	
Age, year, mean (SD)	37.94 (11.70)	37.84 (12.11)	37.96 (11.65)	0.959
Height, cm, mean (SD)	164.31 (12.14)	164.39 (8.64)	164.29 (12.93)	0.971
Weight, kg, mean (SD)	56.28 (11.57)	53.56 (9.21)	56.96 (12.03)	0.151
BMI, kg/cm^2, mean (SD)	21.41 (10.46)	19.74 (2.53)	21.85 (11.65)	0.327
Primary disease, n (%)				0.520
Primary glomerulonephritis	88 (56.8%)	15 (48.4%)	73 (58.9%)	
Polycystic kidney disease	5 (3.2%)	2 (6.5%)	3 (2.4%)	
Hypertensive nephropathy	3 (1.9%)	1 (3.2%)	2 (1.6%)	
Diabetes nephropathy	2 (1.2%)	1 (3.2%)	1 (0.8%)	
Others	57 (36.8%)	12 (38.7%)	45 (36.3%)	
Graft type, n (%)				0.901
DD	96 (61.9%)	20 (64.5%)	76 (61.3%)	
Living	59 (38.1%)	11 (35.5%)	48 (38.7%)	
Time since RT, month, median (IQR)	16.40 (6.60, 21.65)	16.40 (7.30, 20.80)	16.40 (6.60, 21.93)	0.945
IM, n (%)				0.179
Tac	151 (97.4%)	29 (93.5%)	122 (98.4%)	
CsA	4 (2.6%)	2 (6.5%)	2 (1.6%)	
Dialysis duration before RT, month, median (IQR)	24.00 (3.00, 48.00)	21.00 (3.00, 60.00)	24.00 (4.50, 48.00)	0.808
Rejection, n (%)	12 (7.7%)	5 (16.1%)	7 (5.6%)	0.115
CMV infections, n (%)	15 (9.7%)	9 (29.0%)	6 (4.8%)	<0.001
Scr outpatient, μmol/L, mean (SD)	142.42 (84.10)	174.80 (89.15)	134.58 (81.28)	0.018
Lymphocytes[a], /L, mean (SD)	2676.54 (933.70)	2714.96(1500.15)	2669.05 (786.57)	0.826
CD4^{+}, [a], /L, mean (SD)	511.81 (430.67)	354.12 (319.39)	542.58 (443.72)	0.050
CD8^{+}, [a], /L, mean (SD)	317.76 (267.06)	230.38 (181.86)	334.80 (278.07)	0.080
CD4^{+}/CD8^{+}, mean (SD)	1.66 (0.97)	1.69 (1.38)	1.66 (0.88)	0.884

Notes: [a]Theses indicators were recorded one month after transplantation.
Abbreviations: DD, donation after death; BMI body mass index; SD, standard deviation; IQR, interquartile range; RT, renal transplantation; Scr, serum creatinine. IM, immunosuppressive agent; Tac, tacrolimus; CsA, cyclosporin.

was 75.0% in the PJP group with different TMP-SMX regimens. In the control group, 60.6% of recipients used TMP-SMX QSD daily for more than 12 months, while the rate was 37.5% in recipients who used TMP-SMX HSD&SSD daily.

Risk for PJP Among Recipients Used Different TMP-SMX Regimes

Factors with a univariable *p*-value of ≤0.05 were entered into the multivariate conditional logistic regression, including CMV infections, CD4^{+} T lymphocyte counts, serum creatinine outpatient and cumulative dose of TMP-SMX (Table 1 and Table 2). The results of TMP-SMX with a higher cumulative dose were related to lower PJP occurrence (OR 0.077, 95% CI: 0.013–0.459, $p = 0.005$, Table 3). As the cumulative dose of TMP-SMX was related to both TMP-SMX dosage and duration, a subgroup analysis further investigated the effects of different TMP-SMX regimens (Table 4). Factors with a univariable *p*-value of ≤0.05 were entered into the multivariate conditional logistic regression for adjusting (CMV infection, Scr outpatient, and CD4^{+} T lymphocyte counts). The results showed that the minimum duration of 6 months effectively prevented PJP in recipients on quarter-strength daily (SMX/TMP 100/20 mg, $p = 0.022$, Table 4) or half-single strength daily (SMX/TMP 200/40 to 400/80 mg, $p = 0.005$, Table 4) regimens. However, shorter than six months was insufficient. The multivariate conditional logistic regression was conducted in recipients excluded from other centers, and the result was consistent with the primary analysis (Supplement Tables 3 and Supplement Table 4).

Table 2 Prophylaxis Against PJP in Enrolled Patients

Variable	Total (n=155)	PJP Group (n=31)	Control Group (n=124)	*P*
Cumulative TMP-SMX dose, SSD tablets, mean (SD) (IQR)	91(58)	57 (52)	100 (57)	<0.001
TMP-SMX therapy, n (%)				<0.001
None	12 (7.7%)	7 (22.6%)	5 (4.0%)	
QSD daily TMP-SMX	91 (58.7%)	20 (64.5%)	71 (57.3%)	
HSD daily TMP-SMX	50 (32.3%)	3 (9.7%)	47 (37.9%)	
SSD daily TMP-SMX	2 (1.3%)	1 (3.2%)	1 (0.8%)	
TMP-SMX duration,				
Months, median (IQR)	10.00 (6.00, 12.00)	6.00 (0.30, 12.00)	10.00 (6.00, 12.00)	0.004
<6 months	30 (19.4)	13 (41.9)	17 (13.7)	0.001
≥6 months	125 (80.6)	18 (58.1)	107 (86.3)	

Abbreviations: TMP-SMX, sulfamethoxazole-trimethoprim; SSD, single-strength dose (TMP-SMX means 80 mg TMP/400 mg SMX); HSD, half-strength dose (TMP-SMX means 40mg TMP/200 mg SMX); QSD, quarter-strength dose (TMP-SMX means 20mg TMP/100 mg SMX).

Table 3 Risk Factors for PJP After Kidney Transplantation

Variable	OR	Lower 95% CI	Upper 95% CI	*p* Value
CMV infection, n (%)	6.393	0.968	42.217	0.054
Scr outpatient, μmol/L	1.002	0.995	1.010	0.574
$CD4^+$ T lymphocyte counts, /L	0.999	0.998	1.001	0.401
Cumulative TMP-SMX dose, tablets (SSD)	0.077	0.013	0.459	0.005

Abbreviations: Scr, serum creatinine; TMP-SMX, sulfamethoxazole-trimethoprim.

Table 4 Subgroup Analysis of Different TMP-SMX Regimes Against PJP

Variable[a]	OR	Lower 95% CI	Upper 95% CI	*p* Value
TMP-SMX regimes, n (%)				
None	Ref			
QSD daily TMP-SMX, <6 months	0.331	0.023	4.716	0.414
QSD daily TMP-SMX, ≥6 months	0.062	0.006	0.674	0.022
HSD&SSD daily TMP-SMX, <6 months	0.078	0.003	1.791	0.111
HSD&SSD daily TMP-SMX, ≥6 months	0.009	0.0004	0.238	0.005

Notes: [a]Adjusted by CMV infection, Scr outpatient, $CD4^+$ T lymphocyte counts.
Abbreviations: TMP-SMX, sulfamethoxazole-trimethoprim; SSD, single-strength dose (TMP-SMX means 80 mg TMP/400 mg SMX); HSD, half-strength dose (TMP-SMX means 40mg TMP/200 mg SMX); QSD, quarter-strength dose (TMP-SMX means 20mg TMP/100 mg SMX); Scr, serum creatinine.

Outcomes of PJP

Regular follow-up was carried out for those infected recipients. After PJP, one patient died due to treatment failure (TMP-SMX combined caspofungin). This patient developed PJP 8.5 months after discontinuing QSD daily TMP-SMX. Other infected patients recovered after treatments. The treatment details were described in our previous study.[12]

Discussion

For the present, TMP-SMX remains the first-line choice for PJP prophylaxis.[7,8,20] All the other PJP prophylaxis are recommended as second-line treatment, as the disadvantages in efficacy, cost and tolerability.[4,7] However, the current recommended dose of TMP-SMX in guidelines is still associated with a relatively high incidence of adverse events and commonly leads to dose reduction or even discontinuation of TMP-SMX.[14,25–27] So, it is necessary to balance the side-

effect profiles and the efficacy of TMP-SMX by optimizing its dosage. Our study investigated the odds of PJP occurrence among different TMP-SMX regimens and firstly found that both low-dose TMP-SMX strategies (HSD&SSD or QSD daily) with sufficient duration can protect against PJP in recipients who underwent renal transplantation. Our finding demonstrates that QSD or HSD&SSD daily TMP-SMX can provide PJP prophylaxis in kidney transplant recipients with adequate prophylactic duration. The results may challenge current guideline recommendations advocating for higher-dose regimens and reveal a strategic opportunity to optimize prophylaxis protocols. However, robust prospective studies are required to validate the low-dose prophylaxis protocols of TMP-SMX.

Several RCTs studied the prophylaxis for PJP in transplantation patients,[27–30] but the low limit of TMP-SMX's dose in these studies was SSD TMP-SMX daily. Two retrospective cohort studies about kidney transplantation patients investigated the lower prophylactic dose.[14,31] Among these, the efficacy and adverse effects of SSD TMP-SMX thrice weekly were described. The cumulative dose of this regimen per week is near the HSD of TMP-SMX daily in our study. In the two studies, Prasad et al reported a high rate (50%) of reducing the initiating daily SSD TMP-SMX, mainly due to hyperkalemia and leukopenia.[14] The TMP-SMX dose was reduced to SSD thrice or twice weekly, and no PJP occurred in any transplant patients over a follow-up period of 12 months. Zmarlicka et al examined the tolerability of SSD TMP-SMX thrice weekly in 78 kidney transplant patients.[31] Ten patients discontinued TMP-SMX (a median therapy period of 194 days) due to hyperkalemia, leukopenia, and diarrhea. No episodes of PJP occurred in this cohort. The discontinuation rate of this regimen was lower than SSD TMP-SMX daily in other studies (ranging from 25% to 40%).[32,33] Based on these data, the intensity of TMP-SMX lower than SSD daily may be effective and has an advantage in safety and drug retention. However, the efficacy and risks of even low-intensity TMP-SMX have been rarely reported.

In our center, the initial dose of TMP-SMX was mainly HSD daily. The maintenance dose would be adjusted to QSD daily if the serum creatinine increased or other adverse reactions related to TMP-SMX occurred. Therefore, both SSD and HSD TMP-SMX daily were commonly used. Only one patient developed a breakthrough infection during the prophylaxis period, and other PJPs occurred after the discontinuation of TMP-SMX. With the current anti-*Pneumocystis* prophylaxis, the breakthrough infection rate is low (0.06%), and the overall morbidity of PJP was 1.36% in our center, which was similar to the result in previous studies with higher doses of TMP-SMX.[4,34] The results indicate that low-dose TMP-SMX regimens used in our center can protect against PJP.

In a recent study, Chen et al demonstrated that low-dose TMP-SMX prophylaxis significantly reduces the incidence of PJP within 6 months following kidney transplantation and has a favourable safety profile.[13] However, cases of PJP occurring 6 months post-kidney transplantation have been reported in kidney transplant.[35,36] In our previous study, we also discovered that a daily regimen of TMP-SMX, switching from a QSD to HSD, provided robust protection against PJP in kidney transplant recipients during the prophylactic period.[12] Nevertheless, a number of recipients went on to develop PJP following the cessation of the prophylactic medication, with the majority of cases occurring after 6 months post-transplantation. It is essential to determine whether the incidence of PJPs was associated with the duration or the dosage of TMP-SMX. Accordingly, we investigated the combination effect of TMP-SMX dose and duration and found that a minimum duration of 6 months effectively prevented PJP in recipients on a quarter-strength daily or half-single strength daily TMP-SMX regimen. The recommended duration for a standard dose of TMP-SMX is three to six months, or at least four months for transplant recipients, as outlined in Guidelines published prior to 2017.[7,37,38] In the updated guideline from the American Society of Transplantation Infectious Diseases Community, a minimum of 6 months of prophylaxis has been recommended.[4] The necessity of recommending extended prophylaxis periods for low-dose TMP-SMX regimes presents a significant challenge that was not further investigated in our study due to the limitations in the number of participants. Further research is required to determine the optimal specific duration threshold for low-dose prophylaxis. It should be noted that the duration significantly differed in recipients who used different TMP-SMX doses. In the control group, 60.6% of recipients used TMP-SMX QSD daily for more than 12 months, while the rate was 37.5% in recipients who used TMP-SMX HSD&SSD daily. The TMP-SMX dose would be decreased or discontinued with the occurrence of TMP-SMX-related adverse reactions. Longer duration indicated a better tolerance of TMP-SMX QSD daily in kidney transplant recipients. Since the majority of PCP cases occurred after discontinuation of anti-*Pneumocystis* prophylaxis, improved tolerability may contribute to improved outcomes.

Our study highlights that CMV was significantly related to PJP, with prior evidence showing 46.2% of PJP patients had concurrent CMV viremia[39] and a significantly higher prevalence of CMV infection within one year before PJP onset (23% vs 4%, $p < 0.001$),[40] suggesting CMV as a key predisposing factor. Mechanistic studies demonstrate that CMV not only causes lymphopenia but also reshapes the T-cell compartment, disrupts monocyte function (impairing phagocytosis and antigen presentation), and produces immunomodulatory viral IL-10, all of which may contribute to impaired *Pneumocystis jiroveci* clearance.[40–42] Furthermore, univariate analysis confirmed an association between low $CD4^+$ T cell counts and increased PJP susceptibility, aligning with established evidence that lymphopenia—particularly $CD4^+$ counts below 200 cells/μL—constitutes a major risk factor.[43] This association reflects compromised adaptive immunity, heightening vulnerability to PJP. Elevated LDH (>300 IU/mL) and β-D-glucan testing show high sensitivity for PJP, though limited specificity. These biomarkers are routinely employed in clinical practice to assist in diagnosis and risk stratification, particularly for immunocompromised patients presenting with atypical clinical symptoms or inconclusive radiological findings. Current clinical guidelines[4] advocating for combined biomarker assessment, which can facilitate the development of more effective prevention strategy.

There are some limitations of this study. Firstly, this was a retrospective, case–control study with a small sample size. Although the matching method and the multivariate conditional logistic regression were used, the confounding and selection bias cannot be avoided. In the context of universal prophylaxis, the incidence of PJP is low, so the sample size in the PJP group was limited. Seven recipients who underwent renal transplantation in other centers were enrolled in the PJP group, which may introduce heterogeneity. We conducted sensitivity analysis through excluding these recipients, the results consistent with the primary analysis, suggesting that center-related factors had minimal impact on the observed associations. In the future, well-designed, prospective, and multicenter studies are needed to provide more robust evidence. Another limitation was the lack of a direct comparison of the efficacy and risk between HSD daily TMP-SMX and the guideline-recommended regimen. Only three patients used the SSD TMP-SMX as prophylaxis against PJP, so the comparison cannot be performed. Besides, unmeasured infections (such as bacterial/fungal) were not adjusted for due to incomplete retrospective data. Despite these limitations, our study represents a real-world scenario that provides data about promising TMP-SMX prophylaxis with a relatively low dosage, which may contribute to laying the groundwork for the development of strategies with both good tolerance and powerful prevention effects.

Conclusion

TMP-SMX with a dose lower than the guideline-recommended is used in practice to confine its risks. We conducted a case–control study to analyze the odds of PJP from different SMZ prevention programs. After ruling out the effects of other known risk factors, we found that doses of TMP-SMX lower than the guideline-recommended with sufficient duration can protect recipients who underwent kidney transplantation against PJP.

Abbreviation

TMP-SMX, sulfamethoxazole-trimethoprim; PJP, *Pneumocystis jiroveci* pneumonia; SSD, single-strength dose; double-strength dose, DSD; FAHZJ, the First Affiliated Hospital of Zhejiang University; STROBE, Strengthening the Reporting of Observational Studies in Epidemiology; SD, standard deviation; IQR, interquartile range; BMI, body mass index; GMS, Gomori's methenamine silver staining.

Data Sharing Statement

Data is provided within the manuscript.

Ethics Declarations and Consent to Participate

Ethical approval was obtained from the authorized ethics committee of the First Affiliated Hospital of Zhejiang University (approved ID: 2018-1083). The ethics committee exempted informed consent due to the anonymity of the data and the absence of patient identification information. All organs were voluntarily donated with written informed consent and followed the Declaration of Istanbul.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare no competing interests in this work.

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