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CLINICAL AND EPIDEMIOLOGICAL STUDY

Clindamycin–primaquine for pneumocystis jiroveci pneumonia in renal transplant patients

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Abstract
Background Trimethoprim/sulfamethoxazole (TMP/SMX) is considered first-line therapy for pneumocystis jiroveci pneumonia (PCP) in renal transplant patients. Alternatives have not been formally studied. Clindamycin–primaquine (C–P) is effective in HIV-associated PCP, but data in renal transplant patients are lacking.
Patients and methods Retrospective cohort study of 57 consecutive renal transplant patients who developed PCP and were treated with C–P ($n = 23$) or TMP/SMX ($n = 34$).
Results A non-significantly higher failure rate was observed in patients on C–P due to lack of efficacy (30.4 versus 20.6 %, $p = 0.545$). The difference was more pronounced in severe PCP (60 versus 37.5 %, $p = 0.611$) and a significantly lower efficacy of C–P was seen when used as salvage therapy. The two patients who had received C–P after not responding to TMP/SMX failed this regimen, but all seven patients who had failed initial treatment with C–P and had been switched to TMP/SMX were cured ($p = 0.028$). No treatment-limiting adverse reactions were reported for patients on C–P while six patients (17.6 %) on TMP/SMX developed possibly related treatment-limiting toxicity ($p = 0.071$). However, in only two patients adverse events were definitely related to TMP/SMX (5.9 %).
Conclusions Clindamycin–primaquine appears to be safe and well tolerated for treating PCP in renal transplant patients but is probably less effective than TMP/SMX, the standard regimen. However, our data indicates that C–P represents an acceptable alternative for patients with contraindications or treatment emergent toxicities during TMP/SMX use. Notably, TMP/SMX was also acceptably tolerated in most patients. TMP/SMX remains an effective salvage regimen in case of C–P failure.

Keywords Pneumocystis jiroveci pneumonia · Treatment · Renal transplant patients · Clindamycin–primaquine · Trimethoprim/sulfamethoxazole

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Introduction

Pneumocystis jiroveci pneumonia (PCP) is a well-documented complication following renal transplantation and its incidence appears to be increasing [1–3]. Trimethoprim-sulfamethoxazole (TMP/SMX) is considered the first-line treatment option [1, 3–6]. Alternative regimens have not been formally evaluated. Establishing effective second-line options in this setting is not only important for patients with a history of intolerance to TMP/SMX but also due to the inherent side effect profile of TMP/SMX, which may require change of therapy to alternative regimens. TMP/SMX is associated with hepatotoxicity, myelosuppression, and renal dysfunction [7], all of which are common in renal transplant patients. The need to consider alternative regimens has increased due to the recent widespread shortage of intravenous (IV) TMP/SMX.

IV pentamidine, atovaquone, and C–P [1, 3, 4, 6] have been recommended as alternative regimens, however, comparative studies in renal transplant patients as well as in most other populations at risk of PCP, except for HIV, are lacking.

In AIDS patients with mild-to-moderate PCP, C–P has been found to be safe and as effective as TMP/SMX [8, 9]. Adverse events rates were similar, but potentially more severe with TMP/SMX [9]. Data on severe PCP are not available. Following failure of TMP/SMX, however, C–P was shown to be superior to other regimens as salvage treatment in various populations at risk of PCP [10–13]. Therefore, C–P could provide a useful alternative to TMP/SMX in renal transplant patients.

The primary goal of the current study was to compare the relative safety and efficacy of C–P and TMP/SMX in treating primary episodes of PCP in renal transplant patients. The second goal was to establish the relative efficacy of both regimens in salvage therapy.

Patients and methods

Study population

The current study was a non-randomized, retrospective cohort study. The study cohort was comprised of all renal transplant patients who had confirmed PCP and were treated at one of the university hospital sites of the Charité-University medical system (Campus Virchow-Klinikum, Campus Charite Mitte, and Campus Benjamin Franklin) in Berlin, Germany between January 2001 and December 2010. During this 10-year period, primary PCP episodes in renal transplant patients were treated with either TMP/SMX or C-P. At the time, the local treatment protocol considered both treatment options as acceptable alternatives for the treatment of primary PCP episodes. In case of treatment failure or limiting adverse reactions, therapy was usually switched to the alternative regimen.

Prior to the evaluation period, all renal transplant patients had been treated with TMP/SMX. However, there had been a considerable number of patients with severe adverse events and a large part of these events had been attributed to TMP/SMX rather than the severeness of PCP, transplantation-related conditions, and comorbidities. Attending physicians felt increasingly critical about TMP/SMX use.

Considering the data of comparable efficacy of TMP/SMX and C–P in AIDS patients with at least mild-to-moderate PCP, C–P was allowed to be given as an acceptable alternative for the first-line treatment of primary PCP by the Departments of Infectious Diseases, Pulmonary Medicine, and Nephrology. The choice of primary therapy was at the discretion of the senior physician responsible for the patient at the time of treatment initiation. There were no pre-defined individual patient-related criteria to use either C–P or TMP/SMX primarily.

PCP case definition

Patients with PCP were identified by screening the PCP diagnostic laboratory files of the Division of Infectious Diseases and Pulmonary Medicine and of the Department of Microbiology and Hygiene of the Charité-University medical system Berlin. During the evaluation period, all patients at the Charité-University medical system Berlin with suspicion of PCP underwent bronchoscopy with bronchoalveolar lavage (BAL) for diagnosis. A case of PCP was considered confirmed following demonstration of pneumocystis jiroveci cysts or trophocytes in BAL fluid either by Grocott silver staining or by a commercially available standard fluorescent antibody staining test [4, 6].

PCP treatment

Patients on the C–P regimen were treated with 600 mg clindamycin 3–4 times daily plus 15–30 mg primaquine once daily [3, 6, 8, 9]. No dose adjustment was made for renal insufficiency. Glucose-6-phosphatase dehydrogenase deficiency was excluded at the time C–P treatment was started to prevent the risk of primaquine-associated methemoglobinemia.

Trimethoprim/sulfamethoxazole treatment was initiated with a standard dosage of 15–20 mg/kg/day of TMP equivalent in 3–4 doses per day and adjusted for impaired renal function according to international and manufacturer's recommendations [3, 14]. Typically, dosing was reduced to 50 % for a glomerular filtration rate (GFR) between 30 and 10 ml/min. In patients with renal failure

requiring hemodialysis, the dosage was administered either after or before hemodialysis. In the latter case, another 50 % of the administered dosage was given after hemodialysis. For patients on continuous veno-venous hemodiafiltration, TMP/SMX dosing was reduced to 50–75 % of the standard dose.

Transplant-related immunosuppressive drug therapy was continued unchanged in all patients when PCP treatment was initiated, but usually reduced and/or dose modified in case of clinical deterioration.

All patients with any dyspnea or requiring supplemental oxygen support were given adjunct treatment with steroids for improving the alveolar-arterial oxygen transfer. Patients were usually given 40 mg prednisone equivalent twice daily until improvement with dose taper thereafter [1].

Patients with respiratory failure were offered supportive non-invasive and/or invasive positive pressure ventilation. Non-invasive ventilation was administered as continuous positive airway pressure and/or bi-level positive airway pressure.

Patient evaluation

All patients evaluated in this study had a clinical data file available, which included medical history as well as clinical, laboratory, microbiological, and radiological data.

Treatment success was defined as clinical cure with patients being alive and showing significant clinical improvement with resolution of chest infiltrates 30 days after finishing PCP therapy. In agreement with standard practice [8, 9, 11–13], determination of treatment failure was generally made around day 7 and was based on failure to improve or worsening of clinical, laboratory, or radiological findings. For the purpose of this study, treatment failure due to lack of efficacy was defined as switch to the alternative regimen because of deterioration after around 7 days of primary therapy or as PCP-associated death while on primary treatment or up to 30 days after completing primary treatment.

Pneumocystis jiroveci pneumonia was classified as severe if patients developed respiratory failure with the need of supportive non-invasive and/or invasive ventilation for at least 24 h within the initial 3 days following PCP diagnosis. A need for supportive ventilation within the first 3 days was thought to reflect severe initial PCP rather than treatment failure, as clinical deterioration within the first days of effective therapy is not uncommon [15–17].

Patients not fulfilling criteria for severe PCP were classified as mild-to-moderate cases. Those patients either never developed respiratory failure necessitating supportive ventilation or did not require supportive ventilation within the first 3 days after initiation of PCP treatment.

Statistics

Categorical variables were compared using Fisher's exact test. Continuous variables were tested using the Mann–Whitney nonparametric U test. All tests were two-tailed and the results were considered significant when $p < 0.05$.

Results

Fifty-seven renal transplant patients with a confirmed PCP diagnosis were identified. None of the patients had received primary PCP prophylaxis prior to their diagnosis, which was in accordance with institutional protocols used during the study period due to an overall low PCP incidence in renal transplant patients at the time.

The patients' baseline characteristics are summarized in Tables 1 and 2 and are largely equally distributed between C–P und TMP/SMX patients. However, the higher proportion of patients with severe PCP in the TMP/SMX arm approached statistical significance ($p = 0.092$). Significantly higher serum lactate dehydrogenase (LDH) levels and significantly lower hemoglobin levels in patients initiating therapy with TMP/SMX are compatible with more severe PCP in this group [18, 19]. The rate of concurrent co-morbidities was high in both groups.

All patients were found to have typical signs and symptoms of PCP such as non-productive cough, dyspnea, weakness, fatigue, and most presented with elevated body temperatures. Chest X-ray was abnormal in all cases and usually presented typical features such as bilateral interstitial pulmonary infiltrates.

Outcome

Patients' outcome is depicted in Fig. 1. Fifty patients were cured (87.7 %), while seven patients died (12.3 %). Of 23 patients initiating therapy with C–P, seven were switched to TMP/SMX because of a perceived lack of efficacy. All seven experienced cure following the switch. Conversely, none of the seven patients failing TMP/SMX survived. Four died on treatment with TMP/SMX while the other three died despite switch to another regimen.

In an on-treatment evaluation, using a composite score of lack of efficacy and treatment-limiting adverse reactions as failure, success rates of C–P and TMP/SMX were comparable for the entire cohort, as well as in the subgroups of patients with mild-to-moderate and severe PCP, respectively (Table 3).

The proportion of patients with failure because of lack of efficacy, however, was higher for patients treated with

Table 1 Patients' baseline characteristics at time of PCP diagnosis

	Number of patients (%)		*p* value
	C–P ($n = 23$)	TMP/SMX ($n = 34$)	
Gender			
Male	13 (56.5)	20 (58.8)	1.000
Female	10 (43.5)	14 (41.2)	1.000
Age in years, median (range)	57 (38–75)	59 (33–79)	0.552
Race/ethnicity			
Caucasian	22 (95.7)	33 (97.1)	1.000
Black	1 (4.3)	0	0.404
Asian	0	1 (2.9)	1.000
Concurrent non-infectious diseases[a]	23 (100)	32 (82.4)	0.510
Cardiac disease	11 (47.8)	13 (38.2)	0.587
Coronary artery disease	9 (39.1)	10 (29.4)	0.569
Atrial fibrillation	2 (8.7)	3 (8.8 %)	1.000
Arterial hypertension	22 (95.7)	26 (76.4)	0.070
Diabetes mellitus	6 (26.1)	8 (23.5)	1.000
COPD/emphysema	4 (17.4)	4 (11.8)	0.702
Others[b]	2 (8.7)	6 (17.6)	0.453
Chronic hepatitis	3 (13)	3 (8.8)	0.677
Chronic hepatitis B	1 (4.3)	2 (5.9)	1.000
Chronic hepatitis C	2 (8.7)	1 (2.9)	0.559
Laboratory values (median, range)			
Hemoglobin (normal 12.5–16 g/dl)	11.5 (9–13)	10.6 (8–13)	0.018
Leukocyte count (3.9–10.5 cells/nl)	6.5 (2.0–18.5)	7.6 (2.8–19.6)	0.504
Serum AST (normal <35 (U/l)	30 (18–127)	24 (4–40)	0.039
Serum ALT (normal <40 U/l)	19 (8–78)	19 (3–45)	0.938
Serum LDH (normal 135–230 U/l)	327 (199–752)	381 (227–760)	0.042
Glomerular filtration rate (normal 90–120 ml/min)[c]	37.1 (14.6–45.4)	26.7 (17.5–63.3)	0.754
Severity of PCP			
Mild-to-moderate	18 (78.3)	18 (52.9)	0.092
Severe	5 (21.7)	16 (47.1)	0.092

ALT alanine aminotransferase, *AST* aspartate aminotransferase, *C–P* clindamycin–primaquine, *COPD* chronic obstructive lung disease, *LDH* serum lactate dehydrogenase, *PCP* pneumocystis jiroveci pneumonia, *TMP/SMX* trimethoprim-sulfamethoxazole

[a] Concurrent non-infectious diseases are listed if patients were receiving specific therapy for these conditions

[b] Other diseases/conditions include hyperparathyreoidism in four cases and Wegener's granulomatosis, hyperthyreoidism, anti-phospholipid syndrome and rheumatoid arthritis in one case each

[c] Glomerular filtration rate values in TMP/SMX patients include 32 of 34 patients. Two patients received renal replacement therapy for two, respectively, 36 months prior to the start of PCP treatment

Table 2 History of kidney disease and immunosuppressive therapy at the time of PCP diagnosis

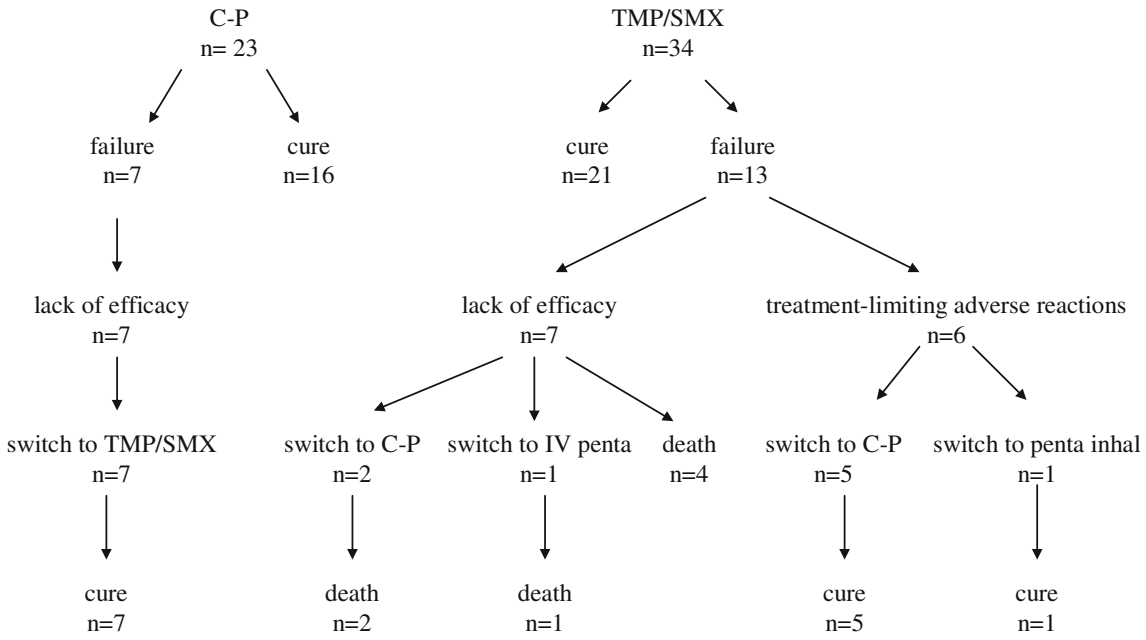
	Number of patients (%)		*p* value
	C–P ($n = 23$)	TMP/SMX ($n = 34$)	
Kidney disease leading to transplantation			
Polycystic kidney disease	4 (17.4)	5 (14.7)	1.000
Chronic glomerulonephritis	4 (17.4)	10 (29.4)	0.361
Chronic pyelonephritis	3 (13.0)	3 (8.8)	0.677
Diabetic nephropathy	0	3 (8.8)	0.265
Nephrosclerosis	2 (8.7)	3 (8.8)	1.000
Interstitial nephritis	1 (4.3)	0	0.404
Other	4 (17.4)	2 (5.9)	0.208
Unknown	5 (21.7)	8 (23.5)	0.539
Re-transplant patients	2 (8.7)	2 (5.9)	1.000
Time from last kidney transplantation weeks (median, range)	6.9 (4–220)	5.4 (0.5–104)	0.279
Immunosuppressive regimen at time of PCP diagnosis	23 (100)	34 (100)	1.000
CNI, MMF, St	18 (78.3)	27 (79.4)	1.000
CNI, AZA, St	1 (4.3)	2 (5.9)	1.000
Triple regimen with mTOR inhibitors	3 (13.0)	2 (5.9)	0.384
Dual regimen (CNI or MMF plus St)	1 (4.3)	3 (8.8)	0.641

AZA azathioprine, *CNI* calcineurin inhibitor (tacrolimus or cyclosporin A), *C–P* clindamycin–primaquine, *MMF* mycophenolate mofetil, *mTOR* mammalian target of rapamycin (sirolimus), *PCP* pneumocystis jiroveci pneumonia, *St* steroids, *TMP/SMX* trimethoprim-sulfamethoxazole

C–P as compared to TMP/SMX (Table 3). The difference between the groups was more pronounced in patients with severe disease.

Of the seven patients in the TMP/SMX group who died because of treatment failure, four underwent a second BAL, one at the time of switch on day 8 and another three prior to their death on TMP/SMX on days 12, 15, and 20 of treatment. In all four patients, repeat testing for pneumocystis jiroveci was negative. No repeat BAL was performed in any of the seven patients with C–P failure prior to their switch to TMP/SMX.

None of the C–P patients but 6 of 34 patients (17.6 %) on TMP/SMX were switched to an alternative regimen because of treatment-limiting adverse reactions ($p = 0.071$, Table 3). Four patients experienced worsening renal function between days 4 and 9 and were suspected to suffer from TMP/SMX-associated nephrotoxity. In all four, this working diagnosis was considered unlikely considering the further course of illness. Serum creatinine values in two patients had already fallen below pre-treatment values on



Abbreviations: C-P = clindamycin-primaquine, IV penta = intravenous pentamidine, TMP/SMX = trimethoprim/sulfamethoxazole, PCP = pneumocystis pneumonia, penta inhal = pentamidine inhalation

Fig. 1 Outcome of PCP treatment in renal transplant patients

the switch day. In the remaining two patients, serum creatinine values had increased while on TMP/SMX treatment but this increase did not resolve after switch to C-P.

Another two patients developed serious liver impairment (serum transaminase increases > ninefold the upper limit of normal) and severe neutropenia (around 750 cells/μl) on days 10 and 14, respectively (20). In both, abnormalities resolved after switching to C–P. In summary, the rate of adverse reactions attributable to TMP/SMX after review was 5.9 % (2 of 34 patients).

All six patients who were switched from TMP/SMX to either C–P (five patients) or pentamidine inhalation (one patient) due to assumed adverse reactions from TMP/SMX had already experienced clinical improvement including resolution of dyspnea on the day of switch and all patients were cured.

Salvage treatment

Two patients with treatment failure while on TMP/SMX were switched to C–P, while seven patients were switched from C–P to TMP/SMX (Table 4). At the time of the switch, all patients had experienced respiratory failure and required ventilatory support. Both patients failing TMP/SMX had already needed ventilatory support at the time of PCP diagnosis. Three out of seven patients failing C–P had also received ventilatory support at the time of PCP diagnosis, while four initially mild-to-moderate PCP cases developed respiratory failure prior to switching on treatment days 6–10.

None of the two patients who were switched from TMP/SMX to C–P due to treatment failure responded to C–P, while all seven patients switched from C–P to TMP/SMX were cured. While the numbers are small, the difference was statistically significant ($p = 0.028$) (Table 4).

Complications and causes of death

Infectious and non-infectious complications were observed more frequently in patients starting with TMP/SMX when compared to C–P patients. The mortality was also significantly higher in patients starting TMP/SMX as compared to those initiating C–P (Table 5).

The higher complication and mortality rates observed in patients started on TMP/SMX appeared to be due to a higher incidence of severe PCP in this patient group (Table 1). The rate of complications in patients receiving TMP/SMX was numerically higher in patients with severe disease compared to those with mild-moderate PCP (infectious complications: 10/16, 62.5 %, versus 6/18, 33.3 %, $p = 0.168$; non-infectious complications: 5/16, 31.3 %, versus 3/18, 16.7 %, $p = 0.429$). Mortality was significantly higher in patients on TMP/SMX with severe PCP as compared to mild-moderate PCP (6/16 versus 1/18, $p = 0.038$).

Sixteen out of 57 patients (28.1 %) suffered from concurrent CMV infection as defined by standard case

Table 3 Outcome of renal transplant patients with primary PCP episodes according to treatment regimen and severity of PCP (on-treatment-analysis)

Severity of PCP	Number of patients (% per patient group)		*p* value
	C–P	TMP/SMX	
PCP (total)	23	34	
Treatment success	16 (69.6)	21 (61.8)	0.545
Treatment days (median, range)	25 (16–50)	19 (12–42)	0.027
Reasons of treatment failure			
Lack of efficacy	7 (30.4)	7 (20.6)	0.532
Treatment switch	7 (30.4)	3 (8.8)	
Treatment days (median, range)	6 (5–10)	8 (7–12)	0.298
Death on primary treatment	0	4 (11.8)	
Treatment days (median, range)	n.a.	21 (13–25)	
Adverse reactions leading to switch	0	6 (17.6)	0.071
Treatment days (median, range)	n.a.	7 (4–12)	
Mild-to-moderate PCP	18	18	
Treatment success	14 (77.8)	15 (83.3)	1.000
Reasons of treatment failure			
Lack of efficacy (treatment switch)	4 (22.2)	1 (5.6)	0.338
Adverse reactions leading to switch	0	2 (11.1)	0.486
Severe PCP	5	16	
Treatment success	2 (40)	6 (37.5)	1.000
Reasons of treatment failure			
Lack of efficacy	3 (60)	6 (37.5)	0.611
Treatment switch	3 (60)	2 (12.5)	
Death on primary treatment	0	4 (25)	
Adverse reactions leading to switch	0	4 (25)	0.532

C–P clindamycin–primaquine, *PCP* pneumocystis jiroveci pneumonia, *TMP/SMX* trimethoprime/sulfamethoxazole

Table 4 Outcome of salvage therapy following failure of primary treatment

	Number of patients		*p* value
	C–P after TMP/SMX ($n = 7$)	TMP/SMX after C–P ($n = 7$)	
Switch due to lack of efficacy	2	7	n.a.
Treatment days until switch (median, range)	9.5 (7–12)	7 (6–10)	
Treatment success after switch	0/2	7/7 (100 %)	0.028
Treatment days after switch (median, range)	8.5 (7, 10)	25 (21–36)	
Switch because of adverse reactions	5	0	n.a.
Treatment days until switch	5 (4–10)		
Treatment success after switch	5/5 (100 %)	n.a.	n.a.
Treatment days after switch (median range)	18 (11–23)		

C–P clindamycin–primaquine, *n.a.* not applicable, *TMP/SMX* trimethoprim-sulfamethoxazole

definition classifications of CMV infection in transplant patients [21]. All 16 patients had a positive quantitative CMV polymerase chain reaction (PCR) assay with a CMV blood viral load of >5,000 copies/ml and all received ganciclovir treatment.

Six patients had a concurrent diagnosis of aspergillosis and all of them were treated with TMP/SMX. Five of these patients died and two had widely disseminated aspergillosis confirmed at autopsy. The remaining four patients had a positive aspergillus antigen (galactomannan) blood test and one of them also had aspergillus cultured from bronchial secretions.

The primary cause of death in all seven fatal cases was respiratory failure due to severe progressive bilateral pneumonia progressing to ARDS and organizing pneumonia associated with sepsis. All patients had also suffered from additional complications with bacterial endocarditis, bilateral pneumothoraces, pulmonary embolism, myocardial infarction, gastrointestinal perforation, gastrointestinal bleeding, and cerebral bleeding confirmed in one case each.

Serious myelosuppression [20] developed in five patients, who all eventually died. Myelosuppression was not considered to be primarily TMP/SMX-associated in any of these five patients. Two patients had a documented neutrophil count of <500 cells/μl prior to diagnosis of PCP, which was attributed to ganciclovir treatment for CMV infection. In another patient, neutropenia developed with concurrent ganciclovir treatment of CMV infection. Three patients developed thrombocytopenia with <20,000 cells/μl which was attributed to concurrent sepsis in all three patients.

TMP/SMX patients were more likely to require renal replacement therapy (RRT) after PCP diagnosis (10/32, 31.5 % versus 2/23, 8.7 %, $p = 0.056$, Table 5). Two TMP/SMX patients were already on RRT at the time of diagnosis. The higher rate of RRT initiation in patients on TMP/SMX appeared to be partly due to the higher incidence of severe PCP in this patient group (7/16 patients

Table 5 Infectious and non-infectious complications, and death associated with PCP according to initial treatment assignment (intent-to-treat-analysis)

	Number of patients (%)		*p* value
	C–P ($n = 23$)	TMP/SMX ($n = 34$)	
Infectious complications (other than PCP)[a]	8 (34.8)	22 (64.7)	0.033
Bacterial infections	5 (21.7)	14 (41.2)	0.159
Pulmonary infection	0	6 (17.6)	0.034
Urinary tract infection	5 (21.7)	9 (26.5)	0.762
Endocarditis	0	1 (2.9)	1.000
Aspergillosis	0	6 (8.8)	0.071
CMV infection	4 (17.4)	12 (35.3)	0.229
Non-infectious complications (non-renal)	0	8 (23.5)	0.016
Pulmonary embolism	0	1 (2.9)	1.000
Bilateral pneumothorax	0	1 (2.9)	1.000
Myocardial infarction	0	1 (2.9)	1.000
Gastrointestinal perforation	0	2 (5.9)	0.510
Gastrointestinal bleeding	0	2 (5.9)	0.510
Cerebral bleeding	0	1 (2.9)	1.000
Acute kidney injury requiring RRT	2 (8.7)	10/32 (31.3)[b]	0.056
Death	0	7 (20.6)	0.034

CMV cytomegalovirus, *C–P* clindamycin–primaquine, *PCP* pneumocystis jiroveci pneumonia, *RRT* renal replacement therapy, *TMP/SMX* trimethoprim/sulfamethoxazole

[a] The number of infections listed may exceed the number of patients as some patients suffered from more than one infection or infectious complication, respectively

[b] Two of 34 patients with TMP/SMX treatment were already receiving renal replacement therapy for two, respectively 36 months prior to PCP diagnosis and were therefore excluded from assessment of PCP-associated renal failure

with severe PCP, 43.8 % versus 3/16 patients with mild-to-moderate PCP, 18.8 %, $p = 0.252$). Both C–P patients requiring RRT suffered from mild-to-moderate PCP.

Six out of 10 patients on TMX/SMX and RRT died of PCP after diagnosis. One of the four surviving patients was still on RRT 1 month after completing PCP treatment and was thereafter lost to follow-up. In the remaining three patients, renal function had recovered sufficiently to allow for termination of RRT. Renal function of both patients on C–P treatment who had required RRT recovered at the end of successful PCP treatment, obviating the need for additional RRT.

Discussion

Pneumocystis jiroveci pneumonia in renal transplant patients often presents with life-threatening disease. TMP/SMX has been the first-line treatment option for PCP in renal transplant patients since the beginning of the kidney transplantation era [1, 3–6]. However, the number of patients with renal transplants receiving treatment for PCP reported is small and comprehensive or comparative data is not available. To our knowledge, reports on series of patients treated with regimens other than TMP/SMX are lacking entirely. The current study is the first to present data on C–P treatment of renal transplant associated PCP and on the relative benefit of TMP/SMX and C–P.

Despite its retrospective nature, this study evaluating a comparably large number of patients contributes to valuable information. While the study was not randomized and therefore subject to allocation bias, essential patient management measures such as evaluation of efficacy and switch criteria applied in case of failure as well as classification into mild-to-moderate and severe PCP were protocol driven and standardized. Treatment switch in case of failure after approximately 7 days is a commonly used approach [8, 9, 11–13]. Definition of severe PCP as early respiratory failure defines a distinct patient group [22].

In the setting studied, C–P appeared to be safe but was probably less effective than TMP/SMX. Of note, TMP/SMX also had an acceptable safety profile even if the rate of treatment-limiting adverse events was slightly higher. Thus, our data support the current role of TMP/SMX as first-line treatment option in renal transplant patients [3]. In patients experiencing treatment failure on C–P, TMP/SMX was also effective as salvage therapy [11].

In an on-treatment evaluation overall treatment success slightly favored C–P with 69.6 % compared to TMP/SMX with 61.8 % ($p = 0.545$). However, important differences in terms of efficacy and safety became apparent when failure rates due to lack of efficacy were separated from those due to treatment-limiting adverse reactions.

In this study, C–P was associated with a higher failure rate due to lack of efficacy. This difference in favor of TMP/SMX was even more pronounced in patients with severe PCP. The lack of statistical significance in the total group and subgroup analysis of primary treatment is likely due to insufficient patients available for such comparisons.

The suggested higher efficacy of TMP/SMX is corroborated by additional observations. Firstly, microbiological efficacy of TMP/SMX was shown in all four patients who died with PCP and had repeat BAL examinations, demonstrating pathogen clearance in all. Most of these patients appear to have died primarily from complications rather than from treatment-unresponsive PCP.

Furthermore, TMP/SMX was significantly more effective in salvage treatment in patients failing C–P when compared to C–P in patients failing on TMP/SMX. Notably, all patients cured with TMP/SMX treatment after C–P failure suffered from respiratory failure requiring

supportive ventilation at the time of switch. The observed effect is in stark contrast with the considerable mortality of PCP in patients requiring ventilatory support reported in the literature [22].

No treatment-limiting adverse reactions were observed in patients on C–P compared to a non-significantly higher rate of adverse reactions seen with TMP/SMX indicating a possibly better tolerability of C–P (0 versus 17.6 %, $p = 0.071$). However, when we excluded reactions in which a causative role of TMP/SMX, upon retrospective review, was considered improbable the rate decreased to 5.9 %. The rate of treatment-limiting reactions was therefore considered low with either regimen. Interestingly, the complete absence of rash, which would have been expected to occur with either regimen, may have been the result of broad use of steroids and immunosuppressive drugs in this patient population.

The significantly higher rates of infectious and non-infectious complications and mortality in patients starting TMP/SMX as compared to C–P is best explained by a distinctly higher rate of severe PCP in the TMP/SMX patient group ($p = 0.092$). Complications and fatal outcome were clearly associated with the severity of PCP in these patients. The mortality rate was significantly higher in severe compared to mild-to-moderate PCP. The higher proportion of severe PCP in patients on TMP/SMX is likely the result of an allocation bias stemming from the preferential use of TMP/SMX instead of C–P in patients with severe PCP.

Notably, there was no clear evidence that TMP/SMX treatment led to a significantly higher rate of renal failure assessed by the need for RRT. The higher rate of patients on TMP/SMX requiring RRT ($p = 0.056$) appeared to be more closely associated with higher rates of severe PCP. Importantly, in patients with successful PCP treatment renal function appeared to recover allowing for termination of RRT and thereby indicating a graft survival irrespective of the regimen used.

Clindamycin–primaquine appears to be a reasonable alternative for patients improving on but developing significant TMP/SMX-associated treatment-limiting adverse reactions as reported from previous studies [12]. C–P may also be considered an acceptable first-line regimen in patients with co-morbid conditions or allergies, which may preclude treatment with TMP/SMX. Notably, all patients who were initially started on C–P eventually achieved cure. The fact that salvage treatment with TMP/SMX led to cure in all patients failing C–P justifies TMP/SMX salvage even in patients with relative contraindications.

In other settings, C–P has been shown to be an effective salvage regimen in patients with TMP/SMX failure [10–13]. In our study, C–P salvage treatment had failed in both patients experiencing TMP/SMX failure.

Overall, the current treatment of PCP is not optimal considering the substantial mortality. Even with treatment mortality rates between 5 and 38 % [3, 23, 24] have been reported. This is in line with a mortality of 12.3 % (7 of 57 patients) seen in this study.

Factors other than microbiological efficacy appear to have a substantial impact on treatment outcome. Despite microbiologically effective treatment, PCP may progress to ARDS, organizing pneumonia, and a variety of other complications associated with respiratory failure and mortality.

Pneumocystis jiroveci pneumonia treatment in renal transplant patients is further complicated by other, as of yet unresolved issues. The role of supportive steroid use in patient populations other than AIDS patients is undefined [25, 26] and the optimal management of immunosuppression is unknown [3, 27, 28]. Reduction of immunosuppression may support efficacy of PCP treatment but may also harm the function of the renal transplant.

Furthermore, optimal dose adjustment of TMP/SMX in underlying or developing renal impairment remains a critical issue. Therapeutic drug monitoring has been recommended for TMP/SMX in renal transplant patients but is not readily available [6, 29].

Prevention of PCP therefore appears to be the preferable option. The efficacy of primary prophylaxis of PCP has been well established in HIV-infected patients and the risk of PCP as a result of severe immunodeficiency has been well defined [30]. Primary prophylaxis has been shown to be effective in patients with solid organ transplants as well. However, the optimal duration of primary prophylaxis in patients with renal transplants is yet unclear [31]. It is not clear how widespread use of primary prophylaxis would have affected the observed results. A better delineation of risk factors for PCP in renal transplant patients would allow for more targeted provision of prophylaxis in patients at higher risk [3, 32].

Conflict of interest On behalf of all authors, the corresponding author states that there is no conflict of interest.

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