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Treatment With Reduced-Dose Trimethoprim-Sulfamethoxazole Is Effective in Mild to Moderate *Pneumocystis jirovecii* Pneumonia in Patients With Hematologic Malignancies

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Background. Recent studies have reported that reduced-dose trimethoprim-sulfamethoxazole (TMP-SMX) may be effective in the treatment of *Pneumocystis jirovecii* pneumonia (PJP), but data are lacking for patients with hematologic malignancies.

Methods. This retrospective study included all adult hematologic patients with PJP between 2013 and 2017 at 6 Swedish university hospitals. Treatment with 7.5–15 mg TMP/kg/day (reduced dose) was compared with >15–20 mg TMP/kg/day (standard dose), after correction for renal function. The primary outcome was the change in respiratory function (Δpartial pressure of oxygen [PaO_2]/fraction of inspired oxygen [FiO_2]) between baseline and day 8. Secondary outcomes were clinical failure and/or death at day 8 and death at day 30.

Results. Of a total of 113 included patients, 80 patients received reduced dose and 33 patients received standard dose. The overall 30-day mortality in the whole cohort was 14%. There were no clinically relevant differences in $\Delta PaO_2/FiO_2$ at day 8 between the treatment groups, either before or after controlling for potential confounders in an adjusted regression model (−13.6 mm Hg [95% confidence interval {CI}, −56.7 to 29.5 mm Hg] and −9.4 mm Hg [95% CI, −50.5 to 31.7 mm Hg], respectively). Clinical failure and/or death at day 8 and 30-day mortality did not differ significantly between the groups (18% vs 21% and 14% vs 15%, respectively). Among patients with mild to moderate pneumonia, defined as PaO_2/FiO_2 >200 mm Hg, all 44 patients receiving the reduced dose were alive at day 30.

Conclusions. In this cohort of 113 patients with hematologic malignancies, reduced-dose TMP-SMX was effective and safe for treating mild to moderate PJP.

Keywords. *Pneumocystis* pneumonia; hematologic malignancies; treatment outcome; trimethoprim-sulfamethoxazole.

Pneumonia caused by *Pneumocystis jirovecii* (PJP) is a life-threatening opportunistic infection in immunocompromised patients. In settings with a low prevalence of untreated human immunodeficiency virus (HIV) infection, patients with hematologic malignancies constitute the largest risk group for developing PJP [1]. Widespread use of trimethoprim-sulfamethoxazole (TMP-SMX) prophylaxis has significantly lowered the incidence of PJP in high-risk hematological patients, but PJP still occurs in high-risk patients not tolerating TMP-SMX or after discontinuing prophylaxis [2, 3], and in low-risk patients not receiving prophylactic treatment, in particular patients who have received treatment with high-dose corticosteroids [4].

The recommended first-line treatment for PJP in patients with hematologic malignancies is TMP-SMX given at a high dose, 15–20 mg/kg of the TMP component [5], but the evidence supporting this high dose is anecdotal [6]. TMP-SMX therapy may cause dose-dependent adverse events, and previous studies have shown that the standard high-dose TMP-SMX for the treatment of PJP may be correlated to an increased frequency of such adverse events [7, 8].

In a recent meta-analysis analyzing reduced-dose vs standard-dose TMP-SMX for the treatment of PJP, there was no statistically significant difference in mortality but an 18%

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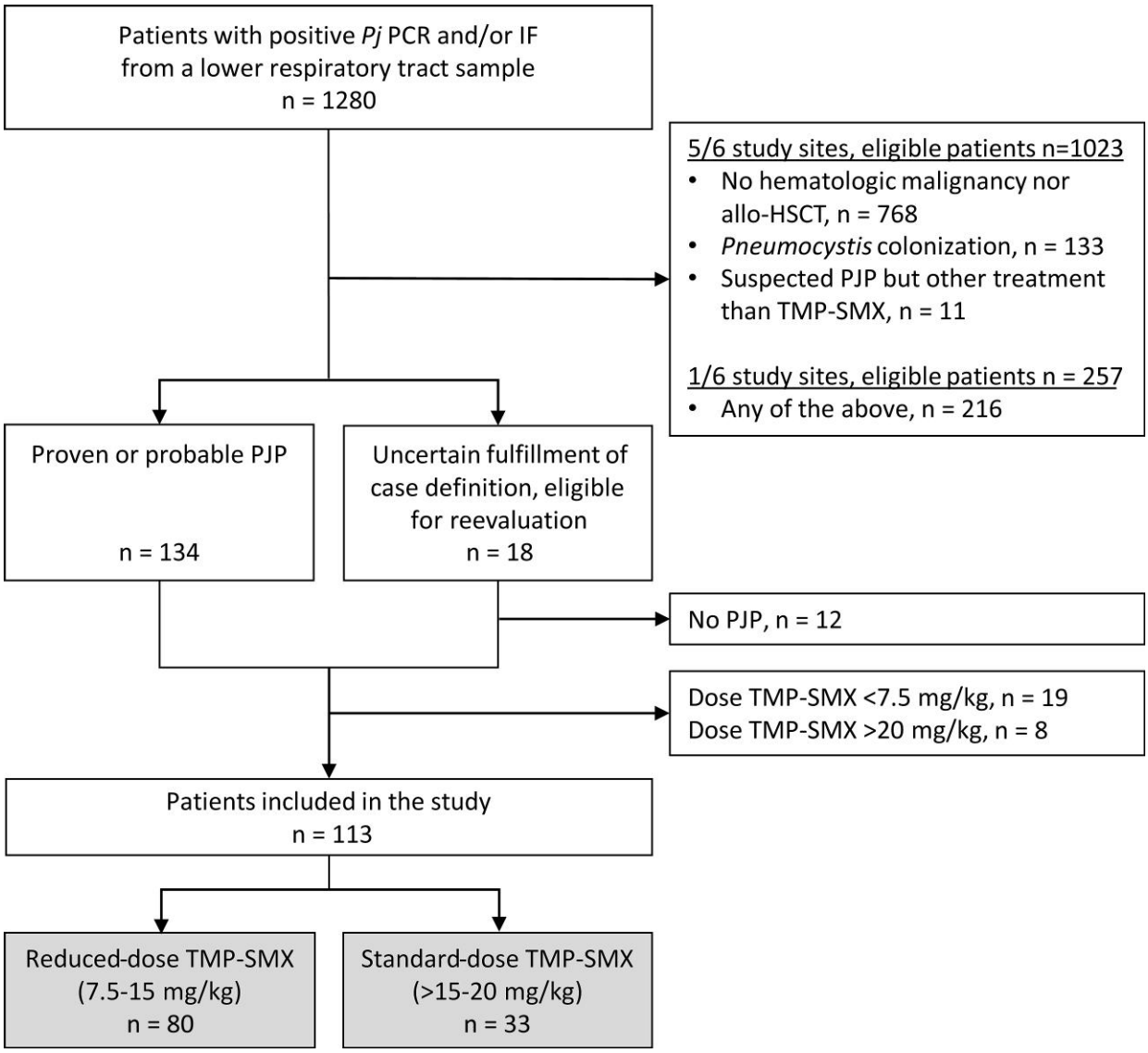

Figure 1. Flowchart showing the patient inclusion process and the assignment to treatment group. Abbreviations: allo-HSCT, allogeneic hematopoietic stem cell transplantation; IF, immunofluorescence; PCR, polymerase chain reaction; *Pj*, *Pneumocystis jirovecii*; PJP, *Pneumocystis jirovecii* pneumonia; TMP-SMX, trimethoprim-sulfamethoxazole.

absolute risk reduction of adverse events with reduced doses of TMP-SMX [9]. However, few patients with hematological malignancies were included in this study, and it is thus unclear if these findings can be generalized to a hematological population. This retrospective multicenter study aimed to fill this knowledge gap by comparing clinical outcomes and adverse events in hematologic patients receiving a reduced vs standard dose of TMP-SMX for the treatment of PJP.

METHODS

Study Design, Patient Inclusion Process, and Case Definition

This retrospective multicenter study included adult hematologic patients with proven or probable PJP [10] treated with TMP-SMX in 6 Swedish university hospitals between 2013 and 2017. The study was approved by the Swedish Ethics Review Board (Dnr 2018/1307-31/2) and performed in accordance with the ethical standards of the 1964 Declaration of Helsinki and its later amendments.

The inclusion process and grouping of patients are presented in Figure 1. Laboratory reports from the departments of clinical microbiology were reviewed to identify eligible patients, that is, patients ≥18 years of age with either positive immunofluorescence (IF) or polymerase chain reaction (PCR) for *P. jirovecii* in a sputum or bronchoalveolar lavage sample. Subsequently, medical records were reviewed, and patients with a hematologic malignancy or previous allogeneic hematopoietic stem cell transplantation were further evaluated regarding the definition

of PJP and TMP-SMX treatment. "Proven" and "probable" PJP were defined according to the revised definitions of invasive fungal disease from the European Organization for Research and Treatment of Cancer and Mycoses Study Group (EORTC/MSG) [10, 11]. In an attempt to make the classification more stringent and to avoid the inclusion of dubious cases, the EORTC/MSG criteria for probable PJP were modified to include both typical radiographic findings (ie, diffuse interstitial infiltrates or ground-glass opacity) and respiratory symptoms (ie, dyspnea, cough, or hypoxia <95% oxygen saturation of arterial blood without oxygen therapy) as requirements for clinical criteria. Additionally, due to large differences in the use of serum ß-D-glucan between study sites during the study period, ß-D-glucan was not considered as a mycological criterion. Eligible patients were primarily assessed by the principal investigator at each study site. Uncertain cases, including patients who had only a chest radiograph and not a computed tomography (CT) scan performed, were reevaluated independently by 2 senior infectious disease specialists (H. H. and O. B.). In the case of divergent assessments, a consensus was reached after discussion. Finally, only patients receiving an initial treatment dose of 7.5–20 mg/kg/day of the TMP component after correction for renal function were eligible for inclusion.

Definition of Treatment Groups

The patients were divided into 2 groups according to the initial treatment dose of TMP-SMX: (1) reduced-dose group receiving 7.5–15 mg/kg/day of TMP component; and (2) standard-dose group receiving >15–20 mg/kg/day of TMP component. The initial treatment dose was defined as the mean daily dose/kg of TMP, corrected for renal function, on the first and second day of PJP treatment (the dose referred to from hereafter). The first treatment day corresponds to the first calendar day of full treatment, generally meaning the day after the start of treatment. This approach was chosen to better reflect the true TMP-SMX exposition as the initial TMP-SMX dose often was adjusted (either increased or decreased) during the first days of treatment. The corrected dose was calculated as the actual given dose multiplied by a correction factor according to creatinine clearance (CrCl): ≥50 mL/minute, factor 1; 30 to <50 mL/minute: factor 1.5; 15 to <30 mL/minute: factor 2.0; <15 mL/minute or hemodialysis: factor 3.0 [12].

Data Collection and Measures

Data regarding baseline characteristics, PJP treatment, and clinical outcome were collected retrospectively from medical records. Respiratory function was defined based on the degree of hypoxemia expressed by the partial pressure of oxygen (PaO_2)/fraction of inspired oxygen (FiO_2) ratio, as estimated regardless of mechanical ventilation. When arterial blood gas data were unavailable, PaO_2 was estimated from the peripheral oxygen saturation as described elsewhere [13]. The severity of PJP at baseline was defined as mild to moderate if PaO_2/FiO_2 was >200 mm Hg (ie, respiratory Sequential Organ Failure Assessment [SOFA] score of 0–2) and severe if PaO_2/FiO_2 was ≤200 mm Hg (ie, respiratory SOFA score 3–4 [14]). The patients' functioning level was assessed according to the Eastern Cooperative Oncology Group (ECOG) Performance Status [15], where ECOG grade 0 reflects no disability in daily living ability; grade 3, a capability of only limited self-care; and grade 5, death. Adverse events were determined according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5 [16], where CTCAE grade 1 refers to mild adverse events requiring no intervention, grades 2–4 refer to moderate to life-threatening events requiring an intervention, and grade 5 refers to death related to adverse events.

Outcome Measures

The primary outcome measurement was the change in respiratory function, measured as the difference in PaO_2/FiO_2 ($\Delta PaO_2/FiO_2$), between baseline and day 8 after the start of PJP treatment, with a positive value reflecting clinical improvement. For patients who died before day 8, the last measurement of respiratory function before death was used [13]. Secondary clinical outcome measures were clinical failure (ie, no clinical improvement or worsening in respiratory function according to clinical judgment as documented by the treating physicians in the medical records) and/or death at day 8, and 30-day mortality after start of PJP treatment. The frequency of any adverse events during the course of PJP treatment with CTCAE grade ≥2, reflecting an adverse event requiring a clinical intervention, was compared between the 2 treatment groups.

Statistical Analysis

Differences in baseline characteristics between the treatment groups were assessed by Fisher exact test for categorical variables and Mann-Whitney *U* test for continuous variables. For the primary outcome, $\Delta PaO_2/FiO_2$, univariable analyses of reduced-dose TMP-SMX and potential confounding covariates were performed using the unpaired *t* test for categorical variables and linear regression for continuous variables. Covariates with *P* values ≤ .1 in the univariable analysis were subsequently included in a multivariable analysis using multivariable linear regression. Univariable analyses of the binary outcomes, clinical failure and/or death at day 8, 30-day mortality, and any adverse event requiring clinical intervention, were performed using Fisher exact test and presented as odds ratios (ORs). The difference in 30-day mortality was also assessed after subgrouping patients according to the severity of pneumonia (PaO_2/FiO_2 >200 mm Hg and ≤200 mm Hg, respectively).

RESULTS

Patients

In total, 113 patients with PJP were included. The mycological criterion was fulfilled by a positive IF only in 5 patients (PCR

not performed), positive IF and PCR in 26 patients, and positive PCR only in 82 patients (39 with negative IF and 43 with no IF performed). The clinical criterion was fulfilled by the combination of respiratory symptoms and a positive chest CT scan in 100 patients (88%) and respiratory symptoms and a positive radiograph in the remaining 13 patients (12%). One patient was receiving prophylaxis for PJP at the time of diagnosis and thus had a breakthrough infection. After correcting for reduced renal function in 7 patients with CrCl <50 mL/minute at baseline, 80 patients were assigned to the reduced-dose group (7.5–15 mg TMP/kg/day) and 33 to the standard-dose group (>15–20 mg TMP/kg/day) (Figure 1). Table 1 shows baseline characteristics of the whole cohort and the 2 treatment groups. There were no differences in median time from onset of symptoms until start of PJP treatment (10 days) in the groups. There was a significantly higher proportion of patients with impaired daily living abilities (ECOG performance status ≥3) in the standard-dose group (27% vs 10%, $P = .04$). Patients receiving the standard dose tended to have more severe pneumonia at baseline than patients receiving the reduced dose (the median PaO_2/FiO_2 was 195 and 216 mm Hg, and the percentage of patients with PaO_2/FiO_2 ≤200 mm Hg was 52% and 45% in the standard and the reduced-dose group, respectively), but these differences were not statistically significant.

Treatment of PJP

The median initial corrected treatment doses were 11.6 mg TMP/kg/day (range 7.9–14.8 mg TMP/kg/day) and 16.7 mg TMP/kg/day (range 15.1–20 mg TMP/kg/day) in the reduced- and standard-dose groups, respectively (Figure 2). Nineteen of 33 patients (58%) in the standard-dose group were subject to dose reductions after the first 2 full days of treatment that resulted in a mean corrected daily dose of TMP-SMX of ≤15 mg/kg on days 3–7. In only 1 of 80 patients in the reduced-dose group, the dose was increased so that the mean corrected daily dose TMP-SMX was >15 mg/kg on days 3–7. This patient was not considered to be a case of clinical failure according to the documentation in the medical record by the treating physician, and the reason for the dose increase was unknown.

Details regarding PJP treatment and duration of TMP-SMX are presented in Table 2. Eighty patients received <21 days of TMP-SMX treatment (median, 14 days [range, 2–20 days]). The reason for TMP-SMX discontinuation was clinical cure in 58 of 80 patients (median TMP-SMX duration, 14.5 days [range, 7–20 days]), adverse reactions and switch to a second-line drug in 6 of 34 patients (median TMP-SMX duration, 8 days [range, 6–12 days]), and death in 16 of 80 patients.

Outcomes

There was no clinically relevant difference in the primary outcome measure, mean $\Delta PaO_2/FiO_2$ (70.2 mm Hg in the reduced-dose group vs 83.8 mm Hg in the standard-dose group) (difference, −13.6 [95% confidence interval {CI}, −56.7 to 29.5]) (Table 3). Univariable analysis investigating potential confounding covariates on $\Delta PaO_2/FiO_2$ found that age, ECOG ≥3, and PaO_2/FiO_2 at baseline had a statistically significant association with $\Delta PaO_2/FiO_2$. Controlling for these 3 covariates in an adjusted linear regression model did not significantly change the result of the primary outcome, $\Delta PaO_2/FiO_2$ (−9.4 [95% CI, −50.5 to 31.7]) (Table 4).

The overall mortality in the whole cohort was 14%. There were no significant differences in clinical failure and/or death at day 8 (18% vs 21%; OR, 0.8 [95% CI, .3–2.0]; $P = 0.8$) or 30-day mortality (14% vs 15%; OR, 0.9 [95% CI, .3–2.5]; $P > 0.9$) (Table 3). There was no statistically significant difference in adverse events requiring a clinical intervention (ie, CTCAE grade ≥2) between the groups (25% vs 33%; OR, 0.7 [95% CI, .3–1.6]; $P = .4$). All adverse events are presented in Supplementary Table 1.

In a univariable analysis of covariates potentially associated with 30-day mortality, baseline PaO_2/FiO_2 was found to be strongly associated with death ($P < .0001$). This finding prompted a post hoc analysis of 30-day mortality by stratification of baseline PaO_2/FiO_2. Among 60 patients with baseline PaO_2/FiO_2 >200 mm Hg (ie, respiratory SOFA score ≤2 corresponding to mild to moderate pneumonia), mortality in the reduced-dose group was 0 (0/44) compared to 6% (1/16) in the standard-dose group ($P = .3$). For patients with baseline PaO_2/FiO_2 ≤200 mm Hg (ie, respiratory SOFA score ≥3 corresponding to severe pneumonia), mortality was 31% and 24% in the reduced-dose and standard-dose groups, respectively ($P = .7$).

DISCUSSION

In this retrospective multicenter study comparing reduced-dose with standard-dose TMP-SMX for the treatment of PJP in patients with hematologic malignancies, we found no clinically or statistically significant difference in the primary outcome, change in PaO_2/FiO_2 ratio between baseline and day 8. Furthermore, there were no significant differences in clinical failure and/or death at day 8 or 30-day mortality between the groups.

The current recommended dose of TMP-SMX for the treatment of PJP is based on findings from a small prospective study on children with PJP from 1975 [17] and subsequently on clinical trials conducted on patients with HIV. Since there are several differences in the pathophysiologic and clinical picture of PJP in patients with HIV compared to non-HIV-related PJP [18], these results cannot readily be extrapolated to the HIV-uninfected population. Accordingly, the authors of a recently published review article concluded that the current recommended dose of TMP-SMX relies on outdated evidence that fails to include the at-risk populations of today, such as patients with hematologic malignancies [6]. In 2020, Butler-Laporte and colleagues published a systematic review on the clinical

Table 1. Baseline Characteristics of the Study Population

Characteristic	All Patients (N = 113)	Reduced Dose (n = 80)	Standard Dose (n = 33)	*P*-Value
Sex				
Male	80 (71)	61 (76)	19 (58)	.07
Female	33 (29)	19 (24)	14 (42)	
Age, y, median (range)	68 (22–88)	68 (27–88)	67 (22–84)	.41
Hematologic diagnosis				
Lymphoid malignancy	69 (61)	51 (64)	18 (55)	.4
B-cell lymphoma	30 (27)	…	…	
T-cell lymphoma	9 (8)	…	…	
Acute lymphoblastic leukemia	8 (7)	…	…	
Chronic lymphocytic leukemia	22 (19)	…	…	
Myeloid malignancy	22 (19)	13 (16)	9 (27)	.2
Acute myeloid leukemia or myelodysplastic syndrome	21 (19)	…	…	
Chronic myeloid leukemia	1 (1)	…	…	
Plasma cell malignancy	20 (18)	14 (18)	6 (18)	>.9
Myeloma	19 (17)	…	…	
Morbus Waldenström	1 (1)	…	…	
Myelofibrosis	2 (2)	…	…	
Immunosuppressants during 6 mo prior to PJP				
Antineoplastic drugs[a]	60 (53)	40 (50)	20 (61)	.41
Antibodies[b]	22 (19)	14 (18)	8 (24)	.43
Small molecules[c]	24 (21)	19 (24)	5 (15)	.45
Other immunosuppressive drugs[d]	2 (2)	2 (3)	0 (0)	
Previous HSCT	22 (19)	12 (15)	8 (24)	.28
Autologous	7	5	2	
Allogeneic	15	7	6	
Prolonged steroids prior to PJP[e]	21 (19)	14 (18)	7 (21)	.79
BMI, kg/m^2, median (range)	24 (16–42)	24 (18–34)	24 (16–42)	.35
CrCl, mL/min, at the day of start of PJP treatment				
≥50	106 (94)	76 (95)	30 (91)	.41
30 to <50	6	3	3	
15 to <30	0	0	0	
<15 or hemodialysis	1	1	0	
ECOG performance status ≥3 at baseline	17 (15)	8 (10)	9 (27)	.04*
Hypoalbuminemia (<30 g/L) at baseline[f]	77 (83)	54 (83)	23 (82)	>.9
Characteristics of PJP at baseline				
Days from onset of symptoms until start of PJP treatment, median (range)	10 (0–65)	10 (2–65)	10.5 (0–57)	.52
PaO_2/FiO_2 at baseline, mm Hg, median (range)	210 (58–690)	216 (58–690)	195 (59–401)	.27
Severity of PJP at baseline				.54
Mild to moderate (PaO_2/FiO_2 >200 mm Hg)	60 (53)	44 (55)	16 (48)	
Severe (PaO_2/FiO_2 ≤200 mm Hg)	53 (47)	36 (45)	17 (52)	
Noninvasive or mechanical ventilation[g]	21[h] (19)	12 (15)	9 (27)	.18

Data are presented as No. (%) unless otherwise indicated.

Abbreviations: BMI, body mass index; CrCl, creatinine clearance; ECOG, Eastern Cooperative Oncology Group; FiO_2, fraction of inspired oxygen; HSCT, hematopoietic stem cell transplant; PaO_2, partial pressure of oxygen; PJP, *Pneumocystis jirovecii* pneumonia.

[a]For example, vincristine, fludarabine, cyclophosphamide, methotrexate, cytarabine, doxorubicin.

[b]Rituximab, alemtuzumab, brentuxumab.

[c]For example, thalidomide, idelalisib, revlemide, ibrutinib.

[d]Tacrolimus or cyclosporine.

[e]≥20 mg daily >4 weeks at any time during the time period of 90 days preceding PJP.

[f]Measurement of albumin was missing in 20 patients (5 in the standard-dose group and 15 in the reduced-dose group).

[g]At baseline or within the first 48 hours of trimethoprim-sulfamethoxazole treatment.

[h]One patient with noninvasive ventilation is excluded due to missing data regarding time of initiation.

outcome of reduced-dose TMP-SMX for the treatment of PJP [9]. No difference in mortality was found between HIV-uninfected patients receiving reduced dose and standard dose, but the 3 studies included in this review all had limitations, making the result difficult to extrapolate to a hematologic population. One of the studies included only 8 patients with

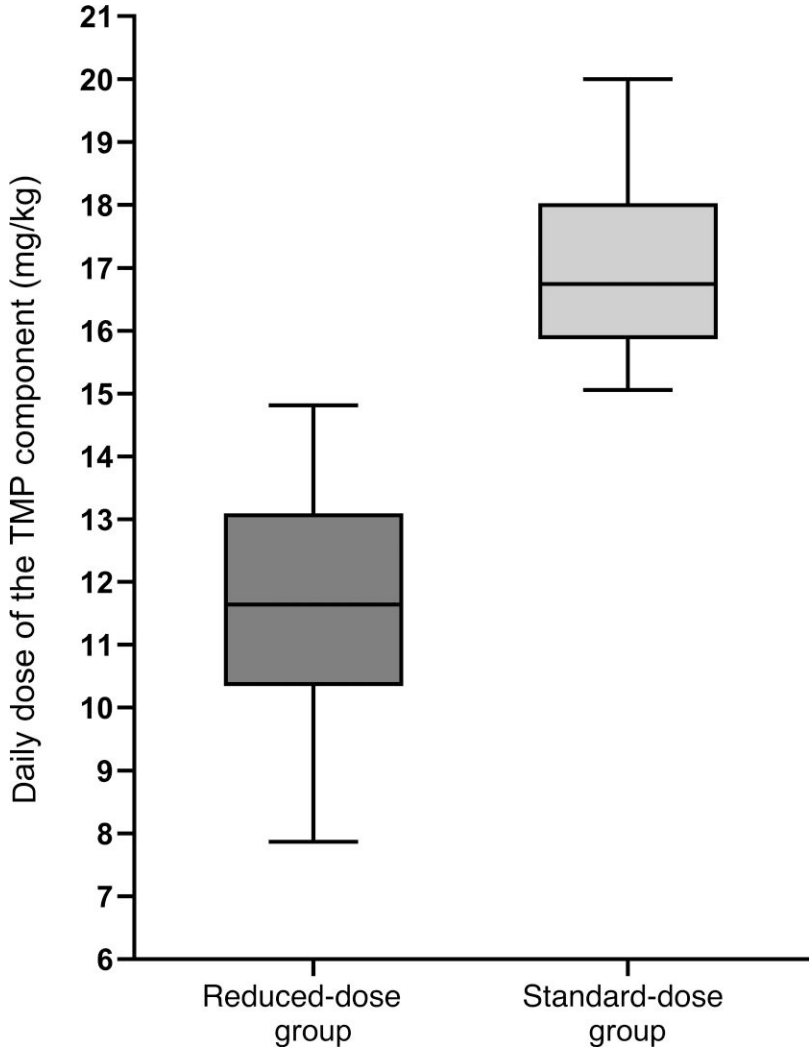

Figure 2. Distribution of initial corrected treatment doses of trimethoprim-sulfamethoxazole in the reduced- and standard-dose groups. The initial treatment dose corresponds to the mean daily dose/kilogram of trimethoprim (TMP) (corrected for renal function) on the first and second day of a full daily treatment. The horizontal lines represent the median values, boxes extend from the 25th to the 75th percentile of each group's distribution of values, and the whiskers represent the minimum and maximum values.

hematologic malignancies, all receiving standard-dose treatment [19]. Another study with 17 included hematological patients had only univariable analysis performed, and no adjustment for potential confounding factors was made [12]. The third study included only patients with systemic rheumatic disease [8].

In the present study including 113 hematological patients with PJP, improvement in PaO_2/FiO_2 between baseline and day 8 did not differ between patients receiving the reduced or standard dose of TMP-SMX. This result remained unchanged when correcting for age, ECOG performance status $\geq$3, and baseline PaO_2/FiO_2 in an adjusted regression analysis. In analogy with a previous study on adjunctive corticosteroids for PJP treatment in HIV-uninfected patients [20], $\Delta PaO_2/FiO_2$ was selected as the primary outcome to reflect the change in oxygenation, the most prominent feature defining severity of PJP. The choice to use day 8 after treatment start for assessment of $\Delta PaO_2/FiO_2$ was made in concordance with previously published guidelines suggesting that this may be an appropriate time point for assessment treatment response in hematologic patients with PJP [5].

Despite the fact that 71% of all patients in our study received reduced-dose TMP-SMX (ie, lower than the standard dose recommended in guidelines [5]), the overall 30-day mortality in our cohort was 14%. This is low compared to 22%–33% found in older studies reporting mortality rates in hematologic patients with PJP [21, 22]. However, most of these studies were performed before IF was replaced by PCR as the standard diagnostic method for PJP. Since the threshold for identifying *P. jirovecii* is higher with IF than PCR [23], it is possible that milder cases of PJP with low fungal loads may not have been included in these studies. This is supported by a recently published study

Table 2. Clinical Course of *Pneumocystis jirovecii* Pneumonia in Patients Receiving Standard Versus Reduced Dose of Trimethoprim-Sulfamethoxazole

Characteristic	All Patients (N = 113)	Reduced Dose (n = 80)	Standard Dose (n = 33)	*P*-Value
Duration of PJP treatment with TMP-SMX, d, median (range)	15 (2–38)	16.5 (2–37)	14 (6–38)	.89
Discontinuation of TMP-SMX prior to day 21	80 (71)	57 (71)	23 (70)	>.99
Early discontinuation of TMP-SMX (<7 d)	10 (9)	9 (11)	1 (3)	.16
Switch to a second-line drug due to adverse reactions, No.	3	3	0	
Discontinuation due to death, No.	7	6	1	
Adjunctive corticosteroids for PJP	85 (75)	58 (73)	27 (82)	.29
Cumulative-dose prednisolone equivalent during the first week of PJP treatment[a], mg, median (range)	220 (21–700)	220 (21–560)	220 (70–700)	
Oxygen therapy	95 (84)	65 (81)	30 (91)	.26
Duration of oxygen therapy, d, median (range)	5 (0–26)	5 (0–24)	7 (0–26)	.25
Start on noninvasive or mechanical ventilation[b] after baseline[c]	5 (4)	3 (4)	2 (6)	

Data are presented as No. (%) unless otherwise indicated.

Abbreviations: PJP, *Pneumocystis jirovecii* pneumonia; TMP-SMX, trimethoprim-sulfamethoxazole.

[a]Median dose for patients receiving adjunctive corticosteroids. For patients treated with corticosteroids prior to PJP, the increase in dose is considered.

[b]Includes patients receiving noninvasive or mechanical ventilation at baseline and/or during the clinical course of PJP.

[c]Baseline refers to the day of treatment start or within the first 48 hours. One patient with noninvasive ventilation is excluded due to missing data regarding time of initiation.

on the epidemiology of PJP patients in Norway that found an annual increase both in the number of PCR tests performed and the number of cases of PJP diagnosed after introduction of PCR, but an overall 30-day mortality of only 16.6% [1]. Another recent study from France reported that patients with severe PJP, defined as requirement for >50% FiO_2, were more often IF positive in bronchoalveolar lavage samples (59% vs 33%) and had a higher mortality rate (45% vs 9%) than patients with nonsevere PJP [24]. In accordance with these data, we found a substantial difference in 30-day mortality between patients with severe PJP (defined as PaO_2/FiO_2 ≤200 mm Hg) and patients with mild to moderate PJP (defined as PaO_2/FiO_2 >200 mm Hg): 28% compared to 2%. None of the 44 patients with mild to moderate PJP who received reduced-dose TMP-SMX died in our study. Thus, in hematologic patients with mild to moderate PJP, the overall mortality appears to be low and treatment with reduced dose of TMP-SMX safe.

Patients with hematologic malignancies are subject to treatment protocols where organ dysfunctions are common complications, and TMP-SMX–associated, dose-dependent adverse events may therefore pose a significant treatment challenge in this patient group. In our study, the number of patients experiencing adverse events requiring clinical intervention was low overall, and no statistically significant difference in adverse events with a CTCAE grade of ≥2 between the treatment groups was found. The low toxicity may in part be explained by the low proportion of patients with renal dysfunction at baseline (6%), a median treatment duration shorter than 21 days (median, 15 days) and the fact that a large proportion of patients (58%) in the standard-dose group had their dose reduced after the first 2 full days of treatment.

Strengths of this study include the multicenter design with participation of 6 Swedish university hospitals, resulting in detailed outcome data for a large and well-defined cohort of hematologic patients with PJP and allowing for a broad generalization of the results. Furthermore, extensive efforts were made to achieve a stringent case classification for PJP and to exclude cases of *Pneumocystis* colonization, in order to increase the validity of the results. On the other hand, this approach resulted in a reduction of the number of included patients, and together with the relatively low 30-day mortality of 14%, we cannot rule out that a relevant difference in

Table 3. Impact of Treatment Dose of Trimethoprim-Sulfamethoxazole on Primary and Secondary Outcomes

	Mean $\Delta PaO_2/FiO_2$ mmHg (±SD)			
Outcome	Reduced Dose (n = 80)	Standard Dose (n = 33)	Difference (95% CI)	*P*-Value
Primary outcome				
$\Delta PaO_2/FiO_2$, mm Hg, at day 8	70.2 (±104.2)	83.8 (±107.5)	−13.6 (−56.7 to 29.5)	.5
	No. (%)		OR (95% CI)	
Secondary outcomes				
Clinical failure or death at day 8	14 (18)	7 (21)	0.8 (.3–2.0)	.8
Overall mortality at day 30	11 (14)	5 (15)	0.9 (.3–2.5)	>.9
Adverse events, CTCAE grade ≥2	20 (25)	11 (33)	0.7 (.3–1.6)	.4

Abbreviations: CI, confidence interval; CTCAE, Common Terminology Criteria for Adverse Events; FiO_2, fraction of inspired oxygen; OR, odds ratio; PaO_2, partial pressure of oxygen.

Table 4. Univariable and Multivariable Regression Analysis for Primary Outcome (Difference in Partial Pressure of Oxygen/Fraction of Inspired Oxygen) at Day 8

	$\Delta PaO_2/FiO_2$ at Day 8 Point Estimate (*P*-Value)[a]	
Characteristic (N = 113 Patients)	Univariable Analysis	Multivariable Analysis
Primary predictor		
Reduced-dose TMP-SMX (n = 80)	−13.6 (.5)	−9.4 (.7)
Covariates		
Male sex (n = 80)	−0.9 (>.9)	…
Age	−1.7 (.03)	−3.5 (.01)
BMI	−0.9 (.7)	…
ECOG ≥3 at baseline (n = 17)	−59.0 (.03)	−65.6 (.02)
Hypoalbuminemia (<30 g/L) at baseline (n = 77)	−25.0 (.2)	…
Cumulative-dose corticosteroids[b] within 90 d prior to PJP	−0.0008 (.9)	…
Delayed start of PJP treatment[c] (n = 55)	8.3 (.7)	…
PaO_2/FiO_2 at baseline	−0.3 (<.005)	−0.34 (<.005)
Concomitant treatment with corticosteroids for PJP during the first 8 d (n = 81)[d]	29.0 (.25)	…

Abbreviations: BMI, body mass index; ECOG, Eastern Cooperative Oncology Group; FiO_2, fraction of inspired oxygen; PaO_2, partial pressure of oxygen; PJP, *Pneumocystis jirovecii* pneumonia; TMP-SMX, trimethoprim-sulfamethoxazole.

[a]In the univariable analysis, categorical variables were analyzed using unpaired *t* test (presented as difference in means) and continuous variables using simple linear regression analysis (presented as β-coefficient). Multivariable analysis refers to multivariable regression analysis.

[b]Prednisolone equivalent.

[c]>10 days from onset of symptoms.

[d]Nine patients who died before day 8 were excluded from this analysis.

mortality between the treatment groups, especially in patients with severe pneumonia, might have been missed.

Other limitations include the risk of selection bias (ie, the risk that patients with a worse baseline prognosis received higher treatment doses), and the risk that other, unrecognized, confounding factors may have impacted the outcomes. Despite attempting to adjust for confounders using adjusted regression analysis, the presence of residual bias cannot be ruled out in retrospective cohort studies.

To the best of our knowledge, this is the first study comparing reduced-dose and standard-dose TMP-SMX for the treatment of PJP exclusively in patients with hematologic malignancies. In summary, our study showed that in patients with mild to moderate PJP, the mortality was low, and treatment with reduced dose of TMP-SMX was effective. No significant differences in mortality between treatment groups were seen among patients with severe PJP, but the numbers were low and the result must be interpreted with caution. Even if compensating statistically for confounders, the risk of residual confounding in retrospective cohort studies is evident and prospective controlled studies are warranted to confirm these findings.

Supplementary Data

Supplementary materials are available at *Clinical 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

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