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Therapeutic Response in Adult Patients with Nonsevere Chronic Paracoccidioidomycosis Treated with Sulfamethoxazole–Trimethoprim: A Retrospective Study

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Abstract. According to the Brazilian Consensus on Paracoccidioidomycosis (PCM), itraconazole is the drug of choice for treatment. However, the combination of sulfamethoxazole and trimethoprim (SMX-TMP) is most commonly used in clinical practice because of its higher availability in the public health services. The aims of this study were to evaluate the therapeutic response of patients with nonsevere chronic PCM to SMX-TMP and highlight the factors related to treatment failure. An adequate therapeutic response was defined as completely improved disease signs and symptoms after medication use for a minimum of 6 months, followed by normalized hematological and biochemical changes, radiological improvements, and negative mycological examination findings. Medical records were analyzed for 244 patients with nonsevere chronic PCM who were treated between 1998 and 2014. In total, 41.9% of the patients had PCM for ≥ 8 months. Seven (2.9%) patients were coinfected with human immunodeficiency virus (HIV). The median (25%, 75% percentiles) treatment duration was 21 (10, 25) months. Adequate treatment adherence was reported by 68.3% of patients. In addition, 73.6% of patients exhibited an adequate therapeutic response. The majority (82.6%) of patients who were treated with SMX-TMP for > 24 months displayed an adequate therapeutic response, and the frequency of adequate therapeutic response gradually decreased as the duration of treatment decreased. Treatment nonadherence ($P < 0.001$) and PCM-HIV coinfection ($P = 0.019$) were factors associated with therapeutic failure. The study results support the good efficacy of SMX-TMP. Attention should be given to PCM-HIV coinfection, emphasizing the concern of a higher risk of PCM therapeutic failure in these patients.

INTRODUCTION

Paracoccidioidomycosis (PCM) is a chronic granulomatous disease caused by the dimorphic fungi *Paracoccidioides brasiliensis* complex and *Paracoccidioides lutzii*. The latter was recently described after isolates found in the Midwestern region of Brazil and Ecuador. The name *P. lutzii* was given as a tribute to Adolfo Lutz, who a century ago discovered the causative agent of PCM.[1–3]

PCM is a major public health problem in South America that predominantly affects specific social groups, for example, male rural workers aged 30–50 years.[4–7] In Brazil, the approximate annual incidence is 1–3 cases/100,000 inhabitants. According to the natural history of the disease, PCM is classified into three clinical forms: PCM infection; PCM disease, which appears in acute, subacute, or chronic form; and residual PCM, characterized by fibrotic sequelae.[5,8] Only a small proportion of the individuals infected by the causative fungi develop PCM, as epidemiological surveys performed using paracoccidioidin revealed a high prevalence of infection in asymptomatic individuals, although the immune response to this antigen is overestimated by histoplasmin crossreaction.[9] In adults, the predominant clinical form of this disease is chronic PCM, which commonly affects the lungs, lymphatic system, mucosa, and skin. Smoking has been identified as a possible risk factor for PCM, and alcoholism is a cofactor for its development.[8,10,11]

The diagnostic confirmation of PCM is based on fungal detection in fresh samples via microscopy, histopathological evaluation, and/or culture of the material obtained from the lesions. According to the Brazilian Consensus on PCM, itraconazole (ITC) is considered the drug of choice for the treatment of mild and moderate clinical forms of PCM because it is effective in less time.[8] The predicted treatment time when prescribing a single daily dose of ITC 200 mg ranges 6–9 months for mild forms and 12–18 months for moderate forms. A recommended alternative therapy is the combination of sulfamethoxazole (SMX; 800–1200 mg) and trimethoprim (TMP; 160–240 mg) administered orally twice daily for 12 months for mild forms and for 18–24 months for moderate forms.[8,12] However, because ITC is not available in the public health services of most Brazilian states, SMX-TMP is most commonly used in clinical practice for the treatment of PCM in Brazil.[13]

Few randomized comparative studies have been conducted to determine the optimal treatment of PCM. The therapeutic schemes currently in use are based on the opinions of experts, case series, and results obtained from nonrandomized clinical trials. A systematic review conducted by Menezes and others (2006) on the effectiveness of drugs used in the treatment of PCM concluded that there are insufficient numbers of randomized clinical trials to draw any conclusions about the drugs used for the treatment of this mycosis.[14] At the time of this review, only one clinical trial had been performed[15]; since then, no other clinical trials have been performed. Cohort studies conducted by Borges and others (2014) and Cavalcante and others (2014) demonstrated that ITC is associated to an early clinical therapeutic response and less adverse reactions than SMX-TMP, in spite of no statistical difference in efficacy.[16,17] However, in contrast, Fiol and others (2013) did not find any statistically significant difference in the efficacy of these treatments or the duration of therapy in the clinical treatment of PCM.[18]

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Little is known about the several aspects that interfere with the effectiveness of the primary treatments for PCM. Therefore, investigations that aim to identify the factors that may facilitate or impair an adequate therapeutic response in a patient with PCM are required.[8,19] In this study, an exploratory analysis of a series of patients treated for PCM in a reference service of the State of Mato Grosso was performed to highlight the evaluation of the therapeutic response and the factors related to therapeutic failure in this disease.

PATIENTS AND METHODS

Place and study type. This is an observational retrospective cohort study based on data obtained from the medical records of patients with nonsevere chronic PCM who visited the Infectious Diseases Clinic of the University Hospital Júlio Müller in Cuiabá, State of Mato Grosso, in the southeastern region of the Brazilian Amazon. In this service, the follow-up of patients undergoing treatment of PCM is systematically performed every month in the first trimester of medication use and subsequently every 3 months until the end of treatment, which typically lasts for a minimum of 12 months.[8]

Study patients. Patients aged 14 years or older who received SMX-TMP to treat PCM between 1998 and 2014 were included in this study. In this analysis, patients with laboratory-confirmed PCM who were undergoing the first round of disease treatment were included. The nonsevere chronic form of the disease was defined according to the classification of PCM proposed by the Brazilian Consensus on PCM, for example, absence of malnutrition (body mass index < 18.5 kg/m^2) or severe systemic involvement, and negative report for resting dyspnea.[8]

Clinical severity assessments were performed to exclude patients with severe PCM. Patients with severe PCM, those exhibiting central nervous system lesions, pregnant women, children < 14 years of age, and patients who did not attend ≥ 50% of the outpatient consultations planned for the follow-up period were excluded from the study. All study participants received an oral formulation of SMX-TMP as a single therapeutic. The planned duration of antifungal therapy was 24 months for all participants. Antifungal treatment was discontinued only after confirmation of marked clinical improvement, regardless of the positivity of anti-*Paracoccidioides* spp. antibodies, and was extended to those patients who had no clinical improvement at 24 months of therapy.

Variables analyzed in the study. Demographic data (e.g., age, sex, profession, and origin), clinical information (time of symptoms, main clinical manifestations, and aggravating disease factors), and laboratory (hematological, biochemical, and radiological changes) and therapeutic data (medication dose and time, treatment adherence, therapeutic outcome, time until therapeutic failure) were collected from the patients' medical records.

PCM was confirmed if the patient presented the causative fungus in at least one of the direct techniques used to detect the fungus. Chest radiography and computed tomography were used to complement the diagnosis of PCM. Adherence to the SMX-TMP therapeutic regimen was measured using self-reported adherence during all follow-up visits. Regular use was defined as the patient not stopping treatment of more than 10 days during the 3 months between each reevaluation.

Data on comorbidities, for example, hypertension, diabetes mellitus, chronic obstructive pulmonary disease, tuberculosis, leishmaniasis, leprosy, cancer, and human immunodeficiency virus (HIV)/AIDS were recorded, as well as information about smoking habits and alcoholism without considering their intensity. Information related to treatment success or failure with SMX-TMP was recorded on each return visit.

Analysis of the results. The data collected from the patients' medical records were entered into a database using the statistical package EpiData 3.1 (EpiData Association, Odense, Denmark) for subsequent analysis using Stata software version 12.0 (Stata Corp., College Station, TX). The patients' demographic, epidemiological, and clinical characteristics were tabulated and properly described in relation to the SMX-TMP treatment outcome.

An appropriate therapeutic response was identified if, after a minimum of 6 months of treatment, the patient exhibited a complete resolution of signs and symptoms, normalization of hematological and biochemical changes, radiological improvement, and a negative result on mycological examination. The absence of reports on a positive follow-up mycological examination associated with the presence of information about the patients' clinical improvement was also considered to indicate an adequate therapeutic response. This is because after resolution of the initial injury, the realization of mycological examinations becomes impossible. Treatment failure was identified if, after a minimum of 6 months of medication, the patient presented with symptom recurrence after clinical and laboratory improvement in addition to a new positive mycological examination result. The time until therapeutic failure was calculated from the beginning of SMX-TMP treatment.

The factors associated with treatment outcome were analyzed using odds ratios and 95% confidence intervals when the characteristic of exposure was binary. In this case, the statistical association was analyzed using the χ^2 test. For continuous independent variables, the analysis was performed by comparing the means using the nonparametric Mann–Whitney *U* test. To verify if the duration of SMX-TMP treatment was associated with outcome, a trend analysis was performed between the duration of medication use and the therapeutic response that was obtained. This trend was then analyzed using the χ^2 test for linear trend.

Risk factors for treatment failure were then evaluated by using stepwise forward logistic regression. Variables achieving a significance level of $P \leq 0.20$ in the univariate analyses were considered for inclusion in the multivariate model. For all analyses, an alpha error of 0.05 was used.

Ethical considerations. The study was approved by the Research Ethics Committee of the University Hospital Júlio Müller (number 344.877/2013).

RESULTS

Of the total 554 patients who were treated at the referral center during the study period, 527 had confirmed diagnosis of PCM. Of 527 patients, 283 were not included in the study because 22 (7.8%) had severe PCM, nine (3.2%) exhibited central nervous system lesions, eight (2.8%) were children < 14 years of age, 52 (18.4%) were treated with ITC, and 192 (67.8%) did not attend ≥ 50% of the outpatient consultations planned for the follow-up. Therefore, 244 (46.3%) patients (mean age, 48.4 [10.9] years; range, 14–83 years) were

included in the study analysis. All patients were living in rural areas, and most performed activities related to agriculture (Table 1).

Almost half (94, 41.9%) of the patients reported a disease duration of ≥ 8 months. Only 62 (27.7%) patients reported a shorter disease duration of < 4 months. Current or previous smoking habits, alcoholism, HIV infection, and previous morbidities such as hypertension, leprosy, tuberculosis, and drug dependence were reported by 225 (92.2%), 110 (45.1%), seven (2.9%), and 40 (16.4%) patients, respectively. The most frequent clinical manifestations were cough (184, 75.4%), weight loss (179, 73.4%), dyspnea (119, 48.8%), sputum (119, 48.8%), lymphadenopathy (116, 47.6%), and asthenia (114, 46.7%). Mucosal involvement was present in 155 (63.5%) patients. Direct mycological examination was the main test used to confirm PCM in this cohort. On admission, only two patients had positive culture as the mycological confirmation method. Values are reported as the median (25%, 75% percentiles). The median hemoglobin and hematocrit levels were slightly reduced at 13.5 (12.2, 14.9) g/dL and 41.3% (37.1%, 45.0%), respectively. The total leukocyte count remained within the normal range. A moderate increase in the erythrocyte sedimentation rate of 30 (14, 60) mm was generally observed in the first hour. The serum levels of alpha-1-acid glycoprotein were high at 160 (107, 196) mg/dL. Glucose, albumin, and globulin levels were 90 (80, 100) mg/dL, 3.9 (3.3, 4.4) g/dL, and 3.8 (2.9, 4.7) g/dL, respectively. A total of 180 (73.8%) patients displayed several radiological changes (Table 1).

The treatment duration was 21 (10, 25) months (range, 7, 60 months). Adequate treatment adherence was reported by 155 (68.3%) patients. Analysis of the therapeutic response

TABLE 1

Demographic, epidemiological, and clinical characteristics of adult patients with nonsevere chronic PCM treated with sulfamethoxazole–trimethoprim

Characteristic	Category	*n*	%
Sex	Male	237	97.1
	Female	7	2.9
Age (years)	14–30	4	1.6
	> 30–50	136	55.7
	≥ 50	104	42.6
		Mean ± SD = 48.4 ± 10.9	
Profession (*N* = 210)	Construction worker	19	9.0
	Miner	8	3.8
	Logger	10	4.8
	Driver	14	6.7
	Machine operator	9	4.3
	Rural worker	117	56
	Other	33	16
Disease duration (months; *N* = 224)	< 4	62	27.7
	> 4–8	68	30.4
	> 8–12	46	20.5
	> 12–24	30	13.4
	> 24	18	8
Aggravating factor	Smoking	225	92.2
	Alcoholism	110	45.1
	Previous morbidities	40	16.4
	HIV/AIDS	7	2.9
Signs and symptoms	Weight loss	179	73.4
	Fever	80	32.8
	Cough	184	75.4
	Sputum	119	48.8
	Lymphadenopathy	116	47.5
	Odynophagia	97	39.8
	Hoarseness	58	23.8
	Asthenia	114	46.7
	Dyspnea	119	48.8
	Mucosal involvement	155	63.5
Diagnostic confirmation method at admission*	Direct mycological examination	189	77.5
	Histopathology	65	26.6
	Culture	2	0.8
Changes on chest X-ray		180	73.8
Treatment adhesion		155	68.3
		Median	25%, 75% percentiles
Hematological changes	Hemoglobin (g/dL)	13.5	12.2, 14.9
	Hematocrit (%)	41.3	37.1, 45.0
	Leukocytes (/mm^3)	9.1	7,305, 11,300
	Erythrocyte sedimentation rate (mm)	30	14, 60
Biochemical alterations	Alpha-1-acid glycoprotein (mg/dL)	160	107, 196
	Glucose (mg/dL)	90	80, 100
	Albumin (g/dL)	3.9	3.3, 4.4
	Globulin (g/dL)	3.8	2.9, 4.7

AIDS = acquired immune deficiency syndrome; HIV = human immunodeficiency virus; SD = standard deviation. The variation in patient number is attributable to missing information in some medical records.

* Some patients tested positive in more than one mycological examination.

revealed that 148 (73.6%) patients had an adequate therapeutic response. Therapeutic failure occurred in 53 (26.4%) patients at 7–60 months after the start of treatment, and therapeutic failure was more frequent after 13 months of treatment (Table 2). The analysis of the records of 52 patients treated with ITC (excluded from this study) showed 26.9% of treatment failure. This high rate of failure was associated with poor adherence to treatment. An adequate therapeutic response was observed in a higher proportion (82.6%) of patients who received SMX-TMP for > 24 months, with the frequency of adequate therapeutic responses gradually decreasing as the treatment duration decreased. Compared with patients who received SMX-TMP for > 24 months, the number of patients with an adequate therapeutic response decreased to 23 (76.7%), 19 (55.9%), and 11 (50.0%) patients for treatment durations of 18–24, 12–18, and < 12 months, respectively. The differences in the frequency of an adequate therapeutic response associated with the duration of treatment were statistically significant (Table 3).

The analysis of factors associated with the therapeutic response illustrated that a shorter SMX-TMP treatment duration ($P = 0.0003$), nonadherence to treatment ($P \leq 0.001$), PCM-HIV coinfection ($P = 0.005$), and younger age ($P = 0.010$) were associated with therapeutic failure in patients with nonsevere chronic PCM. However, after adjustments on multivariate analysis, only nonadherence to treatment ($P < 0.0001$) and PCM-HIV coinfection ($P = 0.019$) remained associated with therapeutic failure (Table 4).

DISCUSSION

Most of the information available about PCM treatment is limited to observational studies or analyses of data obtained from patients' medical records.[16–18] This lack of evidence on the efficacy of antimicrobials is most likely due to the incomplete follow-up of patients, which may result for most of them living in rural areas.[5,7]

The present study demonstrated a satisfactory rate of adequate treatment response to SMX-TMP among patients with nonsevere chronic PCM. Although ITC is recommended as the drug of choice for the treatment of PCM,[8] SMX-TMP became the most commonly prescribed alternative in outpatient therapy because of its low cost and good tolerability. In addition, this treatment regimen is highly available in the public network of health services.[13,20]

The effectiveness of SMX-TMP varies among the few studies available. Barbosa and Vasconcelos (1973)[21] tested this treatment of the first time in Brazil and observed a 100% therapeutic success rate with lesion disappearance within a maximum of 35 days. Other studies performed over the course of the last few decades reported lower success rates of 72%[22] and 60%.[23] However, the authors did not discriminate between severe and mild cases or report the time to treatment failure. Furthermore, a small number of patients received the SMX-TMP regimen in these studies. A recent report published by Borges and others (2014)[16] stated that the cure rate was even lower, that is, only 51.3%, after an average treatment time of 23 months. However, when these authors removed irregularity or adhesion problems from the analysis, the incidence of cure increased to 71.4%, similar to that in the present work.

The occurrence of side effects following SMX-TMP treatment has been suggested as a cause of frequent treatment discontinuation and the subsequent reduction in the observed effectiveness.[17] Therefore, it can be assumed that the high frequency of adequate therapeutic responses found in this study is the result of a greater number of patients that were followed up, a longer treatment time (> 24 months for 57.2% of patients), and the inclusion of only patients with nonsevere clinical forms of PCM.

Although the majority of the studies on the treatment of PCM emphasize the importance of treatment duration,[8,16,17,24] the duration of SMX-TMP treatment among the patients of this study was not independently associated with the frequency of therapeutic failure. However, the adequate therapeutic response rate was higher for patients who received SMX-TMP for > 24 months, with the rate gradually decreasing as the treatment duration decreased. This finding is in agreement with the observations of Cavalcante and others (2014)[17] and Fiol and others (2013),[18] who demonstrated that the average time to the clinical cure of patients with nonsevere chronic PCM treated with SMX-TMP was relatively short, that is, approximately 5 and 15 months, respectively.

The frequency of treatment failure observed in this study was higher than the previously described rates, which varied from 5.2%[25] to 14.5%,[26] although the frequency was lower

TABLE 2
Treatment characteristics in adult patients with nonsevere chronic PCM treated with sulfamethoxazole–trimethoprim

Characteristic	Category	*n*	%
Treatment duration (months; *N* = 201)	≥ 24	115	57.2
	18–23	30	14.9
	13–17	34	16.9
	≤ 12	22	10
		Median (25%, 75% percentiles) = 21 (10, 25)	
Treatment adherence (*N* = 227)	Adequate	155	68.3
	Inadequate	72	31.7
Therapeutic response (*N* = 201)	Adequate	148	73.6
	Therapeutic Failure	53	26.4
Time until therapeutic failure (months; *N* = 53)	7–12	1s8	34.0
	13–23	15	28.3
	≥ 24	20	37.7
		Median (25%, 75% percentiles) = 24 (12, 36)	

The variation in patient number is attributable to missing information in some medical records.

TABLE 3
Analysis of the association between treatment duration and therapeutic response in adults with nonsevere chronic PCM treated with sulfamethoxazole–trimethoprim

		Therapeutic response			
	Category	Failure *n* (%)	Adequate *n* (%)	OR (95% CI)	*P*
Treatment duration (months; *N* = 201)	>24	20 (17.4)	95 (82.6)	1	< 0.0001*
	>18–24	7 (23.3)	23 (76.7)	1.44 (0.51–3.78)	
	>12–18	15 (44.1)	19 (55.9)	3.71 (1.60–8.63)	
	≤ 12	11 (50.0)	11 (50.0)	4.75 (1.76–12.58)	
Total		53 (26.4)	148 (73.6)		

CI = confidence interval; OR = odds ratio. The variation in patient number is attributable to missing information in some medical records.
* Chi-squared test for linear trend.

than that observed among 71 patients from other Brazilian region (29.6%).[13] It should be emphasized that these studies did not discriminate the regimen used for the treatment of PCM, that is, whether patients received ITC or SMX-TMP. In another study evaluating therapeutic responses in 58 patients treated with ITC, the rate of treatment failure was 13.8%.[27] Because the concept of PCM recurrence in relation to treatment duration is not yet well established, it is likely that the shorter treatment duration considered in the definition of therapeutic failure in this study may explain the difference in the aforementioned frequencies.

An analysis of the factors associated with therapeutic response uncovered that treatment nonadherence and PCM-HIV coinfection were independently associated with therapeutic failure in patients with nonsevere chronic PCM. It is possible that the deficit of cellular immunity caused by HIV infection complicates the therapeutic response, which also depends on Th1 immune recovery. PCM and HIV coinfection has been emphasized since the first report describing this association.[28,29] A study that evaluated the effects of HIV on the natural history of PCM illustrated that these patients' clinical characteristics are similar to those of patients with the acute form of the disease.[30] PCM in HIV/AIDS patients results from the reactivation of a latent focus that, in an individual who is not immunocompromised, can result in mild to moderate forms of this mycosis. It is estimated that sulfonamides and imidazoles probably act to maintain *Paracoccidioides* spp. inhibition, which allows the patient to return to a subclinical PCM status. Therefore, the lowest Th1 response of patients with PCM-HIV coinfection would prevent the suppression of the fungus and favor therapeutic failure.[30]

The increased frequency of treatment failure described in this study among patients who did not adhere to the treatment was expected. According to Valle and others (1992)[31] and Paniago and others (2003),[32] early treatment abandonment is common among patients with PCM. Low treatment adherence as a cause of PCM recurrence was also reported by Maciel (2007)[33] in a study of 74 patients presenting with a mucocutaneous form of the disease. The authors observed that 74.3% of the patients took the prescribed medications irregularly, which explained the 50% recurrence rate that manifested during the follow-up of these patients. However, it can be optimistically presumed that this finding points to a low frequency of fungal resistance to SMX-TMP in our environment.

TABLE 4
Analysis of the factors associated with therapeutic failure in adults with nonsevere chronic PCM treated with sulfamethoxazole–trimethoprim

		Therapeutic failure					
Factor	Category	Yes *n* (%)	No *n* (%)	Crude OR (95% CI)	*P*	Adjusted OR (95% CI)	*P*
Sex	Male	53 (27.2)	142 (72.8)	–	0.344*	–	–
	Female	0 (0.0)	6 (100.0)				
Adherence	Yes	20 (14.1)	122 (85.9)	10.5 (5.0–22.2)	< 0.001	10.2 (4.7–22.2)	< 0.001
	No	31 (63.3)	18 (36.7)				
Alcoholism	Yes	25 (27.2)	67 (72.8)	0.9 (0.5–1.7)	0.812	–	–
	No	28 (25.7)	81 (74.3)				
Smoking	Yes	49 (26.3)	137 (73.7)	1.0 (0.3–3.3)	0.999*	–	–
	No	4 (26.7)	11 (73.30				
Comorbidity	Yes	10 (31.3)	22 (68.8)	1.3 (0.6–3.0)	0.494	–	–
	No	43 (25.4)	126 (74.3)				
HIV/AIDS	Yes	5 (83.3)	1 (16.7)	0.1 (0.01–0.6)	0.005*	17.1 (1.6–181.1)	0.019
	No	48 (24.6)	147 (75.4)				
		Median (25%, 75% percentiles)					
Age (years)		43 (39, 53)	48.5 (42, 56)	–	0.01	0.97 (0.9–1.0)	0.072
Treatment duration (months)		18 (12, 24)	24 (18, 28)	–	0.0003	1.0 (0.9–1.0)	0.340
Hemoglobin (g/dL)		13.9 (13.3, 15.2)	13.7 (12.4, 15.0)	–	0.224	–	–
Erythrocyte sedimentation rate (mm)		26.5 (10.5, 50.0)	29 (15, 57.5)	–	0.493	–	–
Alpha-1-acid glycoprotein (mg/dL)		107.5 (102, 152)	172 (138, 191)	–	0.317	–	–

AIDS = acquired immune deficiency syndrome; CI = confidence interval; HIV = human immunodeficiency virus; OR = odds ratio. The variation in patient number is attributable to missing information in some medical records.
* Fisher's exact test.

Some limitations should be considered in the interpretation of this study's results. Data from the medical records are subject to information bias because of either a lack of clarity of the notes taken or their omission. It is also not possible to discard the possibility of selection bias, as all analyzed patients attended a state reference service, at which more severe and complicated cases of PCM converge. It is also important to note that the definition of healing in this study did not include negativity of anti-Pb antibodies after treatment of the disease, as recommended,[8] possibly leading to a misclassification of therapeutic failure. The reason not to use those serologic tests was their low sensitivity for detecting those antibodies in the sera of patients from the studied region.[34] Moreover, not all patients diagnosed with nonsevere chronic PCM were included in the study because of the great difficulty of returning for follow-up treatment. Therefore, no conclusions can be made regarding the therapeutic outcome of these patients who were not included.

Although ITC has not been the subject of this study, 52 patients among all records analyzed in this study were treated with this antifungal agent. Adequate therapeutic response was seen in 73.1% of these ITC-treated patients. This finding is consistent to other studies comparing SMX-TMP to ITC for treating patients with mild, moderate, and severe chronic PCM.[16,17] In spite of the authors had concluded that ITC was a better option for PCM treatment, double-blind randomized studies are necessary to confirm these findings.

Considering the magnitude and relevance of PCM in Brazil, the results of this study point to good effectiveness of the SMX-TMP combination as long as good treatment regularity and adherence are assured. Because the number of cases of HIV infection has increased among people older than 50 years,[35] a phenomenon associated with their ruralization in Brazil, special attention should be devoted to the possible occurrence of PCM-HIV coinfection with an emphasis on the potential higher risk of PCM therapeutic failure in HIV-infected patients treated with SMX-TMP.

CONCLUSION

The adequate treatment response rate to SMX-TMP of 73.6% among patients with nonsevere chronic PCM should be considered satisfactory. Treatment nonadherence was the main factor associated with therapeutic failure after treatment with SMX-TMP. HIV coinfection is independently associated with an increased frequency of SMX-TMP therapeutic failure among patients with PCM.

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