Single-Day Trimethoprim/Sulfamethoxazole Prophylaxis for *Pneumocystis* Pneumonia in Children with Cancer☆

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Objective To determine whether a simplified, 1-day/week regimen of trimethoprim/sulfamethoxazole is sufficient to prevent *Pneumocystis* (*jirovecii* [*carinii*]) pneumonia (PCP). Current recommended regimens for prophylaxis against PCP range from daily administration to 3 consecutive days per week dosing.

Study design A prospective survey of the regimens adopted for the PCP prophylaxis in all patients treated for childhood cancer at pediatric hematology-oncology centers of the Associazione Italiana Ematologia Oncologia Pediatrica.

Results The 20 centers participating in the study reported a total of 2466 patients, including 1093 with solid tumor and 1373 with leukemia/lymphoma (or primary immunodeficiency; n = 2). Of these patients, 1371 (55.6%) received the 3-day/week prophylaxis regimen, 406 (16.5%) received the 2-day/week regimen, and 689 (27.9%), including 439 with leukemia/lymphoma, received the 1-day/week regimen. Overall, only 2 cases of PCP (0.08%) were reported, both in the 2-day/week group. By intention to treat, the cumulative incidence of PCP at 3 years was 0.09% overall (95% CI, 0.00-0.40%) and 0.51% for the 2-day/week group (95% CI, 0.10%-2.00%). Remarkably, both patients who failed had withdrawn from prophylaxis.

Conclusion A single-day course of prophylaxis with trimethoprim/sulfamethoxazole may be sufficient to prevent PCP in children with cancer undergoing intensive chemotherapy regimens. This simplified strategy might have implications for the emerging need for PCP prophylaxis in other patients subjected to the increased use of biological and nonbiological agents that induce higher levels of immune suppression, such as those with rheumatic diseases. *(J Pediatr 2014;164:389-92)*.

Pneumocystis (*jirovecii* [*carinii*]) pneumonia (PCP) is an opportunistic infection first recognized by the middle of the 20th century. Its incidence has increased over the last several decades, owing to the wider use of immunosuppressive therapy in organ transplant recipients and in patients with cancer or congenital or acquired severe immune deficiency.[1-3] Before the use of prophylaxis, up to 43% of children with cancer developed PCP.[4] It is known that asymptomatic or mild pulmonary infections, defined as colonization, are widely observed in the general adult population. Serologic studies have shown that primary *P jirovecii* infection (as defined by the development of antibody responses to antigens) is acquired in early childhood; 70%-90% of healthy children exhibit serum antibodies to the organism by age 2-3 years.[5]

Genetic and epidemiologic data on *P jirovecii* infections in Italy are scarce, limited to defined geographical regions and mainly regarding isolates from patients with HIV infection. Dimonte et al[6] investigated a cohort comprising 263 patients from

AIEOP	Associazione Italiana Ematologia Oncologia Pediatrica
PCP	*Pneumocystis* (*jirovecii* [*carinii*]) pneumonia
SMX	Sulfamethoxazole
TMP	Trimethoprim

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2 major hospitals; 38 immunocompromised patients, including 25 patients with HIV infection; and 225 immunocompetent patients by polymerase chain reaction amplification of the mtLSU-rRNA gene and found that 25.5% were positive.

More than 40 years ago, Hughes et al[4] documented successful prophylaxis with daily trimethoprim (TMP)/sulfamethoxazole (SMX) in pediatric oncology patients. At present, this procedure is considered the standard of care for children with an immune defect due to chemotherapy or prolonged corticosteroid therapy.[7-9] The finding of the efficacy of daily, but intermittent prophylactic dosing of TMP/SMX was recognized in numerous subsequent studies.[7-12]

Current recommendations for TMP/SMX dosing for PCP prophylaxis in immunocompromised patients are based on either daily or 3 consecutive days per week dosing.[4,12] A recent study reported intermittent dosing of TMP/SMX based on a regimen of 2 consecutive days per week, used routinely for PCP prophylaxis in pediatric patients with leukemia and lymphoma. This dosing regimen was derived from studies on bone marrow transplantation recipients.[10]

The aim of the present study was to assess whether a less-intensive, 1-day/week regimen is sufficient to prevent PCP. To explore this issue, we performed a prospective survey of the results of PCP prophylaxis in children treated at pediatric hematology-oncology centers of the Associazione Italiana Ematologia Oncologia Pediatrica (AIEOP).

Methods

All of the AIEOP centers were invited to participate in this prospective survey of PCP prophylaxis. Only patients with newly diagnosed cancer in 2009-2011 requiring chemotherapy and for which PCP prophylaxis was considered indicated according to local policy were eligible for the study.

Data on the total number of patients treated in study years, the number of solid tumors vs leukemia/lymphoma, criteria for prescribing PCP prophylaxis, the schedule of prophylactic regimens, and the number of cases of PCP reported prospectively in this cohort were collected. Data were collected as part of the supportive therapy in the individual disease-related protocol, with the informed consent of the patients' legal guardians. The capture of all PCP cases was performed by each participating center by using individual patient records, local databases, and study-specific data collection forms.

The data were collected on a specific form and pooled. The cumulative incidence of PCP was calculated both overall and in the 3 subgroups defined by duration of PCP prophylaxis. The differences in the cumulative incidence among subgroups were calculated using the Gray test. The analysis was performed on an intention-to-treat basis. The main presenting features (sex and age), the type of cancer diagnosis (hematologic malignancy vs solid tumor) were compared in the different therapeutic groups.

Results

A total of 20 centers participated in the study by reporting data on all of their patients newly diagnosed and treated between 2009 and 2011. These centers reported 3 different dosing regimens for PCP prophylaxis. Eleven centers prescribed a 3-day/week prophylaxis regimen, with TMP 5 mg/kg/day divided into 2 doses (total dose, 15 mg/kg/week). Six centers used a 2-day/week regimen with TMP either 10 mg/kg/day divided into 2 doses in 2 centers (total dose, 20 mg/kg/week) or 5 mg/kg/day divided into 2 doses in 4 centers (total dose, 10 mg/kg/week). The remaining 3 centers used the 1-day/week regimen, including 1 center with TMP 10 mg/kg/day divided into 2 doses, 1 center with 5 mg/kg/day divided into 2 doses, and 1 center with a 2-day/week (5 mg/kg/day divided into 2 doses) regimen for solid tumors and a 1-day/week (10 mg/kg/day divided into 2 doses) regimen for leukemia/lymphoma (**Table**). PCP prophylaxis was prescribed during the entire chemotherapy program.

A total of 2466 patients were analyzed, including 1093 with a solid tumor, 1371 with leukemia/lymphoma, and 2 with primary immunodeficiency. Among these patients, 1371 (55.6%) received the 3-day/week prophylaxis, 406 (16.5%) received the 2-day/week regimen, and 689 (27.9%) received the 1-day/week regimen.

Overall, only 2 cases of PCP (0.08%) were reported from the participating centers (**Table**). Both were enrolled in the group of patients receiving 2-day/week prophylaxis. In both cases, the diagnosis of PCP was suspected based on the clinical and radiologic findings and supported by polymerase chain reaction of bronchial aspirate or nasopharyngeal swab. Both patients were hospitalized and treated with intravenous high-dose TMP/SMX, and subsequently recovered.

The cumulative incidence of PCP at 3 years was as follows: overall, 0.09% (95% CI, 0.00%-0.40%); 2 days/week prophylaxis, 0.51% (95% CI, 0.10%-2.00%). Comparisons of the cumulative incidence of PCP in the 3 groups were as follows: 1-day/week vs 2-day/week, $P = .074$ (Gray test); 2-day/week vs 3-day/week, $P = .012$; 1-day/week vs 3-day/week vs 2-day/week, $P = .002$.

Remarkably, both of the patients who failed prophylaxis (ie, developed PCP during the study period) were not receiving prophylaxis, 1 because of drug intolerance and the other because of nonadherence to PCP prophylaxis.

To exclude a favorable selection bias in the therapeutic groups, we compared the frequency of patients with leukemia/lymphoma, aged up to 14 years (ie, the characteristics of the 2 patients who failed) in the 1-day/week group and the 2-day/week and 3-days/week groups, and were found to be comparable for age and duration of follow-up (P not significant, t test). Furthermore, when patients with leukemia/lymphoma were subdivided by age subgroup and diagnosis, no difference in the incidence of PCP was observed (P not significant, Fisher exact test).

Discussion

Although PCP prophylaxis for pediatric hematology/oncology patients has become the standard of care, the optimal regimen and duration of therapy have not been defined. The cumulative incidence of PCP in the 20

Table. Distribution of 2466 patients with cancer or PID by schedule of PCP prophylaxis, and number of failures observed during the study period (2009-2011) in 20 pediatric hematology-oncology centers

Center and regimen applied	Study population, n		Total number of patients (%); rate × 1000 (95% CI)	PCP cases, 2009-2011
	Solid tumors	Leukemia/ lymphoma		
3 days/wk; total TMP/SMX dose, 15 mg/kg/wk			1371 (55.6); 0.0 (0.0-2.7)	
0201	244	104		0
0601	15	35		0
0307	79	17		0
0801	8	41		0
0401	137	222		0
0402	30	42		0
0305	42	65		0
0603	43	57		0
1303	37	40		0
0318	0	2 (PID)		0
1502	46	65		
Total	681	690		0
2 days/wk; total TMP/SMX dose, 10-20 mg/kg/wk			406 (16.5); 4.9 (0.6-17.7)	
0501	2	44		2
1602	12	41		0
1501	37	71		0
0602	8	26		0
1308	31	0		0
0101	72	62		0
Total	162	244		2
1 day/wk; total TMP/SMX dose, 5-10 mg/kg/wk			689 (27.9); 0.0 (0.0-5.3)	
0302	0	211		0
1308	0	101		0
0901	31	58		0
0701	219	69		0
Total	250	439		0
Total	1093	1373	2466; 0.8 (0.1-2.9)	2

PID, primary immunodeficiency.

participating AIEOP centers during the 3 years of observation (2009-2011) was extremely low (0.09%). Because the empiric antibiotic therapy currently recommended by the AIEOP does not include TMP/SMX unless interstitial pneumonia is suspected and specific diagnostic tests are performed, we suppose that underestimation of PCP in this cohort, although possible, is unlikely. Our findings confirm that pediatric centers are highly committed to perform PCP prophylaxis, which results in effective protection for their patients.

Only 2 cases of failure of prophylaxis (ie, of PCP) were found in the study population. On individual reevaluation, both patients admitted that, despite the prescription based on intention to treat, they were not taking TMP/SMX. One patient was an adolescent who admitted to being nonadherent, and the other patient was considered "intolerant" to TMP/SMX, but was offered no alternative prophylactic regimen. Thus, although we have no data on the actual compliance with PCP prophylaxis, PCP was not detected in patients compliant with prescribed PCP prophylaxis on any dosing schedule.

During the 8 years preceding our study period (2000-2008), 6 cases of PCP had been recorded at the same participating centers (data not shown). The causes of these "failures" of prophylaxis were withdrawal by patient or parental decision (n = 3) and temporary hold of prophylaxis because of concurrent liver toxicity, treatment with another antibiotic, or graft-vs-host disease. Thus, nonadherence remains the sole reason for failure of PCP prophylaxis with TMP/SMX in children with cancer.[13] This concept should be kept in mind by the pediatric oncologists when considering differential diagnosis of interstitial pneumonia in their patients.

There are several patient-related factors not reported here that might have confounded our results, including, but not limited to, different levels of risk for PCP based on intensity of chemotherapy and severity of immunosuppression. Although the Gray test takes "competing risks" into consideration, these confounding factors that might affect the incidence of PCP should be evaluated or discussed. To address this issue, we have compared the main characteristics of the patients receiving single-day prophylaxis and those receiving more extended dosing schedules, and found no positive selection in terms of sex, age, diagnosis, or duration of follow-up. Furthermore, the lack of failure of PCP prophylaxis in all but 2 patients (nonadherence) makes these potentially confounding factors less relevant in this analysis.

Overall, our data confirm that PCP prophylaxis has been very successful in preventing PCP in a large cohort of children with cancer treated at the participating AIEOP centers. This result was achieved using TMP/SMX administration with different dosing schedules, ranging from 1 day to 3 days per week. Although the drug is administered orally and its cost is

very reasonable, this difference may be of interest. Because compliance remains the basis for the success of prophylaxis, and in turn lack of compliance is the main cause of failures, a simpler regimen with shorter duration (eg, with a single, specific day of the week, say on Sunday) may be expected to improve compliance. Available data from the literature suggest that based on the original report of continuous TMP/SMX administration,[4-7] attempts have been made to simplify the administration schedule. The first step was a regimen of 3 consecutive days per week, which was widely adopted for many years.[12] Recently, Agrawal et al[14] reported 87 patients treated twice daily for 2 consecutive days per week, with no proven case of PCP. That study was limited by relatively small patient numbers, however. Souza et al[15] reported a different prophylaxis based on twice-weekly TMP/SMX or weekly dapsone (a nonstandard option for PCP prophylaxis), and their findings with a 2-day/week regimen were comparable with earlier 3-day/week studies. Lindemulder and Albano[10] reported TMP/SMX (TMP 5 mg/kg/day) on 2 consecutive days, with no failures. Ohata et al[16] reported a higher dose (8 mg/kg/day) on 2 nonconsecutive days per week, with no failures. These data suggest that a twice-weekly regimen may be appropriate for common use; however, Agrawal et al[14] suggested that "once-weekly prophylaxis might be successful for some patients."

Because the use of TMP/SMX is associated with mild myelosuppression, which often affects delivery of chemotherapy, a simplified regimen with a lower cumulative dose also might have a reduced impact on chemotherapy, thus favoring more regular administration.[17]

Although the need for PCP prophylaxis in children with solid tumors may be considered less clear or even questioned by some authors, prophylaxis is considered a standard of care in children with hematologic malignancies. In the present study, 439 children with leukemia/lymphoma received a simplified regimen with once-daily TMP/SMX, and none developed PCP. Thus, this study provides suggestive evidence that a simplified, single-day prophylactic regimen with TMP/SMX may be sufficient to prevent PCP in children with either solid tumor or leukemia/lymphoma treated with a contemporary intensive chemotherapy regimen. Of note, the increased use of biological and nonbiological agents that induce higher levels of immune suppression can make this strategy of potential clinical interest for other patient populations as well, such as those with rheumatic diseases.[18,19] In addition, because of improved diagnosis and supportive care, an increasing number of children with congenital immune deficiency survive and thus remain at risk for PCP.[20] ■

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