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Pneumocystis jirovecii Infection in children with solid tumors: Incidence and clinical characteristics in a retrospective cohort (2010–2023)

José M. Vera García[1], *Patricia Streitenberger*[2], *Lucía Pérez*[3], *Vanina Pagotto*[3]

ABSTRACT

Introduction. *Pneumocystis jirovecii* pneumonia (PJP) is a life-threatening infection that affects patients with impaired immunity (primarily cellular immunity). Given that few studies have evaluated the incidence of PJP in pediatric patients with solid tumors, the objective of this study was to estimate the incidence of PJP among pediatric patients with solid tumors treated at a general hospital.

Population and methods. A retrospective cohort study of 251 patients under 18 years of age with a confirmed diagnosis of solid organ cancer treated at a general hospital. Clinical, oncological, and infectious disease characteristics were evaluated. The cumulative incidence and incidence density of PJP were calculated, along with their respective 95% confidence intervals.

Results. The cumulative incidence of PJP was 2.4% (95%CI 0.9-5.1), with an incidence rate of 8.4 cases per 1000 person-years (95%CI 3.8-18.6), and a median time from cancer diagnosis to infection of 2.7 months (IQR 2-4.5)—most patients presented with moderate symptoms.

Conclusion. PJP can occur in children and adolescents with solid tumors, although its incidence is low and the prognosis is generally favorable in this cohort. These findings provide important insights into the risk profile in this population and highlight the need for further studies to determine its clinical impact and the role of prophylaxis.

Keywords: Pneumocystis *infections; children; neoplasms; incidence; antibiotic prophylaxis.*

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[1] Pediatric Clinic; [2] Department of Pediatric Hematology and Oncology; [3] Research Office; Hospital Italiano de Buenos Aires, Autonomous City of Buenos Aires, Argentina.

Correspondence to *José M. Vera García: josemanuelveragarcia@gmail.com*

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INTRODUCTION

Pneumocystis jirovecii pneumonia (PJP) is an infection that affects patients with compromised immune systems.[1] Due to its non-specific clinical presentation (fever lasting more than 48 hours, dry cough, chest pain, dyspnea, hypoxemia, progressive respiratory failure, and fulminant respiratory failure) and the difficulty of microbiological isolation, it is often underdiagnosed or diagnosed late, leading to a delayed start of treatment.[2-4] Although the definitive diagnosis is based on microbiological isolation, and the sensitivity and specificity of clinical diagnosis are low —because most patients do not present with clinical symptoms that warrant it and/or have comorbidities that limit the performance of bronchoalveolar lavage (BAL)— in our setting, a presumptive diagnosis of PJP is still made based on clinical presentation and an adequate response to the therapeutic trial with antimicrobial treatment.[4,5]

Risk factors include human immunodeficiency virus (HIV) infection, use of immunosuppressive drugs, primary immunodeficiencies, various neoplasms (particularly hematologic ones), and hematopoietic stem cell and solid organ transplants, among others.[1,6,7]

There are a few studies evaluating the incidence of PJP in patients with solid tumors. According to Torres and Luo, the incidence of PJP is higher in hematologic malignancies than in solid tumors.[8,9] Sepkowitz reported an incidence of PJP in the adult population of 25% in patients with rhabdomyosarcoma and 1.3% in those with central nervous system tumors.[2] Zahar estimated that 18% of all PJP cases in adults occurred in patients with solid organ tumors.[10] No studies were found evaluating the incidence of this condition in pediatric patients with solid organ tumors.

Antimicrobial prophylaxis is indicated for patients with risk factors; however, the evidence supporting its use in this group is limited, so its indication remains controversial and lacks universal consensus.[11-15]

OBJECTIVES

Primary

To estimate the incidence of PJP in pediatric patients with solid organ tumors treated at the Hospital Italiano (HI) from 2010 to 2023.

Secondary

- Compare the incidence of PJP based on the underlying diagnosis and whether patients received corticosteroid therapy as part of their chemotherapy regimen.
- Assess the time from the diagnosis of cancer to the diagnosis of PJP.
- Describe the severity of PJP cases in the cohort according to predefined criteria.

POPULATION AND METHODS

Study design

A retrospective observational cohort study with descriptive and exploratory comparative analysis of pediatric patients with solid organ tumors treated at HI. The date of entry into the cohort was the date of diagnosis of the solid organ tumor. Patients were followed until the occurrence of the event (first PJP), bone marrow transplant (BMT) or solid organ transplant, diagnosis of a hematologic tumor, death, last date of contact, or administrative closure of the study (set for June 30, 2024), whichever occurred first. Censoring for these events was defined because they entail substantial changes in the immunosuppression profile and the risk of infection, thereby compromising comparability with the initial cohort.

Settting

A private hospital comprising two high-complexity facilities and multiple outpatient centers, where patients with cancer-related conditions are treated, including bone marrow transplants.

Period

The inclusion period ran from January 1, 2010, to June 30, 2023.

Study inclusion criteria

Patients under 18 years of age treated on an outpatient basis or hospitalized with an underlying diagnosis of solid organ tumors (including osteosarcoma, Ewing's sarcoma, medulloblastoma, pineoblastoma, ependymoma, astrocytoma, glioma, meningioma, pituitary tumor, craniopharyngioma, nerve sheath sarcoma, gangliocytoma, primary neuroectodermal tumor, hemangioblastoma, neuroblastoma, hepatoblastoma, synovial sarcoma, rhabdomyosarcoma, nephroblastoma, disgerminoma, teratoma, retinoblastoma) evaluated at HI during the period from January 2010 to June 2023.

Exclusion criteria

Patients were excluded if they had at

least one of the following: a concurrent diagnosis of hematologic malignancies, no date of diagnosis for the solid tumor, not followed by the Pediatric Oncology team or the HI Pediatric Clinic team, and/or who received trimethoprim-sulfamethoxazole (TMS), atovaquone, pentamidine, or dapsone during their chemotherapy treatment, as it was considered that these patients might have a lower risk of experiencing the event and their inclusion could lead to an underestimation.

Definition of an interlocutory proceeding

A patient under 18 years of age with a diagnosis of a solid tumor who had a confirmed or suspected diagnosis of PJP. A diagnosis was considered confirmed when the microorganism was visualized under light microscopy or when PCR was positive in respiratory samples. A suspected diagnosis was considered when all of the following criteria were met: compatible clinical presentation, supporting laboratory and/or radiological findings, good therapeutic response to TMS, and absence of any other cause to explain the clinical presentation. Given that the inclusion of patients with a suspected diagnosis may introduce bias, it was decided to perform two incidence analyses: one on cases with a confirmed diagnosis and another on the total number of cases investigated (both confirmed and suspected).

Variables

All data were obtained through a systematic review of patients' electronic medical records (EMRs). The operationalization of the variables is provided in *Supplementary Material 1*. The variables evaluated were as follows:

- Clinical: sex, age at cancer diagnosis (cohort enrollment), history of HIV infection.
- Oncology: date and initial cancer diagnosis, need for chemotherapy and drugs used, use of glucocorticoids as part of chemotherapy, and use for non-oncological reasons.
- Infectious diseases (in those who contracted the infection): occurrence of PJP, methodology diagnosis, date and age at diagnosis, time elapsed between the cancer diagnosis and the infectious disease diagnosis, clinical presentation, and severity (defined as "mild" if the patient did not require oxygen therapy or intensive care; "moderate" if the patient required oxygen therapy but not intensive care; and "severe" if the patient required intensive care).

Statistical analysis

Qualitative variables were described using absolute and relative frequencies (n %), and quantitative variables were described using measures of central tendency and dispersion appropriate for the distribution (mean and standard deviation [SD] or median and interquartile range [IQR]), assessed using descriptive statistics and the Shapiro-Wilk test. To estimate the cumulative incidence, the numerator consisted of PJP cases, and the denominator was the total number of pediatric patients diagnosed with solid tumors during the follow-up period; results are presented as a percentage with a 95% confidence interval (95%CI).

To estimate the incidence density, the numerator was the number of PJP cases, and the denominator was the total time contributed by all patients from cohort enrollment through the end of follow-up. Crude rates are expressed per 1000 person-years (1000 py) with their 95%CI.

The secondary objectives were designed to be exploratory; however, due to the low number of observed events, it was not possible to produce robust comparative estimates or fit models.

Stata 14 software was used for the analysis.

Sampling and sample size estimation

Given the low reported incidence of this condition and the descriptive nature of the study, we decided to conduct a census of the available population. We included all patients who met the selection criteria.

Ethical considerations

The protocol was approved by the HI Research Protocol Ethics Committee on August 10, 2023 (ruling #6823).

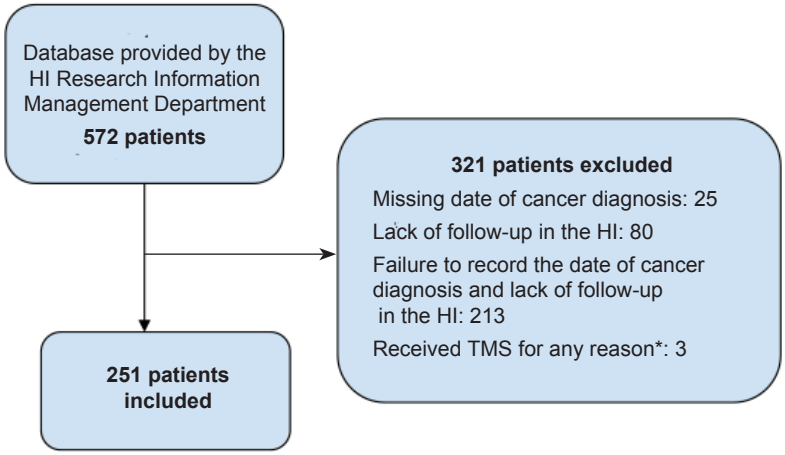
RESULTS

A total of 251 patients who met the inclusion criteria were included. *Figure 1* shows the flowchart of the patients analyzed in the study. *Table 1* summarizes the general characteristics of the study population.

Incidence of *Pneumocystis jirovecii* pneumonia globally and by baseline diagnosis

Six cases of PJP (confirmed and suspected) were identified, of which 4 were confirmed. The overall cumulative incidence was 2.4% (95%CI 0.9-5.1) and the incidence density was 8.4 cases per 1000 person-years (95%CI 3.8-18.6).

Figure 1. Patient flowchart



**No patients were identified who had received atovaquone, pentamidine, or dapsone. HI: Hospital Italiano.*

Confirmed PJP had a cumulative incidence of 1.5% (95%CI 0.5-4.2) and an incidence density of 5.6 cases per 1000 person-years (95%CI 2.1-14.9).

The median time from cancer diagnosis to PJP (n = 6) was 2.7 months (IQR 2-4.5). *Table 2* shows the absolute frequencies of PJP by underlying diagnosis.

2% (n = 5) received corticosteroids as part of their chemotherapy regimen, and 2.8% (n = 7) received them for reasons unrelated to cancer

Table 1. General characteristics of the study sample (n = 251)

Characteristic		N (%)
Male		142 (56.3)
Age at diagnosis in years, median (IQR)		8.2 (3-14.2)
Age <1 year		48 (19)
Baseline cancer diagnoses	Bone tumors	75 (29.9)
	Neuroblastoma	49 (19.5)
	Soft tissue tumors	40 (15.9)
	CNS tumors	36 (14.3)
	Liver tumors	14 (5.6)
	Germ cell tumors	12 (4.8)
	Kidney tumors	9 (3.6)
	Other tumors	16 (6.4)
Patients who received chemotherapy		204 (81.3)
Patients with HIV		0 (0)
Follow-up time in months, median (IQR)		39.6 (13.3-82.6)
End of follow-up criteria	Administrative closure (6-30-24)	186 (74.1)
	Concomitant diagnoses of hematological malignancies*	1 (0.4)
	Bone marrow transplant**	35 (13.9)
	Solid organ transplant***	2 (0.8)
	Death****	28 (11.2)

IQR: interquartile range; CNS: central nervous system; HIV: human immunodeficiency virus.

** Diagnosis of acute myeloid leukemia at 4 years of follow-up.*

*** All transplants were autologous. Median follow-up time until transplantation was 5.9 months (IQR 5.2-6.6).*

**** Liver transplantation in both cases.*

***** In all cases, death was due to cancer. Median follow-up until death was 1.5 years (95%CI 1.1-2.4).*

(one due to a prior diagnosis of systemic lupus erythematosus, one due to a concurrent diagnosis of Addison's disease, and the rest as an anti-inflammatory to alleviate the tumor's effect on the central nervous system).

Temozolomide was administered as chemotherapy in 12.3% (n = 25).

Clinical characteristics of patients with *Pneumocystis jirovecii* pneumonia

All patients (n = 6) presented with fever; 2 had a cough, and 1 had shortness of breath. Of the total number of cases, only 4 patients had a confirmed diagnosis based on a positive PCR test of a lower respiratory tract specimen.

Three patients had mild symptoms (no oxygen therapy), 1 had moderate symptoms (requiring low-flow oxygen therapy), and 2 had severe symptoms (requiring CPAP or high-flow oxygen therapy).

Four patients responded to TMS treatment, and two required adjunct prednisone. No patients died from the infection.

None of the patients with PJP had received corticosteroid therapy or temozolomide as part of the prior chemotherapy regimen, and only one had received dexamethasone as an anti-inflammatory for more than 15 days.

The characteristics of patients with PJP are described in *Supplementary Material 2*.

Due to the small number of observed events, it was not possible to perform comparative analyses stratified by baseline diagnosis or corticosteroid exposure.

DISCUSSION

In our study, the incidence of PJP in pediatric patients with solid organ tumors was found to be 2.4%, with an incidence density of 8.4 cases per 1000 person-years. Torres et al. reported a much lower incidence density,[8] which may be because the study population included adults. These results are also not comparable to those reported by Zahar et al., as we did not study the incidence of PJP in conditions other than solid organ tumors.[10]

Before the introduction of antibiotic prophylaxis, the reported incidence of this condition in patients with acute leukemia was 6.5%.[16] Recent studies, such as the one conducted by Geerlinks, have shown that TMS is superior as a prophylactic agent compared to the other proposed agents.[17]

Although high-dose glucocorticoid regimens are a risk factor for developing PJP,[1,6,7,11,13,18] our study found that only one patient had received prolonged corticosteroid therapy before PJP.

Regarding clinical presentation, all patients presented with fever, which is consistent with the findings reported by Zahar, Roblot, and Luo, who noted that fever was the most common symptom in patients with PJP.[6,9,10]

In contrast to the findings reported by Constantini and Sepkowitz, who reported a mortality rate of nearly 50%,[2,19] none of the patients in our cohort died from the infection. This may be because our cohort included only pediatric patients, who may have a generally milder course compared to the adult population. This difference could be related to the presence of comorbidities or pre-existing chronic conditions caused by other pathogens in the adult population, or to the pediatric population's greater ability to recover from PJP-induced lesions, as proposed by Kumar et al.[13] On the other hand, our findings are consistent with those of Luo, who reported only one death from the infection in his cohort.[9] However, there are no studies on the medium- to long-term prognosis in pediatrics, so more evidence is needed on this topic.

In our cohort, 4 of the 6 patients received TMS alone and showed improvement. In the studies conducted by Roblot and Luo, all patients responded to TMS, and about half of them required adjunctive therapy with glucocorticoids.[6,9]

Table 2. Incidence of *Pneumocystis jirovecii* pneumonia by underlying cancer diagnosis

Oncological diagnosis	n/N
Neuroblastoma	1/46
Osteosarcoma	1/42
Ewing's sarcoma	1/32
Medulloblastoma	2/9
Nephroblastoma	1/6

The strengths of this study lie in its design, conducted at a tertiary care hospital, which may have facilitated the detection of PJP in this population. At HI, the quality of the data collected is enhanced by the availability of an electronic medical record system with established quality standards and by the close monitoring of patients by the Oncology and Pediatric Clinic teams, which ensures that the information remains up to date. The use of a secondary data source is a limitation, as missing data cannot be ruled out and could affect the results. The inclusion of patients with a suspected diagnosis, without microbiological confirmation, could introduce classification bias and overestimate the event; for this reason, a differential analysis was performed between those with a confirmed diagnosis and those with a suspected diagnosis. Likewise, censoring follow-up at the time of transplantation or upon diagnosis of a hematologic malignancy could introduce an information censoring bias, given that these events are associated with a change in patients' risk profile, potentially underestimating the impact of the event.

On the other hand, excluding patients who received TMS, atovaquone, pentamidine, or dapsone could introduce selection bias, as this indication is typically associated with lower baseline risk; therefore, the cohort may not fully represent the risk spectrum of the total population. However, given the small number of patients excluded for this reason, the potential impact of this bias on the estimates would be limited. Furthermore, the very low number of events significantly limits the precision of the estimates and prevents robust inferences.

The findings of this study do not allow for the establishment of recommendations regarding the indication for prophylaxis in this population; therefore, larger studies are needed to assess the actual impact of this condition. This also raises the question of what the clinical threshold should be for prescribing prophylaxis in this population.

CONCLUSION

In this exploratory retrospective study, the cumulative incidence of PJP in pediatric patients with solid tumors was 2.4%. These preliminary findings suggest that infection can occur in this population, although its course is generally benign. Larger prospective studies are needed to better characterize its incidence and clinical significance. ■

The supplementary material provided with this article is presented as submitted by the authors. It is available at: https://www.sap.org.ar/docs/publicaciones/archivosarg/2026/10972_AO_Vera_Garcia_Anexo.pdf

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