Arch Argent Pediatr. 2024;122(5):e202310271

Description of the characteristics of patients with diseases associated with immunosuppression and *Cryptosporidium* spp. infection seen at a referral children's hospital in Argentina, 2018–2023

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ABSTRACT

Cryptosporidium spp. is a diarrhea-causing protozoan. Immunocompromised patients may develop severe and persistent clinical forms.

Here we describe the characteristics of patients with an underlying disease associated with immunosuppression (DAI) and *Cryptosporidium* spp. infection seen at a referral children's hospital in Argentina between 2018 and 2023. Demographic data, DAI, diarrhea characteristics, and co-infections were analyzed. A total of 30 patients with DAI and cryptosporidiosis were included. Most of them had undergone a solid organ transplant, had a hematologic neoplasm, or primary immunodeficiency. Persistent diarrhea was observed in 18 patients at the time of diagnosis. Co-infections were recorded in 6 patients. Cryptosporidiosis should be considered in the differential diagnosis of acute or persistent diarrhea in children with different types of DAI, such as solid organ transplant, hematologic neoplasms, and primary immunodeficiencies.

Keywords: Cryptosporidium*; organ transplant; diarrhea; immunocompromised host; pediatrics.*

doi: http://dx.doi.org/10.5546/aap.2023-10271.eng

To cite: Dumas Marucci M, Genero S, Degiuseppe JI, Pérez Garófalo M, Perazzo J. Description of the characteristics of patients with diseases associated with immunosuppression and *Cryptosporidium* spp. infection seen at a referral children's hospital in Argentina, 2018–2023. *Arch Argent Pediatr*. 2024;122(5):e202310271.

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Funding*: None.*

Conflict of interest*: None.*

Received*: 11-8-2023*
Accepted*: 2-22-2024*

INTRODUCTION

Cryptosporidium spp. is an enteric protozoan that primarily causes diarrhea and is spread through the fecal-oral route.[1] While healthy adults generally experience a mild, self-limited condition that lasts less than 14 days, children and individuals with an impaired immune system may develop more severe and persistent clinical forms of cryptosporidiosis.[2]

Its prevalence in symptomatic pediatric patients varies over a wide range (from 1.7% to 35.0%);[2] it is relatively higher in developing countries.[3] In recent years, there has been an increase in reports of diarrhea due to cryptosporidiosis in children with DAI, both secondary to HIV infection and other causes.[4,5] However, in Argentina, only few studies have described this problem.[6,7] Therefore, the objective of this study was to describe the characteristics of children with DAI and cryptosporidiosis seen at a referral children's hospital in the City of Buenos Aires, between 2018 and 2023.

POPULATION AND METHODS

This was a case series report of children with a DAI and cryptosporidiosis diagnosed in the period between 01-01-2018 and 04-30-2023 at Hospital de Pediatría S.A.M.I.C. Prof. Dr. Juan P. Garrahan. This is a national referral children's hospital that provides free tertiary care, located in the City of Buenos Aires, Argentina. In addition to general outpatient and inpatient clinical care, it has dedicated areas for neonatology, transplants, and comprehensive blood disease and cancer care.

Cryptosporidiosis was defined as any patient in whom *Cryptosporidium* oocysts were detected in stool samples fixed in sodium acetate-acetic acid-formalin solution, subsequently subjected to Ritchie's concentration technique and spontaneous sedimentation. A procedure of auramine-rhodamine staining was used with observation by 200x fluorescence microscopy and confirmation of positive results by Ziehl-Neelsen staining.[8]

The electronic medical records of patients with cryptosporidiosis were reviewed. The following data were extracted: sex and age, underlying disease, type of medical care, length of stay in the hospital, and duration of diarrhea episodes, classified as acute (up to 14 days) or persistent (more than 14 days). Co-infections with other diarrhea-causing bacteria, viruses, or parasites were also analyzed by culture and/or immunochromatographic techniques using fresh stool samples.

Quantitative variables were described as median and interquartile range (p25–p75). Qualitative variables were summarized using absolute counts and fractions. The statistical analysis was carried out using the Epi Info software, version 7.2.5.0, and graphs were developed using MS Office Excel 2013.

This study was approved by the hospital's Ethics Committee and the Teaching and Research Committee (09-21-2023). Data were not used for other purposes than those described for their collection, and investigators protected the identity of data holders.

RESULTS

During the period between 01-01-2018 and 04-30-2023, 30 patients with DAI and cryptosporidiosis were recorded. Of these, 19 were male and 11, female. The median age (p25–p75) was 7 years (3–11) (*Table 1*).

In relation to diarrhea episodes, 18/30 had persistent diarrhea, whereas 7/30 corresponded to acute diarrhea; no data regarding this variable were noted for the 5 remaining cases (*Table 1*).

The co-infection test revealed that, in the 30 patients analyzed, at least 1 other enteropathogen was identified in 6. Detected microorganisms included *Giardia duodenalis* (n = 2), *Clostridioides difficile* (n = 1), and *Dientamoeba fragilis* (n = 1). Two of these 6 patients had co-infection with more than 1 microorganism (*Giardia duodenalis* + *Dientamoeba fragilis and Clostridioides difficile* + *Blastocystis* sp.).

In relation to the type of DAI, 13/30 patients had undergone solid organ transplants (8 kidney, 2 liver, 2 heart, 1 lung); 8/30 presented with some type of hematologic neoplasm (3 had acute lymphoblastic leukemia, 3 had acute myeloid leukemia, 1 had Burkitt lymphoma, and 1 in whom this was not recorded); and 4/30 had some type of primary immunodeficiency (3 had Wiskott-Aldrich syndrome and 1 had hyper-IgM syndrome). To a lesser extent, 2 patients underwent hematopoietic stem cell transplantation (HSCT) for the treatment of a chromosome disease; 2 patients had a solid tumor, and only 1 patient with cryptosporidiosis had HIV infection (*Table 1*).

When analyzing the type of medical care, 25/30 patients were hospitalized at the time of diagnosis of *Cryptosporidium* infection. Among them, the median length of stay (p25–p75) was 17 days (8–43). The death of only 1 patient with HSCT was reported, which occurred in the context

Table 1. Demographic and clinical characteristics of the 30 patients with diseases associated with immunosuppression and diagnosed with *Cryptosporidium* spp. infection seen at Hospital de Pediatría S.A.M.I.C. Prof. Dr. Juan P. Garrahan. City of Buenos Aires, Argentina, 2018–2023 period

Age	
Median (p25–p75) (years)	7 (3–11)
Sex	**N**
Male	19
Female	11
Type of immunosuppression	**N**
Solid organ transplant	13
Hematologic neoplasms	8
Primary immunodeficiencies	4
Chromosome diseases (HSCT)	2
Solid tumor	2
HIV infection	1
Clinical presentation of diarrhea	**N**
Acute diarrhea	7
Persistent diarrhea	18
Unspecified	5
Type of medical care	**N**
Outpatient	5
Hospitalized	25
Length of stay in days (for hospitalized patients)	
Median (p25–p75) (days)	17 (8-43)

N: number. HSCT: hematopoietic stem cell transplantation; HIV: human immunodeficiency virus.

of sepsis, after 29 days of hospitalization, with multiple comorbidities.

Regarding the temporal distribution of the cases, a heterogeneous pattern was observed during the study period. The higher number of cases was reported in 2019 (n = 13), followed by 2018 (n = 9). During 2020, 3 cases were identified, as well as during the months of 2023 that were included in the study. In 2022, 2 cases were reported, while no cases were detected in 2021 (*Figure 1*).

DISCUSSION

In this study, we analyzed those patients with DAI and *Cryptosporidium* spp. infection. Although our case series included more male than female patients, it is important to note that analytical studies of cryptosporidiosis in pediatrics have not found any significant association with sex.[2]

Regarding the characteristics of diarrhea episodes, most of the patients in whom *Cryptosporidium* spp. oocysts were detected had persistent diarrhea at the time of diagnosis. Prior studies documented that immunocompromised children with cryptosporidiosis have a higher risk for severe, prolonged diarrhea episodes.[1,2]

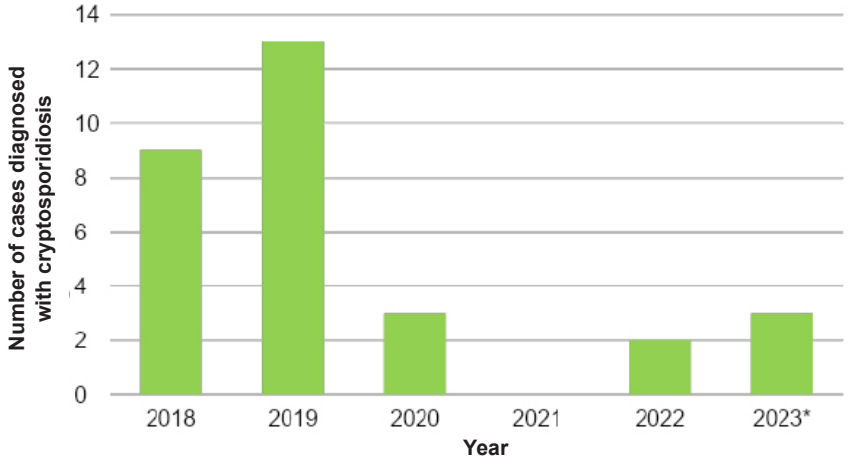
In relation to co-infections, the presence of other enteropathogens, mainly parasites, was identified in 6 patients. This may be because parasites share the same ecological niche, spreading to new hosts through soil, water, and food contaminated with feces.[9]

Regarding the epidemiological profile of patients with cryptosporidiosis, although most studies focused on adults with HIV infection,[10] in recent years, there has been an increase in research on children and adults with various types of immunodeficiency.[11] In our case series, of the 30 patients with DAI, only 1 patient had HIV infection, whereas solid organ transplant was recorded in 13 patients; kidney transplant was the most common type.

This study has some limitations. Firstly, the technique used for the detection of *Cryptosporidium* spp. has low analytical sensitivity compared to other techniques.[12,13] Secondly, in the cases analyzed here, there could be confounding factors due to their underlying disease, such as the administration of immunosuppressive therapies, which could have influenced the assessment of the clinical presentation of diarrhea and the analysis of the type of medical care and the length of hospital stay due to the multidimensional complexity of the patients' underlying disease.

Although descriptive studies do not allow to formally test hypotheses or make causal inferences or generalizations to larger

Figure 1. Temporal distribution of *Cryptosporidium* spp. infections in patients with diseases associated with immunosuppression seen at Hospital de Pediatría S.A.M.I.C. Prof. Dr. Juan P. Garrahan. City of Buenos Aires, Argentina, 2018–2023 period



** Cases corresponding to 2023 were counted up to April 30.*

populations, the description of the epidemiological profile of these cases is useful as a contribution to local knowledge and adds information to the scientific bibliography on this little-explored event.

In any case, the results of this case series of pediatric patients with diarrhea caused by *Cryptosporidium* spp. demonstrated to be prevalent among patients with solid organ transplant. In a setting where there is a progressive increase in the number of transplant patients and a decrease in uncontrolled HIV infections in pediatrics worldwide,[14] in the presence of an episode of acute or persistent diarrhea, it is necessary to take *Cryptosporidium* spp. into account in the differential diagnosis because cryptosporidiosis represents a challenge in the therapeutic approach in immunocompromised patients.

CONCLUSIONS

This study highlights the need to consider cryptosporidiosis in the differential diagnosis of acute or persistent diarrhea in children with DAI not only secondary to HIV infection, but also in the context of other conditions, such as solid organ transplant, hematologic neoplasms, and primary immunodeficiencies. ■

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