# *Clostridioides difficile* infections in children with cancer. A single-center observational study.

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## Summary

**Introduction**: Clostridioides *Clostridioides difficile* is a common cause of nosocomial diarrhea, but little is known about its course in neutropenic patients with hematologic cancers. This is a prospective study on the behavior and complications of *Clostridioides difficile* diarrhea. difficile in neutropenic children receiving cancer treatment, especially those with hematological cancer.

**Methodology:** A prospective observational study was conducted at the pediatric oncology service of the National Cancer Institute, SOLCA (Guayaquil, Ecuador), between April 2024 and March 2025. The calculated sample consisted of 25 pediatric patients admitted for neutropenia secondary to chemotherapy for hematological cancers or solid tumors. Data on age, sex, type of neoplasm, antibiotic use, clinical presentation, and treatment were collected directly from institutional medical records, and the diagnosis of Clostridioides infection was recorded via PCR in gastrointestinal panels.

**Results:** Twenty-five pediatric patients (16 females, 9 males) with neutropenia secondary to chemotherapy, predominantly due to lymphocytic leukemia (20 patients), were analyzed. The average age of Clostridioides detection was 19 days after the onset of neutropenia. The majority (21 patients) had a history of recent antibiotic use, the most common being cefepime and meropenem, and nine used proton pump inhibitors. Diarrhea lasted between 1 and 5 days in 15 patients and was watery, with 32% macroscopic blood and 48% mucus. Sixty percent of the children were afebrile, and 36% showed ultrasound abnormalities with colonic thickening (range 3.1–6.5 mm), progressing to colitis in nine cases, four of whom required CT scans. Three patients experienced concomitant bacteremia (ESBL-producing *E. coli*, *Candida parapsilosis*, and *Klebsiella pneumoniae*). Seven children (28%) experienced recurrences, which were managed in most cases with metronidazole, which was the main treatment and resulted in the resolution of the condition in all 25 patients, with no deaths or need for surgical intervention recorded.

**Conclusion:** Although the disease carries a risk of colitis and the possibility of concomitant bacteremia, treatment with metronidazole was consistently effective for clinical resolution in all patients, and despite a significant recurrence rate (28%), no fatal outcomes or need for surgery were recorded, suggesting that, with adequate surveillance, *C. difficile* infection in this population, although potentially complicated, has a favorable short-term prognosis.

## Keywords:

*Clostridioides difficile*, Neutropenia, Pediatric oncology, Nosocomial diarrhea, Metronidazole.

## Abbreviations

ESBL: extended-spectrum beta-lactamase.
CT scan: computed tomography.

### Supplementary information

No supplementary materials are declared.

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### Authors' contributions

**Aníbal Bonilla Núñez,** Methodology, Data Curation, Formal Analysis, Fundraising, Project Management, Validation, Visualization, Writing – Review and Editing.

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The authors funded the costs of this research.

### Availability of data and materials

The datasets used and analyzed during this study are available to the corresponding author upon reasonable request.

## Introduction

Clostridioides-associated diarrhea caused by *C. difficile* in pediatric patients with neutropenia and hematological cancers is an important cause of nosocomial infectious diarrhea related especially to the administration of antibiotics, such as ampicillin, cephalosporins and clindamycin, which suppress the resident intestinal flora in the intestine and allow the overgrowth of *C. difficile* [1].

Although only toxin-producing strains are pathogenic, most clinically important strains of *C. difficile* produce both toxin A (enterotoxin) and toxin B (cytotoxin). The hypervirulent strain ribotype 027 (BI/NAPI) has not been shown to be prevalent in children [2].

Clinical features range from asymptomatic colonization, mild diarrhea, to fulminant disease characterized by ileus, toxic megacolon or shock [3].

Carriers can act as reservoirs for *C. difficile*. The colonization rate increases from 15% (7–25%) in newborns to 41% (32–50%) in infants aged 6 to 12 months. Therefore, testing in patients under 12 months should be reserved for cases with relevant intestinal comorbidities and in neutropenic patients with diarrhea. The mechanisms of this apparent resistance to the disease are poorly understood, such as the lack of specific receptors for toxins and/or a humoral immune response to toxins A and B [4]. The age at which children become universally susceptible to infection is unknown, and coinfection with other intestinal pathogens is common, which could increase the severity of the infection. Clostridium screening panels for colonization are also not recommended for asymptomatic patients [5].

The risk of acquiring the organism increases in direct proportion to the length of hospital stay; it is estimated to be up to 50% in patients hospitalized for more than 4 weeks. Although it is generally acquired exogenously, in-hospital management constitutes an important source of organisms and spores [6 ].

Other risk factors, in addition to antibiotic exposure and prolonged hospital stays, include the use of antiviral therapy, gastric acid suppressants and feeding tubes, and recent administration of chemotherapy for cancers such as acute and chronic leukemias, Hodgkin and non-Hodgkin lymphomas, or solid tumors and transplants.

In children aged 1 to 2 years, other causes of infectious diarrhea (norovirus, rotavirus, adenovirus, enterovirus) should be ruled out, especially if nausea and vomiting are the predominant symptoms, as well as noninfectious diarrhea, such as malabsorption, food intolerance, milk protein allergy, and opioid withdrawal. In children under 5 years of age, the likelihood of gastrointestinal comorbidities, such as inflammatory bowel disease, cow milk protein allergy, cystic fibrosis, Hirschsprung's disease, immunodeficiencies, and postoperative states with structural bowel problems, should be considered [7].

With respect to symptoms, diarrhea can occur up to 10 weeks after antibiotic treatment. The most common feature is mild to moderate diarrhea; stools are watery and profuse, with more than 5 stools per day. The presence of blood is rare (less than 15%), but fever (37°C) and abdominal pain are common. Abdominal tenderness may be found on physical examination [6].

Laboratory testing for *C. difficile* should be performed only in symptomatic patients with significant diarrhea (more than 3 bowel movements per day), with clinical features suggestive of Clostridium or with predisposing factors, and only in watery, loose, or semiformed stools (stools that take the shape of the container [7]). In special cases, a rectal swab may be performed. Laboratory tests do not distinguish between colonization and infection.

No other laboratory or imaging tests are necessary for diagnosis, but they can be important in determining the severity of the condition. A white blood cell count greater than 15,000, elevated serum creatinine levels, lactic acidosis, or an albumin concentration less than 2.5 g/dL are ominous signs.

For treatment, the first step is to eliminate the causative agent and treat only the symptoms.

On the basis of scientific evidence, clinical experience, and cost, metronidazole and oral vancomycin are the first-line treatments. The efficacy and safety of fidaxomicin and its use in multiple recurrences have been evaluated in children; another option for treating these recurrences is fecal microbiota transplantation. Attempts have been made with toxin-neutralizing agents, such as intravenous immunoglobulin, rifaximin, nitazoxanide, or probiotics, but these have not been sufficiently studied. In children, another new option already approved by the FDA is bezlotoxumab, a human monoclonal antibody that neutralizes toxin B [ 8 ].

This is a prospective study on the behavior and complications of Clostridioides diarrhea difficile in neutropenic children undergoing treatment for cancers, especially hematological cancers, who were hospitalized in the pediatric department of ION SOLCA in Guayaquil, Ecuador.

## Materials and methods

### Studio design

This study is observational. The data source is prospective.

### Scenery

The study was conducted at the pediatric oncology service of the National Cancer Institute (SOLCA) in Guayaquil , Guayas Province, Ecuador. The research period ran from April 1, 2024, to March 31, 2025.

### Participants

Pediatric patients admitted to the institution's pediatric department for neutropenia secondary to chemotherapy for hematological cancers and solid tumors were included. Patients with chronic coinfections, such as tuberculosis or HIV, were excluded.

### Variables

The variables used were age, sex, type of neoplasm, history of antibiotic use, clinical presentation, and treatment administered.

### Data sources/measurements

The data source was direct; an electronic form was completed using information from the institutional medical records. Clostridioides was diagnosed via PCR on gastrointestinal panels of diarrheal stool samples (molecular biology: Biofire Filmarray system). Diarrhea was defined as two or more watery bowel movements.

### Biases

Observation and selection bias were avoided by applying participant selection criteria. To prevent potential interviewer, information, and memory biases, the principal investigator maintained data collection under a guideline and with records approved according to the research protocol. Two researchers independently analyzed each record in duplicate, and variables were entered into the database after their consistency was verified.

### Study size

The sample was probabilistic. In 2019, the National Cancer Institute registered 256 cases of childhood cancer. The number of febrile neutropenia cases requiring hospitalization in children is 10%, corresponding to a population of 26 possible cases per year. With a 99.9% confidence level, a 5% confidence interval, and an expected frequency of 50%, the calculated sample size was 25 cases. Epi Info™ version 7.2 (CDC, Atlanta, March 9, 2025) was used.

### Quantitative variables

The variables were considered continuous, as their entire original distribution was used. No mathematical transformations (such as logarithms or square roots) were applied. Outliers were identified via a Tukey diagram, and extreme values were addressed via primary source verification. Missing data were handled by exclusion. No dichotomization or categorization groups were defined for the continuous variables.

### Statistical analysis

Qualitative variables were analyzed using frequencies and percentages. The statistical package used was IBM Corp. Released 2025. IBM SPSS Statistics for Windows, Version 31.0. Armonk, NY: IBM Corp.

## Results

### Participants

A total of 25 patients who met the inclusion criteria were analyzed, allowing us to reach 100% of the sample.

### Characteristics of the study group

The study included 9 males and 16 females; 6 were under 2 years old, 8 were between 3 and 5 years old, 3 were between 6 and 10 years old, and 8 were over 10 years old. Cancers included 20 lymphocytic leukemias, 2 myeloid leukemias, and 3 solid tumors (neuroblastoma, Ewing sarcoma, and nephroblastoma). Antibiotic use was assessed as a risk factor: 21 patients had previously received antibiotics (11 with cefepime, 9 with meropenem, and 6 with prophylaxis with levofloxacin and fluconazole), whereas 4 had not. Recent chemotherapy was another risk factor: 3 patients received high-dose cytarabine, and 1 received high-dose methotrexate. Nine patients received proton pump inhibitors (omeprazole), 2 received antivirals (valganciclovir and acyclovir), and only one had a nasogastric tube. The average duration of neutropenia at which Clostridium was detected was 19 days (range 1–53 days). The duration of diarrhea in 15 children was 1 to 5 days; in 7, it lasted more than 3 days; and in 3, the diarrhea persisted beyond the sixth day. All presented with watery diarrheal stools; 8 had scant macroscopic blood (32%), and 12 had mucous stools (48%). Seven patients (28%) had a fever greater than 38.5°C, 3 (12%) had a fever less than 38.5°C, and 15 (60%) were fever free. Six children (24%) presented with abdominal pain or tenderness, and 9 did not. Nine patients experienced worsening with progression to colitis with suggestive ultrasound findings; 4 patients required CT scans, two of whom had focal inflammatory disease; and in the other two patients,

mural thickening of the colon was observed, one mild and the other measuring 6 mm. Among the complicated patients, one patient received multiple antibiotics, omeprazole, prolonged hospitalization (52 days), neutropenia for 11 days, and, according to ultrasound, colonic thickening of 6.5 mm; this patient received metronidazole for 10 days and clinically improved within 3 days. Bacteremia was detected in 3 patients: first, ESBL-producing *E. coli* was isolated, with elevated C-reactive protein levels of up to 25.7 mg/dL, fever of 38.5°C, and 5 days of diarrhea, and abdominal ultrasound revealed no signs of intestinal distress; second, *Candida parapsilosis* was isolated, and the patient responded to metronidazole within 6 days, with a C-reactive protein level of 1.51 mg/dL, and a normal ultrasound; third, Klebsiella was isolated, and colitis was detected by ultrasound to reach 3.9 mm, with a C-reactive protein level of 6.3 mg/dL, received intravenous metronidazole and responded within 4 days. Abdominal ultrasounds (soft tissue) were performed on all neutropenic children with diarrhea. Abnormal colonic thickening was considered to be greater than 3 mm with symptoms and 3.5 mm without symptoms. Among the ultrasounds performed, 9 (36%) showed abnormalities, with reported increases in thickness between 3.1 mm and 6.5 mm (in one case, the CT showed focal disease). Intestinal ultrasounds were normal in 13 (52%) patients, and in 3 (12%) patients, only free fluid was found: 1 with enteritis and 2 with nonspecific findings. Seven children (28%) had recurrences, two had 3 recurrences, and the remaining 2. In five cases, recurrence was managed with metronidazole; although it is not our policy to perform follow-up visits at the end of treatment, samples were taken from children with multiple recurrences on two occasions. The presence of *C. difficile* was considered colonization, and diarrhea was attributed to another cause without specific treatment. In terms of treatment, 21 patients received IV metronidazole; 2 patients completed treatment via oral administration; and 2 patients received oral administration only; all patients experienced resolution of the problem. There were no deaths or surgical procedures associated with this condition.

## Discussion

Most presented risk factors such as prior administration of one or more antibiotics, mainly fourth-generation cephalosporins (as prophylaxis or treatment for febrile processes), prolonged hospitalization (more than 2 weeks), recent cytotoxic chemotherapy, proton pump inhibitors,

Treatments with IV, PO or sequential metronidazole were always effective, with rapid improvement.

Considering the patients' clinical conditions, it was difficult to determine whether the diarrhea was secondary to *C. difficile* or to other factors, such as chemotherapy-induced mucositis, other added or concurrent bacterial or viral causes, and whether Clostridium was merely a clinically irrelevant infection [7].

Pseudomembranous enterocolitis cannot be diagnosed since colonoscopy has low sensitivity and is a dangerous procedure in pancytopenic patients due to the risk of perforation, bleeding or bacteremia [8].

The incidence of fever (greater than 38.5°C) was approximately 28%, and that of low-grade fever was 12%, which could be considered significant, although the possibility of concurrent infections in neutropenic patients undergoing chemotherapy must be taken into account. Other organisms found in the gastrointestinal panels included *E. coli* (9), norovirus (4), astrovirus (2), Campylobacter (2), Cryptosporidium (3), and Sapovirus (1). The incidence of concurrent positive blood cultures was 12%; *C. difficile* was not isolated in any of them.

Regarding treatment, the first recommendation is to discontinue the offending antibiotic, which is almost always impossible in neutropenic patients, especially febrile patients, owing to the danger of septicemia.

In terms of treatment, oral metronidazole is the drug of choice; however, because of its unpleasant taste, gastric irritation, and use in patients who sometimes fast, it is preferable for IV or sequential administration (good fecal concentrations of metronidazole are obtained via IV). Oral vancomycin is an alternative, but its cost, availability, and possibility of developing vancomycin-associated enterococci necessitate it as a second-line treatment.

The response to metronidazole, defined as the resolution of diarrhea in less than 6 days, averaged 3.5 days in our children. The poor response of some patients was attributed to chemotherapy-induced immunosuppression and intercurrent infections, and the possibility of longer treatment courses was increased.

PCR has important value in predicting infectious complications of Clostridium; 9 did not have an elevation.

## Conclusions

Molecular biology is currently an important tool in the diagnosis of infectious diseases, but it is an expensive and difficult-to-access procedure. Most of our patients presented with leukemia and had received prior antibiotic treatment. Risk factors included antibiotic use, the use of proton pump inhibitors, prolonged hospitalization, and recent chemotherapy. The diarrhea was characterized by watery stools with little mucus and no blood, accompanied by abdominal tenderness. Gastric panel sampling (PCR) was performed only in neutropenic

patients with diarrhea. Intestinal ultrasound (soft tissue ultrasound) is necessary to detect intestinal involvement, especially colonic involvement. Metronidazole was 100% effective in initial treatment and relapse, with 10 days of treatment at 30 mg/kg/day or 500 mg every 8 hours. The majority (17 patients) responded in less than 5 days of treatment, and 8 responded in more than 5 days. Complications, such as severe enterocolitis, occur infrequently and without mortality or surgical intervention. Three patients had bacteremia; *C. difficile* was not isolated from any of them.

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## Abstract

**Introduction:** *Clostridioides difficile* is a common cause of nosocomial diarrhea, but little is known about its evolution in neutropenic patients with hematological cancers. This is a prospective study on the behavior and complications of diarrhea caused by *Clostridioides difficile* in neutropenic children treated for cancer, especially hematological cancers.

**Methodology:** A prospective observational study was conducted at the pediatric oncology service of the National Oncology Institute (SOLCA) (Guayaquil, Ecuador) from April 2024 to March 2025. The estimated sample size was 25 pediatric patients admitted for neutropenia secondary to chemotherapy for hematological cancers or solid tumors. Data on age, sex, neoplasm type, antibiotic use, clinical features, and treatment were collected directly from institutional medical records, and PCR confirmed the diagnosis of *Clostridioides difficile* infection in gastrointestinal panels.

**Results:** A total of 25 pediatric patients (16 females, 9 males) with chemotherapy-induced neutropenia, mainly lymphocytic leukemia (20 patients), were analyzed. The average duration of *Clostridioides difficile* detection was 19 days after the onset of neutropenia. Most patients (21) had recently used antibiotics, primarily cefepime and meropenem, and nine had used proton pump inhibitors. Diarrhea lasted between 1 and 5 days in 15 patients and was liquid, with 32% macroscopic blood and 48% mucus. Sixty percent of the children were afebrile, and 36% showed ultrasound abnormalities, such as colon thickening (range 3.1–6.5 mm), progressing to colitis in nine cases, four of which required CT scans. Three patients had concomitant bacteremia (*E. coli* ESBL, *Candida parapsilosis*, and *Klebsiella pneumoniae*). Seven children (28%) experienced recurrences, which were managed with metronidazole, resulting in resolution in all 25 patients, with no deaths or need for surgical intervention.

**Conclusion:** Although this disease poses a risk of colitis and concomitant bacteremia, treatment with metronidazole was reliably effective for clinical resolution in all patients. Despite a significant recurrence rate (28%), no fatal outcomes or surgical interventions were recorded, indicating that, with proper surveillance, *C. difficile* infection in this population, while potentially complicated, has a favorable short-term prognosis.


**Keywords:** *Clostridioides difficile*, Neutropenia, Pediatric oncology, Nosocomial diarrhea, Metronidazole.

## Statements

### Ethics committee approval and consent to participate

The study was approved by the bioethics committee of the Faculty of Medical Sciences, University of Guayaquil.

### Publication consent

This information was not needed, as the present study did not publish images, radiographs, or specific patient studies.

### Conflicts of interest

The research has no financial interests or conflicts of interest.

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