Recurrent *Clostridium Difficile* Infection in Pediatrics: Two Case Reports

Abstract

Background: The indiscriminate use of antibiotics is not only related to resistance, but also to the increase of some bacterial infections, such as *clostridium difficile* (CD). Despite adequate treatment, these infections have a high recurrence rate, so it is necessary to have appropriate treatment guidelines and monitoring.

Methodology: Case studies of two pediatric patients with previous episodes of CD reinfection, treated in the of Pediatric Gastroenterology, Hepatology, and Nutrition Center, Gastronutriped, Bogota, Colombia, as well as an update on the identification of risk factors, diagnosis, and treatment of recurrent CD infection.

Conclusion: Cases of infection with CD present a challenge in the pediatric population. The similarity with infectious processes and the presence of bloody stools, with a history of prior use of antibiotics, should be a clue for suspected CD infection. Cases of reinfection can occur up to 3 months after the initial presentation. The management of the first reinfection in mild cases does not require antibiotics, but moderate to severe cases can be treated with the same initial treatment (metronidazole). If there is a second reinfection, the choice is vancomycin. If three or more episodes occur, there are ongoing discussions about what the most appropriate treatment should be. In recent years, we have had seen that the use of probiotics and fecal transplantation may show greater benefits for the reinfection rate, although the available evidence is still inconclusive.

Keywords: *Clostridium difficile*; Pediatrics; Anti-bacterial agents; Diarrhea

Case Report

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Introduction

Clostridium difficile (CD) is an anaerobic bacterium that forms spores [1,2]. The incidence of infection has increased dramatically, leading to an increase in mortality secondary to it [3,4]. Around two-thirds of the cases occur in the community, and the other third in the hospital environment [2]. While it is true that a high percentage of children are colonized by CD and are asymptomatic carriers [5], few develop the illness, and with adequate treatment they show a resolution of the symptoms [6,7]. On the other hand, in those cases that require treatment, a recurrence (RCD) of up to 19.6% is seen.

The intestinal microbiota carries out multiple functions [7,8] and can be altered by diverse factors, among them the manner of giving birth (cesarean), the absence of or short duration of breast feeding, early introduction of complementary feeding, prematurity [9,10], and the use of suppressor agents for gastric acid or the use of antimicrobials [7,11], which individually or together favor the colonization of various pathogens, among them CD [12]. In infants colonized by *Clostridium difficile* an increase in *Ruminococcus* and *Klebsiella*has been observed [13]. Also, infection by CD in patients with inflammatory bowel disease (IBD) [14] or in patients with cystic fibrosis (CF) [15] has been seen. Below we present two pediatric patients with recurrent CD infection attended to in the Pediatric Gastroenterology, Hepatology and Nutrition Center, Gastronutriped, as well as a complementary review of the literature with emphasis on the treatment of the recurrence of infection by this pathogen.

Clinical Cases

Clinical case 1

Female patient three years nine months of age, who during the last year has lived alternately in the U.S. and in Bogota. She presented a clinical history that began with respiratory symptoms, for which reason she attended a medical service in the U.S., and a diagnosis of bronchitis was made, treated with amoxicillin and clavulanic acid for three days. Six days after terminating the treatment, she presented hematochezia associated with intense colic, for which reason she went to an emergency room in the U.S., with a positive for CD toxin among the tests solicited. Treatment with metronidazole at 10 mg/kg/dosis, *Saccharomyces boulardii* for 10 days and a lactose-free diet was begun.

Six days after the initial treatment, the hematochezia recurred, associated with colic, and this time with diarrhea. She was evaluated by a gastroenterological pediatrician, who reconfirmed CD in three cultures, and metronidazole was renewed at 10 mg/kg/dosis for 21 days. The patient showed improvement of the symptoms, but four days after completing the treatment, now in Colombia, the hematochezia reappeared, this time without abdominal pain. A specialist in pediatric infectious diseases was consulted, and because of suspicion of recurrence, oral

vancomycin was begun at 40 mg/kg/day every eight hours for 14 days, and was followed by *Saccharomyces boulardii* with the addition of zinc sulfate.

In the first consultation at Gastronutriped, eight weeks after her initial respiratory symptoms and the pediatric infectious disease specialist consultation, a pondostatural alteration was seen in the physical exam, with a report of personal and family history of atopia. Tests were done in order to discard food allergy, celiac disease, IBD or CF, and colonoscopy was ordered because of the recurrence of lower gastrointestinal bleeding. For its treatment, multivitamins were added and the dosis of vancomycin was readjusted to 30mg/kg/day every six hours for 14 days. In subsequent consultations, immunological pathologies were discounted.

At the end of the antibiotic treatment, there was another recurrence, with Bristol 6 and 7 depositions. Continuation of probiotics and zinc was prescribed, without new antibiotic therapy. The laboratory findings were: negative for toxins A and B of CD and positive for anti-saccharomyces cerevisiae antibodies (ASCAS), for which reason upper gastrointestinal endoscopy was ordered. Colonoscopy was not possible because the parents did not authorize the procedure. Other tests that were carried out are shown in Table 1. At the last control appointment, at 12 months after the first evaluation in Gastronutriped, the patient showed an adequate evolution, studies to discount CF (pancreatic fecal elastase and electrolytes in the sweat) remained pending, and continuation of Saccharomyces boulardii, 200mg every 12 hours for 3 months was prescribed.

Table 1: Results of laboratory tests, clinical case 1.

Laboratory Test	Normal Range*	Result	Interpretation
Immunoglobulin A	22-159 mg/dl	1.49 mg/dl	Low
Specific immunoglobulin E (by ImmunoCAP) for egg yolk and egg white, milk, B lactoglobulin and alfa lactoalbumin, fish, shrimp, soy, peanuts.	Negative (<0.35 Ku/L)	Negative	Negative
D-xylose	32 - 58 mg/dL	43,4 mg/dL	Normal
Carotene	40 - 400 ug/dL	7.33 µg/dL	Low
Tissue anti transglutaminase			
Immunoglobulin A	Negative: Under 9 U/mL	Negative	Negative
Immunoglobulin Gc	Negative: Under 20 U/mL	Negative	Negative
Immunoglobulin G for Saccharomyces cerevisae:	Negative: Under 20.1 U	13.28 KU/L	Positive
ANCAS MPO	Negative	Negative	Negative
Transferrin	2.03-3.6 g/L	2.62 g/L	Normal
Ferritin	7-140 ng/mL	857 ng/mL	Normal

ANCAS MPO: Anti Neutrophil Cytoplasmic Antibodies; *Source: Flerlage J, Engorn, B, Harriet Lane Service (Johns Hopkins Hospital) The Harriet Lane handbook : a manual for pediatric house officers 20th ed. USA Elsevier Mosby, 2015.

Clinical case 2

Male patient, seven years of age, from Bogota, with clinical symptoms of two months of evolution after use of antibiotic (cefuroxime 30 mg/kg/day for 10 days) for rhinosinusitis. The symptoms began with diarrheic depositions with mucus and bloody stools, for two days. Later they turned into stools Bristol 5 and 6 (Bristol Stool Chart). Emergency services of a local institute were consulted, where out-patient treatment with oral saline solution and probiotics (*Bifidobacterium* and *Lactobacilus*) was begun, with no improvement. The patient was reevaluated after 7 days, with a fecal sample that showed evidence of trophozoites of *Entamoeba histolyitica/dispar*, for which reason amoebiasis was diagnosed, and treatment with metronidazole (30 mg/kg/day for 7 days) and Nifuroxazide (5 mg/kg/day for 7 days) was begun. The patient did not improve, so he was hospitalized, and nalidixic acid (50 mg/kg/day for 7 days), intravenous hydration, and oral *Bacillus clausii* were administered. Three days after the initial treatment, whitish membranes appeared in the feces. Tests were performed to discount infection by CD, with results positive for toxins A and B. Also, a colonoscopy was performed. An episode of fever occurred 24 hours after the procedure, for which reason metronidazole (30 mg/kg/day for 7 days) and ampicillin (100 mg/kg/day for 7 days) were prescribed, completing 10 days of treatment. Upon release from the hospital, treatment with symbiotics (*Bifidobacteria, Lactobacilli*, inulin, and fructooligosaccharides) and metronidazole was prescribed. Another relapse followed 5 days later, for which reason it was decided to perform a coproscopy, which was negative for microorganisms, and treatment proceeded with oxantel and pyrantel (10 mg/kg/day for three days).

The patient attended a consultation at Gastronutriped 2 months after the start of symptoms. Two days before the

consultation, he had presented scarce Bristol 6 deposition, with urgency and bloody stools, with no other symptoms, treated with *Saccharomyces boulardii*2 50 mg every 12 hours. There was evidence of acute malnutrition. Colitis due to CD and post enteritis syndrome was considered as a diagnosis due to the persistent diarrhea. Zinc gluconate (sugar-free), L-glutamine, *Lactobacillus reuteri*, and protein supplement were prescribed, and *Saccharomyces boulardii* was continued. Lab tests for IBD and CF were begun. 8 days after the first consultation at Gastronutriped, the diarrhea reappeared, with mucus and blood for 4 days, without fever or general ill effects. The patient was taken to the emergency department, and outpatient treatment with oral rehydration solution and diosmectite was prescribed, continuing with *Saccharomyces boulardii*. At the control consultation, 24 days after the first consultation at Gastronutriped, a resolution of the symptoms was seen, with weight gain. Symptoms suggestive of constipation were observed, so polyethylene glycol without electrolytes was prescribed and nutritional recommendations were given. Among the lab tests ordered, there was a positive result for fecal calprotectin (>300 mcg/gr), which caused a suspicion of IBD. Other tests that were performed are shown in Table 2.

Table 2: Results of laboratory tests, clinical case 2.

Laboratory Test	Normal Range	Result	Interpretation
Alpha-1 Antitrypsin in feces	Lower than or equal to 54 mg/dL	114.7 mg/dL	High
Fecal Calprotectin	Negative: <30 mcg/gr	>300 mcg/gr	Positive
First control	<30 mcg/gr	>300 mcg/gr	Positive
Second control	<30 mcg/gr	<30 mcg/gr	Negative
IgG for Saccharomyces Cerevisae	Negative: Less than 20.1 U	2.83 U	Negative
ANCAS MPO	Negative	Negative	Negative
C3	88-155 mg/dL	122.1 mg/dL	Normal
C4	12-32 mg/dL	28,9 mg/dL	Normal
Coproculture	Negative for growth of pathogenic bacteria	Negative, No growth of salmonella, shigella, campylobacter	Negative

ANCAS MPO: Anti Neutrophil Cytoplasmic Antibodies; C3: Complement Fraction 3; C4: Complement Fraction 4.*Source: Flerlage J, Engorn, B, Harriet Lane Service (Johns Hopkins Hospital) The Harriet Lane handbook : a manual for pediatric house officers 20th ed. USA Elsevier Mosby, 2015.

In a new control appointment, around 6 months after the first consultation at Gastronutriped, fecal calprotectin was still positive (>300 mcg/gr), so it was decided to perform an upper gastrointestinal endoscopy and a colonoscopy (Figures 1 & 2). In the biopsies of the upper gastrointestinal endoscopy, the following were reported: esophagitis grade I, moderate chronic gastritis with reactive foveolar changes, *Helicobacter pylori* negative, and duodenitis grade I. Therefore, treatment with Omeprazole 20 mg every 12 hours for 3 months was begun. The patient had a favorable evolution, without gastrointestinal symptoms, and in a new evaluation (around 7 ½ months after the commencement of symptoms), fecal calprotectin was negative. CF and IBD were discounted.

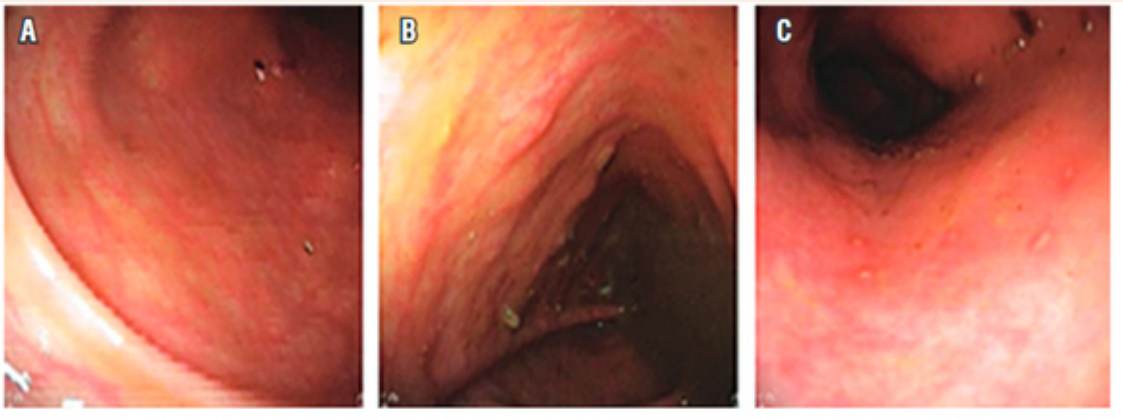

Figure 1: Images of the colonoscopy. A. Erythematous mucosa in patches without ulcerations, or fistulas. B and C. Sigmoid rectum mucosa with micro abscesses with halo erythematosus. Diagnosis: proctocolitis with micro abscesses.

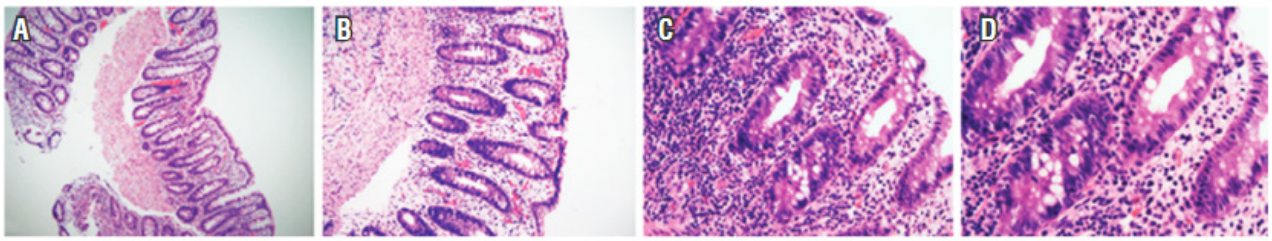

Figure 2: Histopathological report of colon biopsies. Anatomopathological report.
A. Panoramic Colon with preserved architecture, crypts symmetric to muscularis mucosa. B. Approach, colon with increased cellularity in lamina propria. C. Cellularity of mononuclear cells in stroma. D. Permeation of polymorphonuclear cells to foveole cells. Source: Courtesy Dr. Eduardo Yaspe, MD, Pathologist.

Discussion

RCD infection is defined as a new episode of diarrhea within 90 days (confirmed by diagnostic tests) after a resolution of the initial episode, for at least 10 days after the interruption/culmination of the therapy for CD [16]. Up to 20% of the patients will have a recurrence in spite of successful treatment for the initial infection, with a risk of 65% for those that have a previous history [17]. The recurrent infection occurs with greater frequency within a week after the interruption of treatment [18,19].

The risk factors for the development, persistence and RCD are multiple. Exposure to antibiotic therapy is the most important independent risk factor for infection, both on the community level and associated with health care [20-22], and according to the type of antibiotics, the risk of presentation varies (Table 3). The use of suppressor agents for gastric acid is another risk factor [23,24]; however, this topic is still under review. Studies have evaluated the effect of these medications in children infected with CD, finding that (10.4%) exhibit a recurrence of the infection, the recurrence being more frequent when they underwent concomitant treatment with these agents [25].

Table 3: Classification of antibiotics according to risk of infection by CD.

Risk Classification	Antibiotic Group
Low risk	Aminoglycosides
	Vancomycin
	Trimethoprim
	Tetracyclines
	Penicillin (Natural and antipseudomonal)
Intermediate Risk	Macrolides
	Aminopenicillin
High risk	2nd and 3rd. generation cephalosporins
	Lincosamides
	Quinolones

Source: Adapted from: Stanley, J.D. *Clostridium difficile* infection. Current Problems in Surgery 2013; 50:302–337; McFee, Robin B. *Clostridium difficile*. Dis Mon 2009; 55:439-470

Other risk factors for infection by CD that should be mentioned are: previous hospitalization, previous surgical procedures, immunosuppression, and use of oro- or nasogastric catheters [24]. Among the factors associated with RCD, the following should be mentioned: severity of the disease, extreme age of the patient, and parallel antibiotic therapy due to another infection [1]. The cases expounded in this article exhibited a recurrence of the disease, but these risk factors were not present. The clinical spectrum of infection by CD can fluctuate from an asymptomatic colonization to mild symptoms to a severe-complicated presentation (Table 4). The severity and mortality of the infection is associated with extreme ages, but the spectrum can present itself at any age [1,2,26,27]. It is pertinent to point out that it has been reported that the symptoms can occur up to 2 or 3 months after exposure to antibiotics or another risk factor [1,2,18]. In this cases report, the clinical manifestations found were mild clinical manifestations. The symptoms appeared a week after the termination of antibiotics, which agrees with the findings in the literature [1,2,21].

Egressy et al. described adults with infection by CD and CF, finding atypical symptoms and greater risk of pancolitis. Therefore, when patients have another comorbidity, like for example CF, and if various risk factors are in play, the infection should be suspected [28]. The diagnosis is based on a combination of clinical and laboratory findings: clinically significant diarrhea, a positive test for CD, or findings of pseudomembranous colitis through colonoscopy [24].

Diagnostic reference studies during the last 30 years have been a CD cytotoxin neutralization assay and toxigenic culture in samples of fecal material. Nevertheless, this last, in spite of its high rate of prescription, is not currently recommended due to the fact that it is not able to detect the strains that produce the toxin [29], an important factor considering the high frequency of colonization in small children [30]. The enzymatic immunoassay test of feces for toxin A and/or B is widely used for the diagnosis of infection by CD. Other tests, like the detection of the specific antigen for the dehydrogenase glutamate enzyme, an enzyme produced by all the strains of CD, have been implemented and studied during recent years, but they are limited by the fact that they cannot distinguish between toxigenic and nontoxigenic strains. They are only useful as a screening test in a diagnostic algorithm, where

the positive samples are submitted to further tests [31], which could be considered to be a future alternative [2]. Toxins A and B were positive in the patients that were presented, confirming the diagnosis. Afterward, they were negative on completing the treatment, which aided in the follow-up of these patients.

Table 4: Classification of the severity in children infected with *clostridium difficile.*

Degree of Severity	Clinical and/or Paraclinical Findings
Mild	Afebrile
	Diarrhea (without systemic symptoms)
Moderate	Fever
	Profuse Diarrhea
	Abdominal pain
Severe	Fever
	Profuse Diarrhea
	Abdominal pain
	Abdominal distension
	Elevated creatinine for age
	Leukocytosis (>15.000)
	Albumin<2,5 gr/dl
	Pseudomembranous colitis
Severe-complicated	Hypertension
	Shock
	Ileus
	Toxic megacolon

Source: Modified from Crews, J., Edwards, M., Torchia, M. *Clostridium difficile* infection in children: Clinical features and diagnosis. Uptodate 2015.There is no consensus abgout the definition of infection by CD in children. The determining factors for severeity should be guided by clinical judgment.

Some studies report leukocytosis or leukopenia, neutrophilia, alteration of the renal function, and increase in acute-phase reactants. However, if these parameters are located in normal ranges, such as happened in our patients in this study, they don't exclude the diagnosis and are more useful for evaluating complications [1,2,29]. Feghaly et al. [32] showed that the count of neutrophiles, reactive C protein, and proinflammatory cytokines was elevated in patients with serious illness in comparison with asymptomatic controls [32].

Digestive endoscopy is rarely used for diagnosing a CD infection, besides the fact that it can lead to complications. However, it can be justified in emergency situations when infection is suspected and feces tests are negative [27,33]. In children with chronic diarrhea and with alteration of the nutritional state, it is important to evaluate intestinal malabsorption and to discount other differential diagnoses, such as was done in this cases report [34]. Other tests, such as fecal calprotectin, have been evaluated. Given that it is one of the most stable biomarkers and gives information about the inflammatory state of the intestines, it is of great utility for the follow-up and for predicting recurrences of some pathologies of an inflammatory origin [35]. Initially, it was described for IBD, and currently it is beginning to be implemented in other pathologies [36]. In case 2, the fecal calprotectin was high, an aspect that dictated follow-up. In agreement with the foregoing, this patient presented a positive result probably because of the colitis due to CD and not because he suffered from IBD. Nevertheless, studies are lacking for determining the sensitivity, specificity, and utility of this test in patients with CD infection. In Table 5, a comparison of the principal findings in the clinical cases and what is reported in the literature is shown.

As a first step in the treatment, the American Academy of Pediatrics recommends suspending the antibiotic that led to the episode [37]. With this treatment, in a third of the cases the symptoms improve [38]. In case of dehydration, a toxic appearance, and severe illness, hospitalization should be initiated [39]. As an antibiotic treatment for the first episode, starting with metronidazole is suggested. In the cases of a first recurrence, children with mild symptoms can be treated conservatively without antibiotics [40]. Those with moderate to severe symptoms usually respond to a second course of the same treatment (metronidazole) or the use of vancomycin [40]. In cases of a second (or third) recurrence, or when prolonged therapy is decided on, the use of vancomycin is always recommended [40]. In cases of recurrence after a regimen of vancomycin, benefits have been described with the use of fecal microbiota transplant [41-44], exhibiting cure rates of 91% to 98%. However, the best manner of administration should still be determined, and the evidence is insufficient with respect to the consequences and/or complications of a fecal microbiota transplant. In the short term or the long term, some have reported inflammatory colitis after the transplant [45]. In the cases under study, the patients exhibited a recurrence after the implementation of the treatment. In fact, the patient in case 1 required oral vancomycin. In the present article, an algorithm is proposed for the diagnosis and treatment of CD infection (Algorithm N° 1).

Other types of approach, like the use of immunoglobulin, rifaximin, probiotics, or nitazoxanide, have been described, although studies that support them for generating a recommendation are lacking [37,46]. However, two recent meta-analyses back the use of probiotics for the treatment of CD infections. In the one carried out by McFarland, it was found that those treated with *Sacharomyces boulardii* exhibited an RR = 0.50 (IC95%. 0.29-0.85), with *Lactobacillus casei* DN114001 RR = 0.07 (IC 95% 0.01-0.55), a mixture of *Lactobacillus acidophilus* and *Bifidobacterium. bifidum* RR = 0.41 (IC 95% 0.21, 0.80), and a mixture of *L. acidophilus* and *Lactobacillus casei* y *Lactobacillus rhamnosus* RR = 0.21 (IC 95% 0.11-0.40) [47]. In the meta-analysis by Szajewska et al. [48] for children treated with *Sacharoyumices boulardii*, a decrease in the risk of diarrhea in patients with CD was seen, with an RR: 0.25; IC95% (0.08-0.73) [48].

Monoclonal intravenous immunoglobulin could be an option for treating patients for whom the initial therapy has failed or for seriously ill patients [27,33]. However, more studies are needed to evaluate its use and cost effectiveness [27]. Fidaxomicin could be an alternative for treatment, with the additional advantage of scarce negative effects on the count of bacteroides, so it would turn

out to be beneficial for the intestinal microbiota [49]. Likewise, a synthetic mixture of intestinal microbiota has been evaluated, in order to try to reduce the transmission of pathogens. However, studies with respect to this are needed [50,51]. Presently, a vaccine against the difficile toxoid that could be useful for preventing recurrence is in the experimental stage [27].

Table 5: Infection by C*lostridium difficile,* comparison of principal findings in the clinical cases and in the literature.

Report in the Literature	Clinical Case 1	Clinical Case 2
Symptoms		
Diarrhea	Yes	Yes
Hematochezia	Yes	Yes
Abdominal pain	Yes	Yes
Fever	Yes	Yes
Nutritional State		
Normal or Malnutrition	Chronic malnutrition	Acute Malnutrition
Risk Factors		
Previous hospitalization	No	No
Previous surgical procedures	No	No
Immunosuppression	No	No
Use of de gastric acid suppressors	No	No
Use of antibiotics	Yes (intermediate risk antibiotics)	Yes (high risk antibiotics)
Detection Method		
Culture	Not taken	Not taken
Enzyme immunoassay for toxin A	Not taken	Not taken
Enzyme immunoassay for toxin B	Not taken	Not taken
Enzyme Immunoassay for toxin A and B	Positive	Positive
Cytotoxicity study in cellular culture	Not taken	Not taken
Polymerase chain reaction	Not taken	Not taken
Endoscopic Procedure		
Colonoscopy: hyperemic mucosa, yellowish white membranes, membranes are not always observed.	Parents did not authorize	Extra-institutional histopathological report: Nonspecific chronic colitis with outbreaks of activity.
Treatment		
Antibiotic therapy (Metronidazole- 1st. line)	Metronidazole	Metronidazole
Probiotics (lactobacillus GG or *saccharomyces boulardii*)	*Saccharomyces boulardii*	*-Saccharomyces boulardii*
Recurrence	Si	Si
Detection Method		
Culture	Not taken	Not taken
Enzyme Immunoassay for toxin A	Not taken	Not taken
Enzyme Immunoassay for toxin B	Not taken	Not taken
Enzyme Immunoassay for toxin A and B	Positive	Positive
Cytotoxicity study in cellular culture	Not taken	Not taken
-Polymerase chain reaction	Not taken	Not taken

Post Recurrence Endoscopic Procedure		
Upper endoscopy: Hyperemic mucosa. Gastritis	Parents did not authorize	Esophagus normal. Gastric mucosal lining normal. Mucosa with diffuse erythema and nodular aspect. Nodular duodenitis
		Histopathology Report: Esophagitis grade I, moderate chronic gastritis with reactive foveolar changes. Helicobacter P. negative. Duodenitis grade I, findings that suggest peptic etiology.
Colonoscopy: Hyperemic mucosa, yellowish white membranes. Membranes not always observed.	Parents did not authorize	Mucosal erythema in patches without ulcerations or fistulas. Sigmoid rectal mucosa with micro abscesses with halo erythematosus. Proctocolitis with micro abscesses.
		Histopathology report:: descending colon with edema and hemorrhaging in lamina propria, 9 eosinophils per high power field (hpf). Proctitis histologically acute mild nonspecific. Count of 12 eosinophils per high power field (hpf).
Treatment for Recurrence		
Antibiotic therapy (Vancomycin or Metronidazole)	Vancomycin	None
Probiotics (Lactobacillus GG or *Saccharomyces boulardii*)	*Saccharomyces boulardii*	*Saccharomyces boulardii*

Source: Modified from: Stanley, J.D. *Clostridium difficile* infection. Current Problems in Surgery 2013; 50:302–337; McFee, Robin B. *Clostridium difficile*. Dis Mon 2009; 55:439-470.

Conclusion

The cases of CD infection in the pediatric population represent a challenge for medical personnel because of its similarity to other infectious symptoms and the high risk of reinfection. The presence of bloody depositions with a history of previous consumption of antibiotics should raise suspicions of this infection. The treatment of the first reinfection in mild cases does not require antibiotics, and many patients improve with the suspension of the antibiotic treatment. In moderate or severe cases, the initial treatment can be repeated, or vancomycin can be administered. In a new recurrence, the use of vancomycin is recommended. In cases of three or more episodes, there does not yet exist a consensus about which treatment is the most appropriate. During recent years, it has been observed that the use of probiotics has shown greater benefits for the clinical presentation of reinfection, although the available evidence is contradictory.

It is of utmost importance to avoid the indiscriminate use of antibiotics, streamlining the prescriptions in pediatrics, especially for respiratory and gastrointestinal infections, because of their high viral etiology. We consider that the implementation of probiotics could have favorable implications in the treatment of patients with recurrent CD infections, with greater benefit in mild cases that do not require treatment with antibiotics, and as a complement in moderate or severe cases.

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Conflicts and Editorial Independence

The authors of this research declare that they have no conflict of interest related to the objective of this article.

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