Report of Two Cases of Recurrent Clostridium Difficile Infections in Children and Literature Review

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Abstract

Background: Indiscriminate use of antibiotics is not only related to resistance, but also to increased incidence of some bacterial infections such as Clostridium difficile (CD). Despite appropriate treatment, these infections have a high recurrence rate which requires appropriate management and monitoring guidelines. **Methodology:** This article presents the cases of two pediatric patients who experienced CD reinfection on more than one episode. Patients were treated in Gastroenterology, Hepatology and Nutrition Unit of Gastronutriped in Bogotá, Colombia. In addition, the article provides an update on identification of risk factors, diagnosis and treatment of recurrent CD infections. **Conclusions:** Cases of CD infections in the pediatric population present a challenge because of their similarity to other infectious processes. When there are bloody stools in a patient with a history of prior use of antibiotics, the infection should be suspected. Reinfection can occur up to 3 months after the initial infection. Management of the first reinfection in mild cases does not require antibiotics, but moderate or severe may be treated with metronidazole if it was used for initial treatment. In cases of a second reinfection, vancomycin should be used. The most appropriate treatment for cases of three or more episodes is still a matter of debate. In recent years, the use of probiotics and fecal microbiota transplantation have shown great benefits in cases of reinfection, though the available evidence is still inconclusive.

Keywords

Clostridium difficile, pediatrics, antibacterial, diarrhea.

INTRODUCTION

Clostridium difficile (CD) are spore-forming anaerobic bacteria. (1, 2) Rising incidence has led to increased mortality secondary to this infection. (3, 4) About two-thirds of all cases occur in the community while the rest occur in hospitals. (2) Even though many children are colonized with CD and are asymptomatic carriers. (5) Few develop the disease, and in most of these cases the symptoms resolve with proper management. (6, 7) Nevertheless, up to 19.6% of pediatric cases develop into recurrent clostridium difficile (RCD) which requires treatment. (8)

The intestinal microbiota plays multiple roles. (7) It can be altered by several factors, including route of delivery (Caesarian section), absence or short duration of breastfeeding, early initiation of complementary feeding, prematurity, the use of agents to suppress gastric acid and the use of antimicrobials. (7, 9, 10, 11) Individually or together, these factors favor colonization by several pathogens including CD. (12) Increased incidence of Ruminococcus and Klebsiella has been in infants colonized by Clostridium difficile. (13) CD infections have also been observed in patients with inflammatory bowel disease (IBD) and patients with cystic fibrosis (CF). (14, 15)

We present the cases of two pediatric with recurrent CD infections who were cared for at Gastronutriped a Gastroenterology, Hepatology and Nutrition Unit. We also present a supplementary literature review with emphasis on the management of recurrent CD infections.

CLINICAL CASES

Case 1

The patient was a three year and nine month old girl who had lived alternately in the United States of America and Bogotá during the year prior to coming to the clinic. In the United States she developed respiratory symptoms which were diagnosed as bronchitis and treated with amoxicillin and clavulanic acid for three days. Six days after completing treatment, she developed hematochezia associated with very intense cramping abdominal pain. She was taken to an emergency department in the USA and found to be positive for CD toxin . She was treated with 10 mg/kg of metronidazole treatment plus saccharomyces boulardii for 10 days and put on a dairy-free diet.

Six days after the start of treatment, hematochezia associated with cramping abdominal pain recurred, and the child also developed diarrhea. A pediatric gastroenterologist reconfirmed CD with three cultures. Metronidazole at 10 mg/kg was reinstated for 21 days. The patient's symptoms improved, but within four days of the end of treatment hematochezia recurred although without abdominal pain. By this time, the patient was in Colombia. She was taken to a pediatric infectious disease specialist who suspected a relapse and prescribed 40 mg/kg/day of oral vancomycin administered every eight hours for 14 plus continuation of saccharomyces boulardii plus administration of zinc sulfate.

The patient's first consultation at Gastronutriped happened eight weeks after onset of initial respiratory symptoms and the patient had been seen by the pediatric infectious disease specialist. Failure to thrive was evident on physical examination. The child and members of her family had medical histories of atopic diseases. Studies to rule out food allergies, Celiac disease, IBD and cystic fibrosis were conducted. A colonoscopy was performed to check recurrent lower gastrointestinal bleeding. Multivitamins were added to the girl's treatment and the dosage of vancomycin was adjusted to 30 mg/kg/day administered every six hours for 14 days. At subsequent consultations, immune system pathologies were discarded.

At the end of antibiotic treatment, the child suffered another relapse with Bristol type 6 and 7 stool. Probiotics and zinc were prescribed, but no additional antibiotics were prescribed. Laboratory tests were negative for CD toxins A and B but were positive for Immunoglobulin G for Saccharomyces cerevisiae. An upper endoscopy was conducted because colonoscopy was not authorized by the child's parents. Other studies are presented in Table 1. At her last follow-up examination 12 weeks after her first assessment at Gastronutriped, the patient's evolution was adequate, but results of tests to rule out CF (pancreatic fecal elastase and electrolytes in perspiration) were still pending. Treatment with saccharomyces boulardii continued at a dosage of 200 mg every 12 hours to complete 3 months.

Case 2

This patient was a seven-year-old boy from Bogotá who, two months after taking 30 mg/kg/day of cefuroxime for 10 days for rhinitis and sinusitis, suffered a two-day bout of non-explosive diarrhea with mucus and blood.

Table 1. Laboratory Test Results for Case 1

Laboratory test	Normal range*	Result	Interpretation
Immunoglobulin A	22-159 mg/dL	1.49 mg/dl	Diminished
Immunoglobulin E specific for ImmunoCAP for egg whites and yolk, milk, alpha-lactalbumin, beta-lactoglobulin, fish, shrimp, soybeans, peanuts	Negative (<0.35 Ku/L)	Negative	Negative
D-xylose	32 - 58 mg/dL	43.4 mg/dL	Normal
Carotenes	40 - 400 ug/dL	7.33 µg/dL	Diminished
Tissue transglutaminase antibody			
Immunoglobulin A	Negative: Less than 9 U/mL	Negative	Negative
Immunoglobulin G	Negative: Less than 20 U/mL	Negative	Negative
Immunoglobulin G for *Saccharomyces Cerevisiae*	Negative: Less than 20.1 U	13.28 KU/L	Positive
MPO ANCA	Negative	Negative	Negative
Transferrin	2.03-3.6 g/L	2.62 g/L	Normal
Ferritin	7-140 ng/mL	85.7 ng/mL	Normal

ANCAS MPO: Anticuerpos anticitoplasma de neutrófilos; *Fuente: 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.

Subsequently his stools became Bristol types 5 and 6. The child was brought to the emergency room of a local institution which began outpatient management with oral rehydration solution and bifidobacteria and freeze-dried live lactobacilli. The patient did not improvement and was reexamined seven days later. The patient was diagnosed with amebiasis after stool samples showed trophozoites of Entamoeba histolyitica and Entamoeba dispar. Treatment was begun with 30 mg/kg/ day of metronidazole and 5 mg/kg/day of nifuroxazide for 7 days.

Symptoms persisted, so the boy was hospitalized and treated with 50 mg/kg/day of nalidixic acid for 7 days together with intravenous hydration and oral Bacillus clausii. Three days after this treatment began, white membranes began to appear in the patient's stool. Lab studies for CD were positive for toxins A and B. A colonoscopy was performed. Within 24 hours, the patient became feverish. He was treated with 30 mg/kg/day of metronidazole and 100 mg/kg/day of ampicillin for 7 days. After completing a total of 10 days of treatment in the hospital, he was discharged with a prescription for symbiotic treatment with bifidobacteria, lactobacilli, inulin and fructooligosaccharides together with metronidazole. Five days later he suffered a relapse, but stool samples showed no microorganisms. It was decided to treat the patient with 10 mg/kg/ day of pyrantel pamoate for three days.

The patient came to Gastronutriped two months after the onset of symptoms. Two days prior to consultation, his had sparse Bristol 6 stool with tenesmus and blood but without other symptoms. He was treated with 50 mg of Saccharomyces boulardii 2 every 12 hours. Acute malnutrition was evident. He was diagnosed with colitis due to CD and post enteritis syndrome due to persistent diarrhea. He was treated with sugar-free zinc gluconate, L-glutamine, Lactobacillus reuteri, protein supplement, and Saccharomyces boulardii was continued. Testing for IBD and CF began. Eight days after the first consultation at Gastronutriped, he suffered a four-day recurrence of diarrhea with mucus and blood without fever or general commitment. The patient was taken to the emergency room, where outpatient management with oral rehydration solution, diosmectite, and continued Saccharomyces boulardii was prescribed. A follow-up examination 24 days after the first consultation in Gastronutriped showed a resolution of symptoms, evident weight gain, and symptoms suggestive of constipation. Polyethylene glycol without electrolytes was prescribed and nutritional recommendations were made. Laboratory tests were positive for fecal calprotectin (> 300mcg/g) indicating the possibility of IBD. Other test results are presented in Table 2.

Tests for fecal calprotectin continued to be positive (> 300 mcg/g) at the patient's six month follow-up examination in Gastronutriped, so we decided to perform an upper endoscopy and colonoscopy (Figures 1 and 2). Biopsies from the upper endoscopy (Figure 3) indicated grade I esophagitis, mild chronic foveolar gastritis, grade I duodenitis, but no Helicobacter pylori. Treatment with 20 mg of Omeprazole every 12 hours for 3 months was begun. The patient's evolution was favorable and without gastrointestinal symptom. At a follow-up examination a month and a half later, the patient tested negative for fecal calprotectin. Diagnoses of CF and IBD were ruled out.

Table 2. Laboratory Test Results for Case 2

Laboratory test	Normal range	Result	Interpretation
Fecal alpha 1 antitrypsin	Less than or equal to 54 mg/dL	114.7 mg/dL	Increased
Fecal calprotectin	Negative: <30 mcg/gr	>300 mcg/gr	Positive
First follow-up	<30 mcg/gr	>300mcg/gr	Positive
Second follow-up	<30 mcg/gr	<30 mcg/gr	Negative
IgG for Saccharomyces Cerevisiae	Negative: Less than 20.1 U	2.83 U	Negative
MPO ANCA	Negative	Negative	Negative
C3	88-155 mg/dL	122.1 mg/dL	Normal
C4	12-32 mg/dL	28.9 mg/dL	Normal
Stool culture	Negative for bacterial pathogens	Negative for Salmonella, Shigella and Campylobacter	Negative

MPO ANCA: antineutrophil 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.

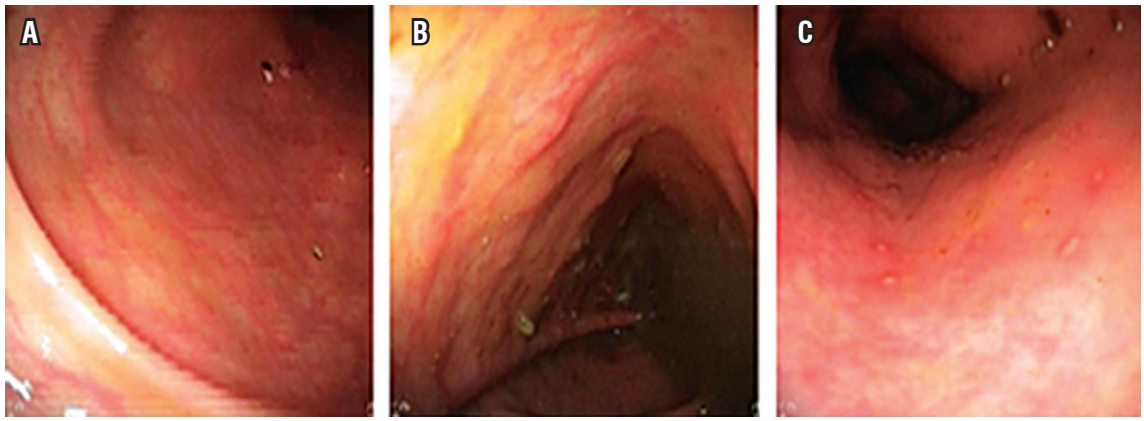

Figure 1. Images of colonoscopy. A: Patchy erythematous mucosa without ulcerations or fistulas. B and C: Rectal sigmoid mucosa with erythematous halo and micro abscesses. Diagnosis: Proctocolitis with micro abscesses and diffuse nodular erythematous. Diagnosis: Nodular duodenitis.

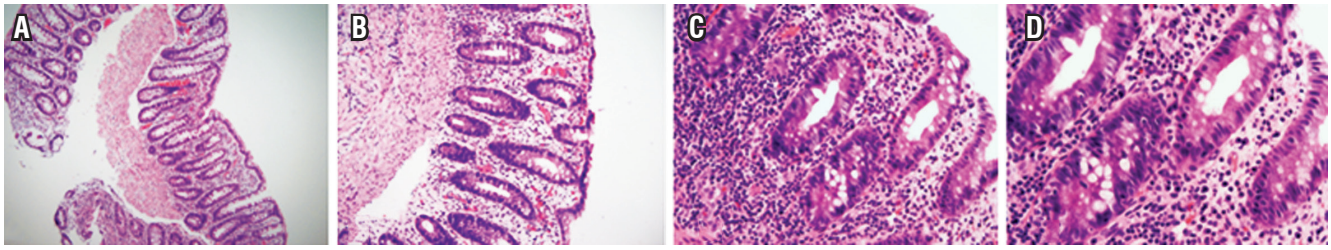

Figure 2. Histopathological reports of colon biopsies. Pathological report: A: Panorama of colon shows preserved architecture with symmetrical crypts attached to muscularis mucosa. B: Colon with increased cellularity in lamina propria. C: Mononuclear cellularity in stroma. D: Permeation of polymorphonuclear foveolar cells. (Courtesy of Dr. Eduardo Yaspe, MD and Pathologist)

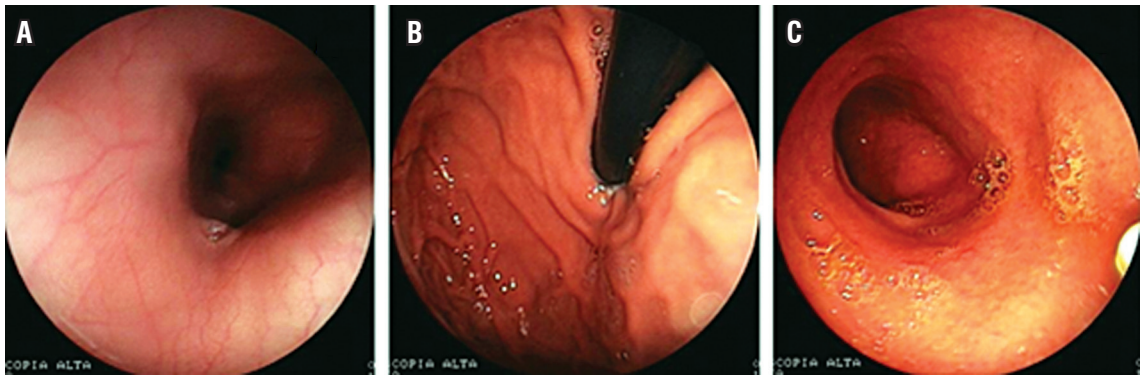

Figure 3. Images from upper endoscopy. A: Normal esophagus. B: Normal gastric mucosa of fundus. C: Mucosa

DISCUSSION

A recurrent clostridium difficile (RCD) infection is defined as laboratory confirmation of a new episode of diarrhea within 90 days of resolution of the initial episode and at least ten days after discontinuation or completion of therapy for CD. (16) Infections recur in up to 20% of patients despite successful treatment of initial infection. The risk increases to 65% for those who have a previous history. (17) Recurrent infections most often occur within a week treatment interruption. (18, 19)

There are many factors that predisposing patients to development, persistence and recurrence of CD infections, but the most important independent risk factor for

infection is treatment with antibiotics. This is true at the community level and at the level of the health care provider. (20-22) Risk varies according to the type of antibiotic administered (Table 3). The use of agents that suppress gastric acid is another risk factor, (23, 24) but this topic is still under review. Studies that evaluated the effect of these drugs in children infected with CD have found finding that recurrence of infection in 10.4% of those treated and that relapses occurred most frequently among patients who had taken medications to suppress gastric acid. (25)

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

Risk Classification	Antibiotic Group
Low risk	Aminoglycosides Vancomycin Trimethoprim Tetracycline Penicillin (Natural and antipseudomonal)
Intermediate risk	Macrolides Aminopenicillins
High Risk	Second and third generation cephalosporins Lincosamides Quinolones

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

Other factors that have been mentioned as posing risks for CD infections include previous hospitalization, previous surgical procedures, immunosuppression and use of oral or nasal gastric feeding tubes. (24) Factors associated with RCD include severity of disease, extreme age, and parallel antibiotic therapy for another infection. (1) The two patients discussed in this article did not present these risk factors although CD did reoccur.

The clinical spectrum of CD infections ranges from asymptomatic colonization through mild illnesses to severely complicated presentations (Table 4). Severity of the infection and mortality are associated with extreme ages, however instances of the entire spectrum occur at all ages. (1, 2, 26, 27) It is important to note, that there are reports of onset of symptoms two to three months after exposure to antibiotics or other risk factors. (1, 2, 18) The patients studies here had mild clinical manifestations that developed a week after antibiotic treatment had ended. This correlates with findings from the literature. (1, 2, 21)

Egressy et al. described infected adults with both CD and CF who had atypical symptoms and increased risk of pancolitis. Therefore, when a patient has other comorbidities such as CF, and if several risk factors are combined, a CD infection should be suspected. (28)

Table 4. Classification of severity of Clostridium difficile infections in children

Severity	Clinical and/or paraclinical findings
Mild	Feverish Diarrhea (without systemic symptoms)
Moderate	Fever Profuse diarrhea Abdominal pain
Severe	Fever Profuse diarrhea Abdominal pain Bloating Elevated creatinine for patient 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. Up dated in 2015. There is no consensus on the definition of CD infections in children. The determinants of severity should be guided by clinical judgment.

Diagnosis is based on a combination of clinical and laboratory findings: clinically significant diarrhea, a positive lab test for CD, or colonoscopic evidence of pseudomembranous colitis. (24)

The key diagnostic reference studies used over the past 30 years have been the CD cytotoxin neutralization assay and toxigenic culturing of stool samples. The latter, despite frequent prescription, is not currently recommended because it fails to detect toxin producing strains which is important considering the high frequency of colonization in children. (29, 30) The enzyme immunoassay test for stool toxin A and/or B is widely used for diagnosis of CD infections. Other studies, such as specific antigen tests for glutamate dehydrogenase, an enzyme produced by all strains of CD, have been implemented and studied in recent years. Nevertheless, it cannot distinguish between toxigenic and non-toxigenic strains which makes it is useful only as a screening test in a diagnostic algorithm in which samples that test positive must be subjected to additional tests. (31) This may be an alternative in the future. (2) The patients studied in this article both tested positive for Toxins A and B which confirmed the diagnosis. Subsequent to treatment, they tested negative which helped the monitoring of these patients.

Some studies have report that leukocytosis, leukopenia, neutrophilia, impaired renal function, and increased acute phase reactants can be used as indicators of CD infections,

but these parameters can be within normal ranges, as happened in our patients, but a CD diagnosis cannot be excluded. These factors are more useful for assessing complications. (1, 2, 29). Feghaly et al. have shown that neutrophil count, C-reactive protein and proinflammatory cytokines were all higher in patients with severe cases of the disease than among asymptomatic controls. (32)

Gastrointestinal endoscopy is rarely used to diagnose CD infections because it can lead to complications. Nevertheless, it may be justified in emergency situations when infection is suspected and stool tests are negative. (27, 33) For children who suffer from chronic diarrhea and impaired nutritional status, it is important to assess intestinal malabsorption and rule out other differential diagnoses as was done in the patients studied here. (34)

Studies of other factors such as fecal calprotectin have also been evaluated. Fecal calprotectin is one of the most stable biomarkers and provides information on intestinal inflammation. It is useful for tracking and predicting relapses of some diseases of inflammatory origins. (35) Its use was initially described in cases of IBD, but it is currently beginning to be used for other pathologies as well. (36) In case 2, the fecal calprotectin level was high which led to follow-up. This patient's positive test result indicated colitis that was probably due to CD rather than IBD. However, there are insufficient studies of the sensitivity, specificity and usefulness of this study for patients infected CD. Table 5 shows a comparison of key findings in our clinical cases and reported in the literature.

The American Academy of Pediatrics recommends that the first step in treatment be suspension of the antibiotic that led to the episode. (37) This action by itself leads to improvement in up to a third of CD cases. (38) When patients are dehydrated, appear toxic and/or have severe illness, they should be hospitalized. (39) When antibiotic treatment is used for a first-time CD infection, metronidazole is the drug of choice. First recurrences in children with mild symptoms can be managed conservatively without antibiotic treatment. (40) Those with moderate to severe symptoms usually respond to a second course of metronidazole or to vancomycin. (40) In case of a second or third recurrence, or when prolonged therapy is decided upon, the use of vancomycin is always recommended. (40) In cases of recurrence after a regimen of vancomycin, fecal microbiota transplants have been shown to produce benefits with cure rates of 91-98%. (41-44) Nevertheless, the optimal route of administration remains to be determined, and there is insufficient evidence regarding the short and long term consequences and/or complications of fecal microbiota transplants. Some studies have reported inflammatory colitis following transplants. (45) In case-studies, patients have relapsed following this treatment. In fact, in Case 1, the patient required oral vancomycin. This article proposes an algorithm for diagnosis and treatment of CD infections (Figure 4).

Although other approaches such as the use of immunoglobulin, probiotics and nitazoxanide rifaximin have been described, more studies are required before they can be recommended. (37, 46) Two recent meta-analyses support the use of probiotics for management of CD infections. A study by Mcfarland found that patients managed with S. boulardii had RR = 0.50 (95% CI: 0.29 - 0.85), those managed with L. casei DN114001 had RR = 0.07 (95% CI: 0.01 to 0.55), a mixture of L. acidophilus and Bifido. bifidum had RR = 0.41 (95% CI: 0.21 to 0.80), and the mixture of L. acidophilus, L. casei and L. rhamnosus had RR = 0.21 (95% CI: 0.11 to 0.40). (47) The meta-analysis by Szajewska et al. showed that the risk of diarrhea decreased among pediatric patients with CD treated with S. boulardii with an RR = 0.25 (95% CI: 0.08 to 0.73). (48)

Intravenous administration of monoclonal immunoglobulin could be an option for treating patients whose initial therapy has failed or for seriously ill patients. (27, 33) However, more studies are needed in order to evaluate usefulness and cost effectiveness. (27) Fidaxomicin may be a treatment alternative, especially because it has few negative effects on the Bacteroid count and could be beneficial for intestinal microbiota. (49) A synthetic mixture of intestinal microbiota has also been evaluated as a way to reduce transmission of pathogens. However, more studies are needed. (50, 51). Currently, a vaccine against CD toxins is being experimented with. It may prove to be useful for preventing recurrences. (27)

CONCLUSIONS

CD infections in the pediatric population present challenges for medical staff because of their similarities to infectious diseases and because of the high risk of re-infection. When a patient with a history of administration of antibiotics has bloody stools, an infection should be suspected.

Treatment of first reinfections when symptoms are mild does not require antibiotics. Many of these patients improve with discontinuation of antibiotic therapy. In moderate and severe cases, vancomycin is an option for initial treatment. Vancomycin can also be used to treat a second recurrence, but there is still no consensus about the most appropriate treatment for the third recurrence and for cases of more than three recurrences.

In recent years, the use of probiotics has shown great benefits for treating reinfections, but the available evidence is still contradictory.

It is important to avoid the indiscriminate use of antibiotics for pediatric patients especially because such a high percentage of respiratory and gastrointestinal infections

Table 5. Comparison of key findings for Clostridium difficile infections in clinical cases and literature

Report in the Literature	Clinical Case 1	Clinical Case 2
Symptoms		
Diarrhea	Yes	Yes
Hematoquezia	Yes	Yes
Abdominal pain	Yes	Yes
Fever	Yes	Yes
Nutritional status		
Normal or Malnourished	Chronic Malnutrition	Acute Malnutrition
Risk factors		
Prior Hospitalization	No	No
Previous surgery	No	No
Immunosuppression	No	No
Gastric acid suppression	No	No
Antibiotics	Yes (*Intermediate Risk Antibiotics*)	Yes (*High Risk Antibiotics*)
Detection Method		
Culture	Not done	Not done
Enzymatic Immunoassay for Toxin A	Not done	Not done
Enzymatic Immunoassay for Toxin B	Not done	Not done
Enzymatic Immunoassay for Toxins A and B	Positive	Positive
Cytotoxicity in Cell Culture	Not done	Not done
Polymerase Chain Reaction	Not done	Not done
Endoscopic procedure		
Colonoscopy: hyperemic mucosa, yellowish white membranes, the membranes are not always observed.	Not authorized by parents	Extra-institutional pathology report: chronic nonspecific colitis with pockets of activity.
Treatment		
First line antibiotic: Metronidazole	Metronidazole	Metronidazole
Probiotics (*Lactobacillus GG* or *Saccharomyces boulardii*)	*Saccharomyces boulardii*	*Saccharomyces boulardii*
RELAPSE	**Yes**	**Yes**
Detection Method		
Culture	Not done	Not done
Enzymatic Immunoassay for Toxin A	Not done	Not done
Enzymatic Immunoassay for Toxin B	Not done	Not done
Enzymatic Immunoassay for Toxins A and B	Positive	Positive
Cytotoxicity in Cell Culture	Not done	Not done
Polymerase Chain Reaction	Not done	Not done
Endoscopic procedure following relapse		
Esophagogastroduodenoscopy: hyperemic mucosa. Gastritis	Not authorized by parents	Normal gastric fundus mucosa. Mucosa with diffuse and nodular erythema. Nodular duodenitis. *Histopathology Report*: Grade I esophagitis, mild chronic gastritis with reactive foveal changes. No helicobacter pylori. Grade I duodenitis. Findings suggest peptic etiology.
Colonoscopy: hyperemic mucosa, yellowish white membranes, the membranes are not always observed.	Not authorized by parents	Patchy erythematous mucosa without ulcerations or fistulas. Rectosigmoid mucosa with erythematous halo of micro abscesses. Proctocolitis with micro abscesses. *Histopathology Report*: Descending colon with edema and hemorrhaging of lamina propria. Nine eosinophils per high-power field. Acute, mild histologically nonspecific proctitis. Twelve eosinophils per high-power field.
Treatment Relapse		
Antibiotics: Vancomycin or Metronidazole)	Vancomycin	None
Probiotics (*Lactobacillus GG* or *Saccharomyces boulardii*)	*Saccharomyces boulardii*	*Saccharomyces boulardii*

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

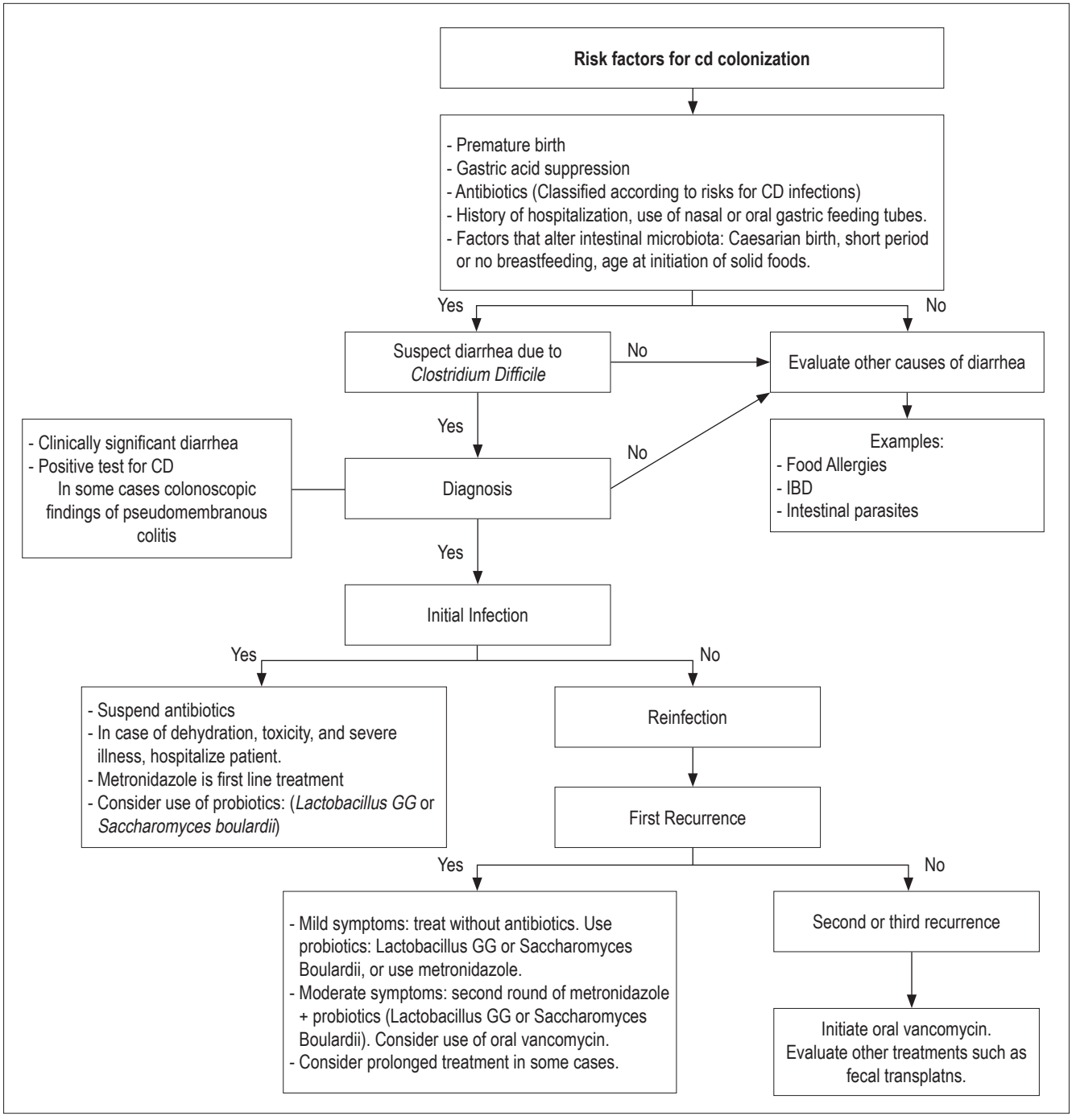

Figure 4. The authors proposal for an algorithm to guide the approach to patients with CD infections.

have viral etiologies. We believe that the use of probiotics could have favorable implications for management of patients with recurrent CD infections. The benefits are greatest in mild cases in which antibiotics are not required, but probiotics can be used as supplement therapy for moderate and severe cases.

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Conflicts of interest

The authors of this research state that they have no conflicts of interest related to this study's objective.

REFERENCES

1. Stanley JD, Bartlett JG, Dart BWt, Ashcraft JH. *Clostridium difficile* infection. Curr Probl Surg. 2013 Jul;50(7):302-337.
2. McFee RB, Abdelsayed GG. *Clostridium difficile*. Dis Mon. 2009;55(7):439-470.
3. Loo VG, Poirier L, Miller MA, Oughton M, Libman MD, Michaud S, *et al*. A predominantly clonal multi-institutional outbreak of *Clostridium difficile*–associated diarrhea with high morbidity and mortality. N Engl J Med. 2005;353(23):2442-2449.
4. Borali E, Ortisi G, Moretti C, Stacul EF, Lipreri R, Gesu GP, *et al*. Community-acquired *Clostridium difficile* infection in children: A retrospective study. Dig Liver Dis. 2015;47(10):842-846.
5. Collignon A, Ticchi L, Depitre C, Gaudelus J, Delmee M, Corthier G. Heterogeneity of *Clostridium difficile* isolates from infants. Eur J Pediatr. 1993;152(4):319-322.
6. Rousseau C, Poilane I, De Pontual L, Maherault A-C, Le Monnier A, Collignon A. *Clostridium difficile* carriage in healthy infants in the community: A potential reservoir for pathogenic strains. Clin Infect Dis. 2012;55(9):1209-1215.
7. Seekatz AM, Young VB. *Clostridium difficile* and the microbiota. J Clin Invest. 2014;124(10):4182-819.
8. Khanna S, Baddour LM, Huskins WC, Kammer PP, Faubion WA, Zinsmeister AR, *et al*. The epidemiology of *Clostridium difficile* infection in children: A population-based study. Clin Infect Dis. 2013;56(10):1401-146.
9. Claesson MJ, Cusack S, O'Sullivan O, Greene-Diniz R, de Weerd H, Flannery E, *et al*. Composition, variability, and temporal stability of the intestinal microbiota of the elderly. Proc Natl Acad Sci USA. 2011;108(1):4586-4591.
10. Hopkins MJ, Sharp R, Macfarlane GT. Age and disease related changes in intestinal bacterial populations assessed by cell culture, 16S rRNA abundance, and community cellular fatty acid profiles. Gut. 2001;48(2):198-205.
11. Zanella Terrier MC, Simonet ML, Bichard P, Frossard JL Recurrent *Clostridium difficile* infections: The importance of the intestinal microbiota. World J Gastroenterol. 2014;20(23):7416-7423.
12. Faber F, Bäumler AJ. The impact of intestinal inflammation on the nutritional environment of the gut microbiota. Immunol Lett. 2014;162(2):48-53.
13. Rousseau C, Levenez F, Fouqueray C, Doré J, Collignon A, Lepage P. *Clostridium difficile* colonization in early infancy is accompanied by changes in intestinal microbiota composition. J Clin Microbiol. 2011;49(3):858-865.
14. Nagalingam NA, Lynch SV. Role of the microbiota in inflammatory bowel diseases. Inflamm Bowel Dis. 2012 May;18(5):968-984.
15. Com G, Cetin N, O'Brien CE. Complicated *Clostridium difficile* colitis in children with cystic fibrosis: Association with gastric acid suppression? J Cyst Fibros. 2014;13(1):37-42.
16. Abdelfatah M, Nayfe R, Nijim A, Enriquez K, Ali E, Watkins RR, *et al*. Factors Predicting Recurrence of *Clostridium difficile* Infection (CDI) in Hospitalized Patients: Retrospective Study of More Than 2000 Patients. J Investig Med. 2015;63(5):747-751.
17. Hu MY, Katchar K, Kyne L, Maroo S, Tummala S, Dreisbach V, *et al*. Prospective derivation and validation of a clinical prediction rule for recurrent *Clostridium difficile* infection. Gastroenterology. 2009;136(4):1206-1214.
18. Olson MM, Shanholtzer CJ, Lee JT, Gerding DN. Ten years of prospective *Clostridium difficile*-associated disease surveillance and treatment at the Minneapolis VA Medical Center, 1982–1991. Infect Control Hosp Epidemiol. 1994;15(6):371-381.
19. Bartlett JG. Narrative review: the new epidemic of *Clostridium difficile*–associated enteric disease. Ann Intern Med. 2006;45(10):758-764.
20. Deshpande A, Pasupuleti V, Thota P, Pant C, Rolston DDK, Sferra TJ, *et al*. Community-associated *Clostridium difficile* infection and antibiotics: a meta-analysis. J Antimicrob Chemother. 2013;68(9):1951-1961.
21. Sandora TJ, Fung M, Flaherty K, Helsing L, Scanlon P, Potter-Bynoe G, *et al*. Epidemiology and risk factors for *Clostridium difficile* infection in children. Pediatr Infect Dis J. 2011;30(7):580-584.
22. Tamma PD, Sandora TJ. *Clostridium difficile* infection in children: Current state and unanswered questions. J Pediatric Infect Dis Soc. 2012;1(3):230-243.
23. Leonard Ad, Ho KM, Flexman J. Proton pump inhibitors and diarrhea related to *Clostridium difficile* infection in hospitalised patients: A case-control study. Intern Med J. 2012;42(5):591-594.
24. Tschudin-Sutter S, Tamma P, Milstone AM, Perl TM. Predictors of first recurrence of *Clostridium difficile* infections in children. Pediatr Infect Dis J. 2014;33(4):414-216.
25. Nylund CM, Eide M, Gorman GH. Association of *Clostridium difficile* infections with acid suppression medications in children. J Pediatr. 2014;165:979-984.
26. Lessa FC, Mu Y, Bamberg WM, Beldavs ZG, Dumyati GK, Dunn JR, *et al*. Burden of *Clostridium difficile* infection in the United States. N Engl J Med. 2015;372(9):825-834.
27. Vecchio AL, Zacur GM. *Clostridium difficile* infection: An update on epidemiology, risk factors, and therapeutic options. Curr Opin Gastroenterol. 2012;28(1):1-9.
28. Egressy K, Jansen M, Meyer KC. Recurrent *Clostridium difficile* colitis in cystic fibrosis: An emerging problem. J Cyst Fibros. 2013;12:92–96.
29. Shim JO. *Clostridium difficile* in Children: To Treat or Not to Treat? Pediatr Gastroenterol Hepatol Nutr. 2014;17(2):80-4.
30. Wendt JM, Cohen JA, Mu Y, Dumyati GK, Dunn JR, Holzbauer SM, *et al*. *Clostridium difficile* infection among children across diverse US geographic locations. Pediatrics. 2014;133(4):651-8.

31. Bagdasarian N, Rao K, Malani PN. Diagnosis and treatment of *Clostridium difficile* in adults: A systematic review. JAMA. 2015;313(4):398-408.
32. Feghaly RE, Stauber JL, Tarr PI, Haslam DB. Intestinal Inflammatory biomarkers and outcome in Pediatric *Clostridium difficile* Infections. J Pediatr. 2013;163:1697-704.
33. Aslam S, Musher DM. An update on diagnosis, treatment, and prevention of *Clostridium difficile*–associated disease. Gastroenterol Clin North Am. 2006;35(2):315-35.
34. Daza W, Dadán S. Síndrome de malabsorción. En: Leal Q, Francisco. El pediatra eficiente. 7a. Ed. Bogotá, Editorial Médica Panamericana; 2013: 418-428.
35. Pang T, Leach ST, Katz T, Day AS, Ooi CY. Fecal biomarkers of intestinal health and disease in children. Front Pediatr. 2014;2(6):1-12.
36. Walkiewicz D, Werlin SL, Fish D, Scanlon M, Hanaway P, Kugathasan S. Fecal calprotectin is useful in predicting disease relapse in pediatric inflammatory bowel disease. Inflamm Bowel Dis. 2008;14(5):669-673.
37. Schutze GE, Willoughby RE, Brady MT, Byington CL, Davies HD, Edwards KM, *et al*. *Clostridium difficile* infection in infants and children. Pediatrics. 2013;131(1):196-200.
38. Morinville V, McDonald J. *Clostridium difficile*-associated diarrhea in 200 Canadian children. Can J Gastroenterol. 2005;19(8):497-501.
39. Lübbert C, John E, von Müller L. *Clostridium Difficile* Infection: Guideline-Based Diagnosis and Treatment. Dtsch Arztebl Int. 2014;111(43):723-731.
40. Cohen SH, Gerding DN, Johnson S, Kelly CP, Loo VG, McDonald LC, *et al*. Clinical practice guidelines for *Clostridium difficile* infection in adults: 2010 update by the Society for Healthcare Epidemiology of America (SHEA) and the Infectious Diseases Society of America (IDSA). Infect Control Hosp Epidemiol. 2010;31(5):431-455.
41. Varier RU, Biltaji E, Smith KJ, Roberts MS, Kyle Jensen M, LaFleur J, *et al*. Cost-Effectiveness Analysis of Fecal Microbiota Transplantation for Recurrent *Clostridium difficile* Infection. Infect Control Hosp Epidemiol. 2015;36(4):438-44.
42. Surawicz CM, Brandt LJ, Binion DG, Ananthakrishnan AN, Curry SR, Gilligan PH, *et al*. Guidelines for diagnosis, treatment, and prevention of *Clostridium difficile* infections. Am J Gastroenterol. 2013;108(4):478-498.
43. Gough E, Shaikh H, Manges AR. Systematic review of intestinal microbiota transplantation (fecal bacteriotherapy) for recurrent *Clostridium difficile* infection. Clin Infect Dis. 2011;53(10):994-1002.
44. Walia R, Garg S, Song Y, Girotra M, Cuffari C, Fricke WF, *et al*. Efficacy of fecal microbiota transplantation in 2 children with recurrent *Clostridium difficile* infection and its impact on their growth and gut microbiome. J Pediatr Gastroenterol Nutr. 2014;59(5):565-570.
45. Vandenplas Y, Veereman G, van der Werff Ten Bosch J, Goossens A, Pierard D, *et al*. Fecal microbial transplantation in a one-year-old girl with early onset colitis caution advised. J Pediatr Gastroenterol Nutr. 2015;61(3):12–14.
46. Pillai A1, Nelson R. Probiotics for treatment of *Clostridium difficile*-associated colitis in adults. Cochrane Database Syst Rev. 2008 Jan 23;(1):CD004611.
47. McFarland LV. Probiotics for the Primary and Secondary Prevention of *C. difficile* Infections: A Meta-analysis and Systematic Review. Antibiotics. 2015;4(2):160-78.
48. Szajewska H, Kołodziej M. Systematic review with meta-analysis: *Saccharomyces boulardii* in the prevention of antibiotic-associated diarrhea. Aliment Pharmacol Ther. 2015;42(7):793-801.
49. Louie TJ, Emery J, Krulicki W, Byrne B, Mah M. OPT-80 eliminates *Clostridium difficile* and is sparing of bacteroides species during treatment of *C. difficile* infection. Antimicrob Agents Chemother. 2009;53(1):261-263.
50. Lawley TD, Clare S, Walker AW, Stares MD, Connor TR, Raisen C, *et al*. Targeted restoration of the intestinal microbiota with a simple, defined bacteriotherapy resolves relapsing *Clostridium difficile* disease in mice. PLoS Pathog. 2012;8(10):e1002995.
51. Crews J, Edwards M, Torchia M. *Clostridium difficile* infection in children: Clinical features and diagnosis. Uptodate 2015. Disponible en: http://www.uptodate.com/contents/clostridium-difficile-infection-in-children-clinical-features-and-diagnosis. [Consultado Diciembre 08 de 2015]