CANADIAN PAEDIATRIC SOCIETY STATEMENT

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Clostridium difficile – Pathogen or pest?

In the current climate of frequent injudicious use of oral antibiotics, adverse effects that outweigh treatment benefits may be encountered; antibiotic-associated diarrhea is one such common effect. *Clostridium difficile* is found frequently in the stool of children with antibiotic-associated diarrhea; however, its role as an etiological agent in children is controversial. The purpose of this statement is to review the literature on *C difficile* in childhood diarrhea, and to provide recommendations for diagnosis and therapy. The recommendations are based on limited published observations and expert consensus. Gaps in current knowledge are indicated.

EPIDEMIOLOGY

C difficile is a ubiquitous bacterium found in soil, hospital environments, child care facilities and nursing homes (1,2). It is a spore-forming, Gram-positive bacillus, which can spread via the fecal-oral route (1,2); patient-to-patient transmission has been well documented within hospitals (1,2). Whereas the incubation period for *C difficile*-associated disease is difficult to determine accurately, diarrhea associated with it may occur within days or up to eight weeks after therapy with medications that alter the gastrointestinal (GI) flora (1).

A wide range of oral antibiotics (eg, penicillins, clindamycin, cephalosporins) and chemotherapeutic agents (eg, fluorouracil, methotrexate) can alter the natural GI flora and favour the emergence of *C difficile* (3). However, it is not known whether the length of therapy and number of courses of antibiotics or chemotherapeutic agents enhance the likelihood that *C difficile* will be recovered from stool. Hypogammaglobulinemic or other immunosuppressed patients appear to be at enhanced risk of harbouring *C difficile* in their stool, but it is not clear whether this is due to the increased use of antibiotics in this vulnerable population (4).

Infants and children are more likely to carry *C difficile* asymptomatically in the GI tract than adults (3); it is estimated that 15% to 63% of neonates, 3% to 33% of infants and toddlers younger than two years of age, and up to 8.3% of children older than two years of age are asymptomatic carriers (5). Because the rates of symptomatic carriage (coexisting diarrhea) are not dissimilar to that for asymptomatic carriage (5), it is often difficult to establish a clear role for *C difficile* in causing mild GI disease in children.

C difficile may be found in stool in association with other putative GI pathogens, such as *Salmonella* species, *Campylobacter* species, *Giardia* species or rotavirus, regardless of whether antibiotics have been administered recently (5).

PATHOPHYSIOLOGY

Important pathophysiological features of *C difficile* include heat-resistance of the spore (allowing environmental persistence) and toxin production. Two toxins (A and B) can be produced; the latter is more potent in tissue culture, and this characteristic is used for diagnosis (1,2,6). The toxins bind to intestinal epithelial cells, enter the cells and cause damage as demonstrated by actin disaggregation and cytoskeletal rearrangement (1,2,6). Toxin A is capable of intoxicating neurons and causing the aberrant release of calcium (1,2,6). Finally, toxin A exerts its effect on leukocytes by altering the chemotaxis of neutrophils, the activation of macrophages and mast cells, and the induction of inflammatory mediator release (1,2,6). The end result of toxin activity in the intestine is fluid secretion, mucosal damage and interstitial inflammation (1,2,6).

TABLE 1: Treatment of *Clostridium difficile*-associated enteritis in children

Drug	Recommended paediatric dose	Duration of treatment	Comments	Cost of treatment per day for 30 kg child (drug cost only)
Oral metronidazole	35 to 50 mg/kg/day by mouth qid or tid	7 to 10 days	• Drug of choice and drug delivery method of choice.	$0.15 to $0.22
Oral vancomycin	10 to 50 mg/kg/day by mouth qid	7 to 10 days	• Equally as effective as metronidazole, but may enhance emergence of antibiotic-resistant bacteria. Should be used only in extraordinary circumstances.	$25 to $50
Parenteral metronidazole	35 to 50 mg/kg/day parenterally every 6 h	7 to 10 days	• Should be used only when oral administration is impossible. Excreted into the intestine.	$2.75 to $4
Teicoplanin	–	–	• Recommended paediatric dose is not provided because this agent is rarely indicated for *Clostridium difficile*-associated enteritis in children.	–
Fusidic acid	–	–	• Recommended paediatric dose is not provided because this agent is rarely indicated for *Clostridium difficile*-associated enteritis in children.	–

CLINICAL PRESENTATION AND DIFFERENTIAL DIAGNOSIS OF ILLNESSES ATTRIBUTED TO *C DIFFICILE*

The presence of *C difficile* in stool is associated with a wide spectrum of GI manifestations ranging from asymptomatic carriage to pseudomembranous colitis. The common asymptomatic carriage of the organism renders diagnosis of *C difficile*-associated disease extremely problematic.

Watery diarrhea

Watery diarrhea is the disease most frequently associated with *C difficile* in children. Because the toxins produced by *C difficile* can cause intestinal cell water secretion, it seems logical that watery diarrhea may result. However, because the organism is found so frequently in asymptomatic children, it is difficult to prove that *C difficile* is the cause of this syndrome, which is often mild. Other agents capable of causing mild secretory diarrhea include *Escherichia coli* (enterotoxigenic or enteropathogenic), enteric viruses (rotavirus, Calicivirus, enteric adenovirus and Astrovirus), *Giardia* species and other pathogens such as *Cryptosporidium* species.

Bloody diarrhea

Pseudomembranous colitis is a very serious disease; a role for *C difficile* in this disease has been clearly established. Characteristic features include progressively severe diarrhea, abdominal pain, fever, leukocytosis, systemic toxicity, and stool containing blood, mucus and leukocytes. The most severe manifestation of pseudomembranous colitis is toxic megacolon, which may lead to intestinal perforation.

Other infectious causes of bloody diarrhea include enteroinvasive or enterohemorrhagic *E coli*, *Campylobacter* species, *Yersinia* species, *Salmonella* species, *Shigella* species *or Entamoeba histolytica*.

DIAGNOSIS

C difficile may be recovered frequently from the stool of symptomatic children, but disease due to this organism can only be established if its toxin(s) is identified. A bacterial culture requires up to 72 h under anaerobic conditions, and it has an overall sensitivity of approximately 95% (7). However, its low specificity necessitates testing for the toxins, for which multiple assays are available.

The 'gold standard' toxin bioassay evaluates the cytotoxicity of cells in tissue culture. This requires 24 to 48 h, but it has a high sensitivity and specificity (7). Other rapid tests that provide answers in minutes to hours include enzyme immunoassays, polymerase chain reaction, latex agglutination, and Immunocard (Meridian Diagnostics, United States). Each of these tests is rapid and highly specific, but they all suffer from a lack of sensitivity (with up to 20% false negative results) (1,6). In some cases, it may be desirable to confirm the diagnosis by colonoscopy.

TREATMENT

Watery diarrhea

The high frequency of *C difficile* and its toxins in the GI tract of healthy infants and children confounds the diagnosis of *C difficile* disease in a child with mild to

moderate watery diarrhea with a toxin present in the stool. This therapeutic decision should be guided by a number of factors, including the severity of the diarrhea, the presence of another putative pathogen and the coexistence of an immunodeficiency disorder (inborn or acquired). In all cases of antibiotic-associated diarrhea, the offending agent should be discontinued immediately if possible. If the diarrhea worsens or fails to improve within 48 h and a decision is made to treat for *C difficile*, the agent of choice is oral metronidazole (Table 1). If bloody diarrhea develops, see the following section for treatment advice. It must be emphasized that many cases of secretory diarrhea, in which *C difficile* and/or its toxins are identified, are probably due to etiologies other than *C difficile*.

Bloody diarrhea

If a patient has colitis and a *C difficile* toxin is identified, specific therapy is indicated. As with secretory diarrhea, the offending agent should be discontinued immediately. Several oral antibiotics are effective in treating *C difficile*-associated colitis, but metronidazole is the treatment of choice because of its excellent track record and low cost. (See Table 1 for dose and duration of therapy.)

Very few studies involving children have been conducted, but in adults, oral metronidazole, vancomycin, bacitracin, teicoplanin and fusidic acid are each highly effective (approximately 93% to 94%) in resolving symptom of the disease. However, each antibiotic is associated with a high relapse rate upon discontinuation (metronidazole 16%, vancomycin 16%, teicoplanin 7% and fusidic acid 28%) (8). Furthermore, the use of oral vancomycin may enhance the emergence of vancomycin-resistant enterococci.

In patients unable to tolerate oral medication, intravenous metronidazole (35 to 50 mg/kg/day divided every six hours) is the drug of choice because it is excreted in the intestine.

Recurrent or relapsing *C difficile*-associated colitis is not due to the development of antibiotic resistance, and it usually resolves with a second course of one of the antibiotics recommended above. Therefore, a repeated course of metronidazole is indicated, and there is no reason to choose an alternative agent. Some patients may require multiple repeat courses of antibiotic. Other approaches, which have been suggested but have not yet proven to be as good as the currently recommended therapies, include treatment with cholestyramine or probiotics (1-3).

PROGNOSIS

The prognosis for full recovery in previously healthy children with *C difficile*-associated watery diarrhea is excellent. Discontinuation of the offending antibiotic is usually sufficient to resolve symptoms. In patients with *C difficile*-associated pseudomembranous colitis, the prognosis of untreated disease is much graver; the disease may progress rapidly to toxic megacolon with severe morbidity, particularly in adults. Therapy for such patients should be initiated immediately, and the offending agent discontinued.

Chronic or recurrent diarrhea is a complication of bona fide *C difficile*-associated disease. However, most cases fully resolve with repeated courses of therapy.

SUMMARY

C difficile is frequently recovered from the stool of infants and children, but its role in gastrointestinal disease is poorly understood. This statement reviews the current knowledge about *C difficile* as a paediatric pathogen and provides recommendations for diagnosis and therapy. *C difficile* is present in the stool of many asymptomatic infants and children, and its presence is enhanced by previous antibiotic therapy. It should probably only be considered a potential pathogen under certain clinical conditions, which include bloody diarrhea with or without pseudomembranous colitis or watery diarrhea in immunocompromised hosts. The diagnosis of *C difficile*-associated diarrhea should only be made if a toxin is demonstrated in the stool; the presence of *C difficile* without toxin is not sufficient evidence to establish the diagnosis. The most sensitive means for detecting toxin is a tissue culture assay, which requires 24 to 48 h. Therapy consists of discontinuing the offending agent (usually an antibiotic) and the administration of oral metronidazole. In healthy children with antibiotic-associated watery diarrhea, with *C difficile* toxin present in their stool, discontinuation of the provocative agent is usually sufficient to resolve the diarrhea.

RECOMMENDATIONS

1. The diagnosis of *C difficile*-associated colitis should be considered in any patient who is receiving or who has received antibiotics within the previous two weeks, and who has the following: bloody diarrhea with or without systemic toxicity, fever and crampy abdominal pain.
2. The diagnosis of *C difficile*-associated diarrhea should be considered in immunocompromised patients who are receiving or have received antibiotics or chemotherapy within the previous two weeks, and who have any diarrheal illness (either watery or bloody).
3. The diagnosis of *C difficile*-associated diarrhea should only be made if a toxin is found in the stool. Culture of the bacteria is not sufficient evidence to support the diagnosis.
4. In immunocompetent patients with mild to moderate watery diarrhea and evidence of a *C difficile* toxin in the stool, discontinuation of the offending antibiotic is usually adequate therapy.
5. The treatment of choice for *C difficile*-

associated colitis (after discontinuation of the offending antibiotic, if possible) is oral metronidazole (35 to 50 mg/kg/day for seven to 10 days).

6. Enteric precautions, hand washing and other standard infection control strategies are recommended to limit the nosocomial spread of *C difficile*.

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ANNOTATED RECOMMENDED READING

Bartlett JG. *Clostridium difficile*: History of its role as an enteric pathogen and the current state of knowledge about the organism. Clin Infect Dis 1994;18(Suppl 4):S265-72.

A comprehensive review of Clostridium difficile, *its pathogenicity, epidemiology and diagnosis, with the main focus on the adult population.*

Cerquetti M, Luzzi I, Caprioli A, Sebastianelli A, Mastrantonio, P. Role of *Clostridium difficile* in childhood diarrhea. Pediatr Infect Dis J 1995;14:598-603.

A multicenter, prospective, control study providing additional evidence that Clostridium difficile *may not be involved in the etiology of childhood diarrhea.*

Fekety R. Guidelines for the diagnosis and management of *Clostridium difficile*-associated diarrhea and colitis. American College of Gastroenterology. Practice Parameters Committee. Am J Gastroenterol 1997;92:739-50.

A very comprehensive review that focuses mainly on adults; multiple suggestions and guidelines for therapy are applicable to pediatrics.

Johnson S, Gerding DN: *Clostridium difficile*-associated diarrhea. Clin Infect Dis 1998;26:1027-36.

An excellent, up-to-date review of the topic with a specific discussion of the large number of children who carry Clostridium difficile *in the stool without any specific symptomatology.*

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