

# *Clostridium difficile* in paediatric populations

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An increase in *Clostridium difficile* infection incidence has been observed among hospitalized children in the United States. The present statement, targeted at clinicians caring for infants and children in community and institutional settings, summarizes the relevant information relating to the role of *C difficile* in childhood diarrhea and provides recommendations for diagnosis, prevention and treatment. Significant differences between adult and paediatric risk factors and disease are discussed, along with emerging therapies. The relationship between age and disease severity in children with a newly emergent and more fluoroquinolone-resistant strain of *C difficile* (North American Pulse-field type-1 [NAP1]) remains unknown. The importance of antimicrobial stewardship as a preventive strategy is highlighted. This statement replaces a previous Canadian Paediatric Society position statement on *C difficile* published in 2000.

**Key Words:** CDI; Colitis; Diarrhea; Immunocompromise; Megacolon; Metronidazole; NAP1; Vancomycin

## Le *Clostridium difficile* dans les populations d'âge pédiatrique

On a observé une augmentation de l'incidence d'infections par le *Clostridium difficile* chez les enfants hospitalisés des États-Unis. Le présent document de principes, qui s'adresse aux cliniciens qui s'occupent de nourrissons et d'enfants de la collectivité et en établissement, contient un résumé de l'information pertinente sur le rôle du *C difficile* dans la diarrhée infantile et propose des recommandations sur le diagnostic, la prévention et le traitement. On y traite des différences importantes des facteurs de risque et de la maladie entre les adultes et les enfants, de même que des thérapies émergentes. On ne connaît toujours pas la relation entre l'âge et la gravité de la maladie chez les enfants ayant une souche de *C difficile* nouvellement émergente et plus résistante aux fluoroquinolones (nord-américain type 1 en champ pulsé [NAP1]). On y souligne l'importance de la gestion des antimicrobiens à titre de stratégie préventive. Le présent document de principes remplace celui qui a été publié par la Société canadienne de pédiatrie sur le *C difficile* en 2000.

### EPIDEMIOLOGY AND RISK FACTORS

*Clostridium difficile* is a spore-forming bacterium found in soil, hospital environments, child care facilities and nursing homes.(1,2) Person-to-person spread by the fecal-oral route is the primary mode of transmission, with health care facilities being a notably common and problematic setting for infection. Spores are transferred to patients mainly on the hands of health care staff who have touched a contaminated surface or item. Infants and children are significantly more likely to carry *C difficile* asymptomatically in the gastrointestinal (GI) tract than are 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.(4) Infants and young children rarely develop symptoms, possibly because of immature surface receptors for these microbes, and because they are protected by maternal antibodies acquired transplacentally or in breast milk.(5)

The incubation period from exposure to onset of symptomatic *C difficile* infection (CDI) is an estimated median of two to three days.(6-9) A history of therapy with antibiotics or antineoplastic agents is present in most adult patients with CDI.(10)

In the United States, an increase in CDI incidence has been observed among hospitalized children.(11,12) Duration of hospital stay, older age(13) and exposure to multiple antibiotic classes are risk factors for paediatric CDI.(14) Among children with severe disease, complications are infrequent. The recurrent infection rate is similar to rates reported in adults (approximately 25%).(14)

Virtually all antimicrobials used in humans have been associated with CDI, including those used for surgical prophylaxis.(15) It has been suggested that the relative risk of therapy with a given

antimicrobial agent and its association with CDI depends on the local prevalence of strains that are highly resistant to the antimicrobial being used; such agents increase the risk for CDI by suppressing the growth of susceptible microbial flora.(16)

Chemotherapy is associated with an increased risk for CDI, possibly due to the antimicrobial properties of chemotherapeutic agents, the effects of immunosuppression and neutropenia, and changes in the gut mucosa. In one paediatric study, comorbid diagnoses associated with CDI included inflammatory bowel disease and other diseases associated with immunosuppression or antibiotic administration.(11) The prominence of *C difficile* in HIV-infected adults in the United States suggests that underlying immunosuppression likely contributes to increasing the risk for CDI.(17)

The humoral immune response is important in influencing the risk for CDI, as evidenced by the fourfold increase in risk for CDI in patients who are either newly infected with HIV or lack pre-existing immunity to *C difficile*.(18,19) Hypogammaglobulinemia is associated with an increased risk for CDI.(20,21) Antibodies from previous exposures confer some protection. Other risk factors include GI surgery(22) or manipulation of the GI tract, including tube feeding.(23) Some studies have suggested an association between the use of stomach acid-suppressing medications, primarily proton pump inhibitors, and CDI,(24-28) while others suggest the association exists simply because patients with classic risk factors for CDI(29-31) are likely to receive acid-suppressing medications. In one paediatric report, H<sub>2</sub> receptor antagonists were actually associated with decreased colonization by *C difficile*.(32)

A previously uncommon strain of *C difficile* (North American Pulse-field type-1 [NAP1]; currently designated as NAP1/B1/027)

**TABLE 1**  
**Treating *Clostridium difficile* infections**

Clinical scenario	Supportive clinical findings*	Recommended treatment
Mild illness	Watery diarrhea without systemic toxicity; typically <4 abnormal stools/day	Discontinue precipitating antibiotic; adequate follow-up and reassessment
Initial episode, moderate or mild, not responding to discontinuation of precipitating antibiotic	Moderate illness, typically ≥4 abnormal stools/day; no systemic toxicity	Metronidazole, 30 mg/kg/day in four divided doses by mouth for 10 to 14 days; maximum 2 g/day
Initial episode, severe	Evidence of systemic toxicity (eg, high-grade fevers, rigors)	Vancomycin, 40 mg/kg/day in four divided doses by mouth for 10 to 14 days; maximum 500 mg/day (125 mg per dose orally four times per day)
Initial episode, severe, complicated	Evidence of systemic toxicity and severe colitis, including hypotension, shock, peritonitis, ileus or megacolon	Vancomycin 40 mg/kg/day in four divided doses by mouth or by nasogastric tube, <b>plus</b> intravenous metronidazole, 30 mg/kg/day in four divided doses for 10 to 14 days. If complete ileus, consider adding rectal instillation of vancomycin; maximum 2 g/day
First recurrence	–	Repeat regimen used for initial episode
Second recurrence	–	Vancomycin in a tapered or pulsed regimen†

\*The supportive clinical findings are based on expert opinion in the absence of prospectively validated indicators of disease severity in infants and children;

†Vancomycin, 40 mg/kg/day in four divided doses for 10 to 14 days (10 mg/kg/dose, maximum 125 mg/dose), then 10 mg/kg/dose twice per day for one week, then 10 mg/kg/dose once per day for one week, and finally 10 mg/kg/dose every two or three days for two to eight weeks. Adapted from reference 6

has recently emerged, with variations in toxin genes and a tendency to resist fluoroquinolones.(33) This strain is now widely distributed in several regions of the world, including Canada.(34-41) While outbreaks and severe disease have been reported mostly in adults, paediatric disease is also being reported.(42-44) In one Canadian study, patients 60 to 90 years of age infected with NAP1/B1/027 were approximately twice as likely to die or to experience a severe CDI-related outcome, compared with individuals who were infected with a non-NAP1/B1/027 CDI.(45) The relationship between age and disease severity in children with this strain is unknown.

Recent reports have challenged the belief that *C difficile* is less pathogenic in young infants and children.(12,46) In one study, 26% of paediatric disease that was treated as CDI occurred in children younger than one year of age and 5% of all cases occurred in infants younger than one month of age. It has been speculated that one reason for this finding may be related to the emergence of the NAP1 strain. If such strains are associated with greater pathogenicity relative to non-NAP1 strains, the very small minority of infants who acquire *C difficile*-related disease may be more likely to be clinically recognized. However, this relationship has not been proven and additional research is required.

#### PATHOPHYSIOLOGY

Important pathophysiological features of *C difficile* include heat resistance of the spore (allowing environmental persistence), acid resistance of spores and toxin production. Their acid resistance allows spores to pass readily through the stomach, enabling germination in the small bowel on exposure to bile acids.(47) Pathogenic strains of *C difficile* produce two distinct toxins: toxin A is an enterotoxin; and toxin B is a cytotoxin. Both are high-molecular-weight proteins capable of binding to specific receptors on intestinal mucosal cells. Toxin A can disrupt neuronal function and cause the aberrant release of calcium.(1,2,5) Toxin B 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.(1,2,5) The end result of toxin activity in the intestine is fluid secretion, mucosal damage and interstitial inflammation.(1,2,5)

#### CLINICAL PRESENTATION OF ILLNESSES ATTRIBUTED TO *C DIFFICILE*

The presence of toxin-producing *C difficile* in stool is associated with a wide spectrum of GI manifestations, ranging from

asymptomatic carriage to pseudomembranous colitis. The high rates of asymptomatic carriage in infants and young children make the diagnosis of *C difficile*-associated disease extremely problematic in this age group.

#### Definitions

A case definition of CDI includes the presence of symptoms (usually diarrhea) and either a stool test result that is positive for *C difficile* toxins or colonoscopic findings demonstrating pseudomembranous colitis.(6) Watery diarrhea is the most frequent manifestation of CDI in children. Because the toxins produced by *C difficile* can cause intestinal cell water secretion, 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.

Symptomatic illness may be mild, moderate or severe. While clinical judgment is required to assign severity and guide treatment (Table 1), mild-to-moderate illness is usually characterized by watery diarrhea, low-grade fever and mild abdominal pain.(48) Mild illness typically involves watery diarrhea without systemic toxicity and, typically, fewer than four abnormal stools per day.(49) Moderate illness is typically four or more abnormal stools per day, with no systemic toxicity (though mild abdominal pain and low-grade fever may be present). Severe disease involves evidence of systemic toxicity (eg, high-grade fever, rigors). Severe illness may be complicated by hypotension, shock, peritonitis, ileus or megacolon. In this regard, *C difficile* is a well-established cause of pseudomembranous colitis. Characteristic features include progressively severe diarrhea, abdominal pain, fever, leukocytosis, systemic toxicity, and stool containing blood, mucous and leukocytes. The most severe manifestation of pseudomembranous colitis is toxic megacolon, which may lead to intestinal perforation. Severe or fatal disease is rare in children; however, complications are more likely to occur among neutropenic children with hematological malignancies or those treated with hematopoietic stem cell transplantation,(48) infants with Hirschsprung's disease and patients with inflammatory bowel disease.

#### LABORATORY DIAGNOSIS

*C difficile* disease can only be firmly diagnosed once its toxin(s) is identified. However, it is also important to note that children can be asymptomatic hosts of toxin-producing strains. It is generally recommended that testing for *C difficile* or its toxins should be performed only on diarrheal stool, unless ileus due to *C difficile* is

suspected.(6) While bacterial culture has been the benchmark for other forms of testing, it is not clinically practical for testing CDI due to the slow turnaround time. Also, while the overall sensitivity of culture testing is approximately 95%,(50) its specificity is low.

Laboratory testing methods have been recently reviewed, and recommendations were made by the Society for Healthcare Epidemiology of America and the Infectious Diseases Society of America.(6) Tests commonly used for diagnosis are:

- The enzyme immunoassay (EIA) for glutamate dehydrogenase (GDH), which is present in almost all strains of *C difficile*, including strains that do not produce toxin;
- EIA for toxins A and B; and
- A cell cytotoxin assay that typically demonstrates cytotoxicity of stool for human foreskin fibroblast cells.

EIA toxin testing has been the primary mode of testing until recently but is hampered by its lack of sensitivity, while cytotoxin assays are labour-intensive and expensive. A strategy that has been proposed is a two-step method using GDH(51,52) as the initial screening, followed by the toxin EIA or (preferably) a cell cytotoxin assay as the confirmatory test for GDH-positive stool specimens. Polymerase chain reaction testing is rapid, sensitive and specific, and appears promising in addressing toxin testing concerns.(53,54) Significant variations exist in testing methodologies and kits used in different Canadian laboratories. While polymerase chain reaction testing is increasingly being used, further evaluation of its utility in different settings is warranted.

### PREVENTING CDI

A detailed review of strategies to prevent CDI is beyond the scope of this statement, and current protocols have been summarized elsewhere.(6,55) Infection control and prevention measures were described in guidelines published in 2010 by the Society for Healthcare Epidemiology of America and the Infectious Diseases Society of America:(6) [www.cdc.gov/HAI/pdfs/cdiff/Cohen-IDSASHEA-CDI-guidelines-2010.pdf](http://www.cdc.gov/HAI/pdfs/cdiff/Cohen-IDSASHEA-CDI-guidelines-2010.pdf). Infection prevention and control strategies are important for preventing the spread of CDI.

Strategies include but are not limited to:

- Meticulous hand hygiene;
- Identifying and removing environmental sources of *C difficile*, and using chlorine-containing or other sporicidal cleaning agents to eliminate environmental contamination in areas associated with increased rates or outbreaks of CDI. Alcohol-based hand hygiene products do not kill *C difficile* spores;
- Contact precautions for the duration of symptoms (48 h with no diarrhea);
- Use of private rooms or cohorting. Stool should not be retested once symptoms abate. The decision to isolate patients should be based on symptoms alone because stools often remain toxin-positive despite cure.

While several factors contribute to the risk for CDI, the importance of antimicrobial pressure cannot be overstated. The implementation of antimicrobial stewardship initiatives in institutions is regarded as a key step in reducing CDI risk.(6)

Emerging data from meta-analyses suggest that probiotics may be beneficial in preventing CDI.(56-58) However, additional research is needed to better define which probiotics work the best and in which patient groups, including children.(59)

### TREATMENT

Much of the evidence for treatment approaches to CDI has been derived from adult populations and extrapolated to children.

However, the vast differences between CDI in infants and young children versus adults limit this approach.

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 (nonbloody) diarrhea with toxin present in the stool. In many cases, the illness resolves without specific treatment. Even if a decision is made to treat *C difficile*, clinicians should be aware of the possible presence of another pathogen. In all cases of antibiotic-associated diarrhea, the offending agent should be discontinued immediately, if possible. In situations in which antibiotic therapy cannot be stopped (eg, treatment of infective endocarditis), an antibiotic less commonly associated with CDI or one from a different class may be considered, when this is feasible without compromising care. One report found that removing antimicrobial pressure on the normal bowel flora was curative in 15% to 25% of immunocompetent patients.(60)

For patients with moderate-to-severe diarrhea and *C difficile* toxin, specific therapy is indicated. Individuals with severe or complicated CDI should be started on treatment as soon as the diagnosis is suspected as opposed to waiting for laboratory confirmation. Metronidazole (given orally) is the treatment of choice in most cases of *C difficile* colitis in children (Table 1). In adults, oral vancomycin is the agent of choice for severe *C difficile* colitis. (6) In the most severe cases, this agent (given orally, or rectally if ileus is present) may be used in conjunction with metronidazole (which can be given intravenously because enterohepatic circulation deposits some drug in the gut).(6) Vancomycin has no efficacy for CDI if given intravenously. Colectomy may be required in intractable cases.

Treatment does not eradicate *C difficile* or the toxin from the stool. Asymptomatic patients, if tested, should not be treated again simply because the stool test is positive.

The above agents are associated with clinical relapse rates of 15% to 35%.(61) Such relapses do not imply drug resistance and, typically, the initial regimen will result in prompt improvement with the first recurrence. The risk of a second recurrence does not appear to be related to the choice of drug (vancomycin or metronidazole) used to treat a first recurrence. Repeated courses of treatment may be needed in some patients. Metronidazole treatment is not recommended for chronic, long-term use because of theoretical concerns regarding neurotoxicity.(62)

For the treatment of the second or later recurrence of CDI, a tapered and/or pulse regimen with oral vancomycin is usually preferred. One tapered regimen is as follows: after the usual daily treatment dose of vancomycin for 10 to 14 days, vancomycin is administered at the same mg per dose but given two times per day for one week, then once per day for one week, and finally every two or three days for two to eight weeks. The goal is that *C difficile* vegetative forms will be kept in check while allowing restoration of the normal flora.

The management of intractable cases and multiple recurrences is challenging and consultation with individuals experienced in managing these cases is advised. Investigational agents have been used with varying degrees of success. Some agents (cholestyramine, colestipol and other anion-exchange resins) bind vancomycin and may render the drug ineffective if used concurrently.(6) Rifaximin appears promising, but there is the potential for the development of resistance during treatment. (63,64) Rifaximin is not available in Canada, but rifampin, which is available, may also have some efficacy. A randomized trial among adults indicated that the use of oral *Saccharomyces boulardii* in combination with oral vancomycin or metronidazole

decreased the number of recurrences but had no beneficial effect on the initial episode.(65) The Canadian Paediatric Society has determined that while there is no available current evidence to support the use of probiotics to treat *C difficile* in either children or adults, there may be a role for probiotics in preventing relapses in patients with recurrent CDI.(59) However, although the risk is believed to be low, the use of *S boulardii* has been associated with fungemia in immunocompromised patients and in patients with central venous lines.(66)

Other agents used to treat CDI include teicoplanin, which is likely to be as effective as vancomycin,(67) bacitracin and fusidic acid. The latter two agents were shown to be associated with lower efficacy or higher recurrence compared with vancomycin and metronidazole.(68,69) Fidaxomicin is now licensed in Canada for individuals 18 years of age and older. Fidaxomicin is expensive but has been shown to be noninferior to vancomycin for initial treatment of CDI and associated with a lower rate of recurrence only for non-NAP1 strains.(70,71) Other investigational treatment agents include nitazoxanide, tinidazole, intravenous immunoglobulin and fecal transplants.(6) The latter approach has been used successfully in case series of adult patients(72,73) and in one randomized trial.(74) Paediatric use has also been reported.(75) In a recent randomized trial, duodenal infusion of donor feces was found to be more effective for the treatment of CDI than standard vancomycin therapy.(74) A recent proof-of-principle study demonstrated that a stool substitute mixture comprising multiple species of bacteria showed promise in the treatment of antibiotic-resistant *C difficile* colitis.(76) Further research is warranted on these approaches to treatment. CDI is currently the subject of candidate vaccine trials in Europe and North America.(77-79)

## RECOMMENDATIONS

### Diagnosis

- *C difficile*-associated colitis should be considered in any patient who is receiving or who has received antibiotics within the previous 12 weeks, and who has the following signs: bloody diarrhea with or without systemic toxicity, fever and abdominal pain.
- *C difficile*-associated diarrhea should be considered in immunocompromised patients who are receiving or have received antibiotics or chemotherapy within the previous 12 weeks, and who have any diarrheal illness (either watery or bloody).
- *C difficile*-associated diarrhea should only be diagnosed if toxin is detected in the stool. Culture of the bacteria is not sufficient evidence to support the diagnosis in symptomatic patients.
- The testing of stool samples from asymptomatic patients or from patients whose symptoms have resolved is not recommended; a positive test is of no clinical significance in these patients.
- Diarrheal disease in previously healthy infants younger than one year of age is not likely to be due to *C difficile*; testing for *C difficile* is not routinely recommended for these infants.

### Prevention

- In addition to the recommended infection control and prevention measures,(6,49) the Canadian Paediatric Society fully supports the implementation of antimicrobial stewardship initiatives in all hospitals as a component of strategies to prevent transmission of CDI.

## Treatment

### First-line therapies

#### Initial episode

- **Mild illness.** Children with mild *C difficile*-associated diarrhea do not require antibiotics. If the illness is precipitated by antibiotics, these should be stopped, if possible. Parents should be advised to seek help if symptoms worsen or if a child has not improved within 48 h.
- **Moderate illness.** The treatment of choice for initial episodes of moderate cases of *C difficile*-associated colitis (along with discontinuing the offending antibiotic, if possible) is oral metronidazole (30 mg/kg/day in four divided doses for 10 to 14 days; maximum 2 g/day).
- **Severe illness.** The treatment of choice for severe, uncomplicated *C difficile*-associated colitis (along with discontinuing the presumed offending antibiotic, if possible) is oral vancomycin (40 mg/kg/day in four divided doses for 10 to 14 days; maximum 500 mg/day).
- **Treat severe, complicated CDI** (with ileus, megacolon, shock, peritonitis or hypotension) with vancomycin (oral, or rectal if ileus is present; 40 mg/kg/day in four divided doses for 10 to 14 days; maximum 500 mg/day) and with intravenous metronidazole (30 mg/kg/day in four divided doses for 10 to 14 days; maximum 2 g/day).

#### First recurrence

- The regimens used to treat patients with first episodes of *C difficile*-associated colitis can be repeated for the first recurrence.

#### Second or later recurrences

- Second or later recurrences should typically be treated with vancomycin, using a tapered and/or pulsed regimen. An acceptable tapered regimen is as follows:
  - 40 mg/kg/day in four divided doses for 10 to 14 days (10 mg/kg per dose, maximum 125 mg/kg per dose); then
  - 10 mg/kg per dose twice per day for one week; then
  - 10 mg/kg per dose once per day for one week; and finally,
  - 10 mg/kg per dose every two or three days for two to eight weeks.

#### Second-line and experimental therapies:

- Beyond the use of metronidazole and vancomycin as above, other therapies should only be considered on a case-by-case basis and in consultation with a specialist in infectious diseases.

**Note:** Information for parents, '*C difficile* (*Clostridium difficile*)', can be accessed at [www.caringforkids.cps.ca](http://www.caringforkids.cps.ca).

**ACKNOWLEDGEMENTS:** This position statement has been reviewed by the Acute Care and Community Paediatrics Committees of the Canadian Paediatric Society.

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