

# Association of Medical Microbiology and Infectious Disease Canada treatment practice guidelines for *Clostridium difficile* infection

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**MOTS-CLÉS:** ICD, *Clostridium difficile*, therapy, guides

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## INTRODUCTION

These guidelines review the evidence and provide recommendations on the management of initial and recurrent episodes of *Clostridium difficile* infection (CDI). A panel of 15 experts in the management of CDI was convened to develop these guidelines on the basis of consensus as requested by AMMI Canada.

Published literature was retrieved through searches of MEDLINE, PubMed, and the Cochrane Library from January 1980 to February 2017 using keywords and MeSH terms (*Clostridium difficile*, antibiotic therapy, epidemiology, probiotics, microbiome, fecal transplants, colonization, cost-effectiveness). Results were restricted to systematic reviews, randomized control trials/controlled clinical trials, and observational studies in the English language. The quality of evidence in this document was rated using

the criteria delineated in the Report of the Canadian Task Force on Preventive Health Care (Table 1) (1). The pharmacoeconomic data are summarized at the end of the document and cost-effectiveness was taken into consideration where the data clearly supported a particular therapy.

## CLOSTRIDIUM DIFFICILE INFECTION EPIDEMIOLOGY

*Clostridium difficile* is recognized as a major cause of infection in health care facilities, associated with substantial morbidity and mortality, prolonged length of hospital stay, and excess costs. The frequency and severity of CDI increased dramatically in North America and in many parts of Europe approximately 15 years ago, with the emergence of a hyper-virulent strain of *C. difficile*, designated based on various strain typing methods as either



**Table 1:** Key to evidence statements and grading of recommendations using the ranking of the Canadian Task Force on Preventive Health Care

Quality of evidence assessment*	Classification of recommendations†
I: Evidence obtained from at least one properly randomized controlled trial	A. There is good evidence to recommend the clinical preventive action
II - 1: Evidence from well-designed controlled trials without randomization	B. There is fair evidence to recommend the clinical preventive action
II - 2: Evidence from well-designed cohort (prospective or retrospective) or case-control studies, preferably from more than one centre or research group	C. The existing evidence is conflicting and does not allow to make a recommendation for or against use of the clinical preventive action; however, other factors may influence decision-making
II - 3: Evidence obtained from comparisons between times or places with or without the intervention. Dramatic results in uncontrolled experiments (such as the results of treatment with penicillin in the 1940s) could also be included in this category	D. There is fair evidence to recommend against the clinical preventive action E. There is good evidence to recommend against the clinical preventive action
III: Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees	I. There is insufficient evidence (in quantity or quality) to make a recommendation; however, other factors may influence decision-making

\* The quality of evidence reported in these guidelines has been adapted from the evidence evaluation criteria described in the Canadian Task Force on Preventive Health Care

† Recommendations included in these guidelines have been adapted from the classification of recommendations criteria described in the Canadian Task Force on Preventive Health Care

NAP1, ribotype 027, or the BI strain (2–4). In the United States, *C. difficile* is now the single most common pathogen identified as a cause of health care–associated infection (5,6). In surveillance conducted by the Canadian Nosocomial Infection Surveillance Program, the incidence of health care–associated CDI decreased in participating hospitals from a peak of 7.9/10,000 patient-days in 2011 to 4.3/10,000 patient-days in 2015 (7). Typing of *C. difficile* by the National Microbiology Laboratory indicates that nationally, NAP1 strains accounted for approximately 24% of isolates from hospitalized patients in 2015 (7). The recent decrease in CDI rates in Canadian hospitals may be attributable, at least in part, to an increased emphasis on implementation of antimicrobial stewardship programs and of evidence-based CDI infection prevention and control bundles (8,9).

*C. difficile* infection is predominantly a health care–associated infection, most often affecting older adults, and those with underlying comorbidities (6,10,11). In the past few years, there have been reports suggesting an increase in the occurrence of community-associated CDI, with the majority of these patients having had antecedent outpatient health care exposure (12). Health care–associated CDI can be severe, with an attributable 30-day mortality

rate of 5.7% and an attributable increased length of hospital stay of approximately 3.6 days per episode and greater risk for recurrent disease (11,13).

### CLOSTRIDIUM DIFFICILE INFECTION VERSUS ASYMPTOMATIC COLONIZATION

Asymptomatic colonization of the gut by *C. difficile* has been detected in 3%–14% of persons admitted to hospital and has been observed to increase with increasing lengths of hospital stay (14–19). Patients colonized with toxigenic *C. difficile* strains can progress to clinical CDI, although the estimated risk varies considerably, from 14% to 71% (14,20–22). The ratio of patients with *C. difficile* asymptomatic colonization to patients with CDI is approximately 5:1 (16,17,21). Host factors such as age and immune response to *C. difficile* and its toxins may significantly modulate the spectrum of disease presentation. It is important to recognize that individuals colonized with *C. difficile* may have diarrhea attributable to another reason such as laxatives, enteral feeds, and other clinical disorders (23).

Diagnostic tests for *C. difficile* have variable performance characteristics and considerable debate persists regarding the optimal method of detection. It is beyond the scope

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of this document to describe these diagnostic tests. However, it is of critical importance to test only those patients who have a clinical presentation consistent with CDI to avoid detecting patients who may be asymptotically colonized and have diarrhea for another reason (e.g. laxatives, enteral feeds). Moreover, there is no need to perform a test of cure because patients with CDI may continue to shed *C. difficile* in the stool for several weeks after responding to a course of therapy (24).

## DETERMINATION OF SEVERITY OF CLOSTRIDIUM DIFFICILE INFECTION

There is no clear consensus for the determination of severity of CDI, which is a dynamic process and can change rapidly. A variety of clinical severity prediction (CSP) tools have been developed. The Infectious Diseases Society of America (IDSA) last revised their CSP tool in 2010 and classifies a patient with severe disease when the leukocytes are  $\geq 15,000$  cells/uL and/or serum creatinine (sCr)  $\geq 1.5$  baseline (premorbid level) (23). In addition, severe complicated disease includes patients with hypotension, shock, ileus, or megacolon. Other scoring systems (e.g., ATLAS) have correlated reasonably well with the IDSA CSP tool (25–29).

While these factors have been included in various combinations as case definitions in clinical trials, they are not evaluable in all patients, and ultimately it is the treating clinician's judgment as to whether a patient has mild, moderate, or severe disease.

## TREATMENT OF CLOSTRIDIUM DIFFICILE INFECTION IN ADULTS

### Treatment of the initial mild to moderate episode of *Clostridium difficile* infection in adults

Table 2 provides a summary of the treatment recommendations for adults for the initial episode of CDI as well as recurrences. Treatment recommendations have been based on the IDSA-based severity of CDI as described above (28–31). An important principle of CDI management is that other concurrent antimicrobials should be stopped if possible. In addition, patients with an alternative cause of diarrhea (e.g., laxatives or enteral feeds) or spontaneously self-resolved diarrhea and a positive *C. difficile* assay should not receive treatment, even if they had diarrhea at the time the specimen was sent.

For the past three decades, metronidazole was considered to be the agent of choice for the treatment of mild to moderate CDI, with vancomycin being the alternate

therapy for those with severe episodes of CDI or who have failed treatment with metronidazole (23,30). Recent studies have demonstrated that vancomycin provides superior cure rates compared with metronidazole, with reduced side effects, even in mild cases (30–33). A prospective, randomized, double-blind placebo-controlled trial evaluating vancomycin treatment versus metronidazole treatment was conducted, where the 150 participants were stratified by disease severity (30). Among patients with mild CDI, clinical cure was achieved in 90% of patients treated with metronidazole versus 98% of patients who received vancomycin ( $p = 0.36$ ). In contrast, among patients with severe CDI, vancomycin was demonstrated to be superior to metronidazole in terms of clinical cure (97% versus 76%,  $p = 0.02$ ). This study had several limitations including that the definition of severe CDI was not validated and that the dose of metronidazole at 250 mg oral four times per day is not the usual treatment dose. A recent multicentre study compared the efficacy of tolevamer, a non-antibiotic, toxin-binding polymer, with vancomycin 125 mg oral four times per day for 10 days and metronidazole 375 mg oral four times per day for 10 days (31). In a pooled analysis, 563 patients received tolevamer, 289 received metronidazole, and 266 received vancomycin. While the clinical success of tolevamer was inferior to both metronidazole and vancomycin ( $p < 0.001$ ), this study was important in determining that metronidazole was inferior to vancomycin ( $p = 0.02$ ; 44.2%, 72.7%, and 81.1% success, respectively). Among patients with severe CDI (defined as  $>10$  BM/d, WBC  $\geq 20,000$  cells/uL or severe abdominal pain), clinical success was demonstrated in 66.3% who received metronidazole compared with 78.5% among those with vancomycin ( $p = 0.059$ ). These studies compared 10-day treatment regimens but extension to 14 days of therapy should be considered if symptoms are not resolved by day 10. Patients with ongoing diarrhea should be carefully assessed for overall clinical improvement and alternative causes for diarrhea should be considered.

Clinical trials have compared oral fidaxomicin with oral vancomycin (28,34). The key findings of these studies were that both agents had similar results for the primary end point of resolution of diarrhea at the end of the 10-day treatment course. Fidaxomicin was however deemed superior to vancomycin in terms of decreased rates of recurrence at 36–40 days (15.4% versus 25.3%,  $p = 0.005$ ), the secondary end point of the studies (28,34,35). Subgroup analyses suggested superiority of fidaxomicin in initial and global cure among patients receiving concomitant antibiotics, but was similar to vancomycin in global cure among patients infected with the NAP1/BI/027 strain. Although the rates of NAP1/BI/027 have declined globally,

**Table 2:** Treatment recommendations for *Clostridium difficile* infection (CDI) in adults

Clinical definition	Parameters	Treatment recommendations
<b>Initial episode</b>		
Mild to moderate	<ul style="list-style-type: none"> <li>• WBC* <math>\leq 15.0 \times 10^9/L</math>, and</li> <li>• Serum creatinine <math>\leq 1.5 \times</math> baseline</li> </ul>	First line: <ul style="list-style-type: none"> <li>• Vancomycin 125 mg po QID for 10–14 days</li> </ul> Alternative Choices: <ul style="list-style-type: none"> <li>• Fidaxomicin 200 mg po BID for 10 days</li> <li>• Metronidazole 500 mg po TID for 10–14 days can be used in patients with mild diarrhea when the costs of vancomycin or fidaxomicin may be prohibitive for their use.</li> </ul>
Severe, uncomplicated†	<ul style="list-style-type: none"> <li>• WBC* <math>&gt; 15.0 \times 10^9/L</math> or</li> <li>• Serum creatinine <math>&gt; 1.5 \times</math> baseline</li> <li>• Hypoalbuminemia</li> </ul>	<ul style="list-style-type: none"> <li>• Vancomycin 125 mg po QID for 10–14 days, or</li> <li>• Fidaxomicin 200 mg po BID for 10 days</li> </ul>
Severe, complicated	<ul style="list-style-type: none"> <li>• Hypotension or shock, ileus, megacolon</li> </ul>	<ul style="list-style-type: none"> <li>• Vancomycin 125–500 mg po QID for 10–14 days or via nasogastric tube in conjunction with intravenous metronidazole 500 mg Q 8 H</li> <li>• Alternative: Fidaxomicin 200 mg po BID for 10 days with intravenous metronidazole 500 mg Q 8 H if severe allergy to oral vancomycin</li> <li>• If paralytic ileus is present, consider administering vancomycin rectally 500 mg in approximately 100 mL normal saline per rectum every 6 hours as a retention enema, in conjunction with intravenous metronidazole 500 mg Q 8 H and oral vancomycin</li> </ul>
<b>Recurrent episodes</b>		
First recurrence, mild to moderate	<ul style="list-style-type: none"> <li>• WBC* <math>\leq 15.0 \times 10^9/L</math>, and</li> <li>• Serum creatinine <math>\leq 1.5</math> baseline</li> </ul>	First line: <ul style="list-style-type: none"> <li>• Vancomycin 125 mg po QID for 14 days</li> </ul> Alternative choices: <ul style="list-style-type: none"> <li>• Fidaxomicin 200 mg po BID for 10 days</li> <li>• Metronidazole 500 mg po TID for 10–14 days if vancomycin or fidaxomicin cannot be used.</li> </ul>
First recurrence, severe, uncomplicated†	<ul style="list-style-type: none"> <li>• WBC* <math>&gt; 15.0 \times 10^9/L</math>, or</li> <li>• Serum creatinine <math>&gt; 1.5 \times</math> baseline</li> <li>• Hypoalbuminemia</li> </ul>	<ul style="list-style-type: none"> <li>• Vancomycin 125 mg po QID for 14 days, or</li> <li>• Fidaxomicin 200 mg po BID for 10 days</li> </ul>
Second or subsequent recurrences		<ul style="list-style-type: none"> <li>• Vancomycin as a prolonged tapered and/or pulsed regimen (e.g., 125 mg po QID for 14 days; 125 mg po TID for 7 days; 125 mg po BID for 7 days; 125 mg po once daily for 7 days, and then every 2 or 3 days for 2–8 weeks)</li> <li>• Consider fecal microbiota transplantation for recurrence following a vancomycin taper</li> </ul>

\* WBC refers to peripheral white blood cell count

† Criteria to define severe CDI based on expert opinion

recurrent CDI is a significant problem with high associated costs. Therefore, we recommend fidaxomicin as an alternative agent when vancomycin cannot be used as a first-line treatment (36).

There are no reported studies of combination therapy for mild to moderate CDI.

### Recommendations for treatment of the initial mild to moderate *Clostridium difficile* infection in adults:

- Discontinue antibiotics for other indications if possible.
- For patients whose diarrhea is deemed a result of CDI, we recommend:
  - First line: vancomycin 125 mg po QID × 10–14 days (A-I).
  - Alternative: fidaxomicin 200 mg po BID × 10 days (A-I).
  - Alternative: metronidazole 500 mg po TID × 10–14 days can be used in patients with mild diarrhea when the costs of vancomycin or fidaxomicin may be prohibitive for their use (A-I).
- Patients on vancomycin or fidaxomicin whose diarrhea persists beyond 7 days should be continued on their treatment to complete a 10-day course; therapy may need to be prolonged to 14 days (C-III). If diarrhea persists, investigate for other causes of diarrhea and reassess severity of diarrhea with clinical parameters such as white blood cell count, renal function and abdominal pain to determine if persistence is due to treatment failure.
- Addition of metronidazole to vancomycin or fidaxomicin in cases of treatment failure is not recommended (C-III).

### Treatment of severe uncomplicated *Clostridium difficile* infection in adults

Recognition of the early signs and markers of severe disease, as well as prompt appropriate therapy, is important in the management of patients to help reduce morbidity and mortality. Several studies have demonstrated the superiority of vancomycin over metronidazole in severe disease, including one randomized control trial (30,31,37). Based on these studies, patients who have severe disease should be treated with vancomycin 125 mg orally four times per day for 10–14 days. Higher doses of vancomycin have not been shown to be incrementally beneficial (38,39). There is no evidence that combination therapy is more effective for severe uncomplicated disease and some evidence of higher risk of adverse events (40). There is also currently no evidence to suggest that longer treatment durations are beneficial in this setting.

Newer agents have been developed to treat CDI but have not been well studied in patients with severe or complicated disease. Fidaxomicin has been used in ICU patients and has shown similar response and recurrence rates to general medicine patients in a retrospective study but with no clear advantage (41). Case series of the use of other agents such as intravenous immunoglobulins, tigecycline and fecal microbiota therapy (FMT) for severe disease have been reported but none have been studied rigorously and therefore no recommendation can be made for their routine use in patients with severe CDI (42–44).

### Recommendations for treatment of severe uncomplicated *Clostridium difficile* infection in adults:

- First line: vancomycin 125 mg po QID for 10–14 days (A-I).
- Alternative: fidaxomicin 200 mg po BID for 10 days (B-II-2).
- Combination therapy (ie. vancomycin and metronidazole) is not recommended (D-III).

### Treatment of severe complicated *Clostridium difficile* infection in adults

In patients with severe complicated CDI and ileus, oral medication may not reliably reach the colon. A recent retrospective study showed improved outcomes with a combination of oral vancomycin and intravenous metronidazole versus vancomycin alone in patients admitted to the intensive care unit (ICU), with decreased hospital mortality (15.9% and 36.4% respectively) (45). The majority of patients in this study had received the standard dose of vancomycin (125 mg po QID) although the proportion was lower in the combination arm versus the monotherapy arm (59% versus 79%). For the remaining patients in the combination arm, higher doses of vancomycin (i.e., 250 mg or 500 mg QID) were used. It is also important to note that more patients in the combination therapy arm received intra-rectal vancomycin, which could have influenced the mortality benefit but the difference did not reach statistical significance (18% versus 5%,  $p = 0.09$ ) (45). With higher doses of oral vancomycin, systemic absorption has been observed as well as the potential for toxic serum concentrations (46). This has particularly been observed in patients with risk factors such as severe colonic disease, renal failure, longer duration of high dose vancomycin, intracolonic administration and ICU admission (46).

Vancomycin can be given by rectal retention enema in combination with oral vancomycin and/or intravenous metronidazole but the rectal dosing has varied between 1–4 g per day (47,48). There are no RCTs evaluating rectal vancomycin administration and there are several studies with variable reported results (47–49). Rectal administration of vancomycin does have a theoretical risk of perforation although it is rare and should be performed with caution.

In cases of severe complicated CDI, surgery can be life-saving if performed early enough (50). Laboratory parameters that can predict severe complicated CDI with associated perioperative mortality exceeding 70% include WBC > 50,000 cells/uL and serum lactate > 5.0 mmol/L (51). Therefore, surgery should be considered before developing this degree of severity to improve outcomes. The historically recommended surgery is a subtotal colectomy with preservation of the rectum (52). However, a retrospective study comparing this approach to a colon-sparing procedure of diverting loop ileostomy with colonic lavage using polyethylene glycol followed by intracolonic vancomycin instillation had promising results (53). There was a decreased mortality benefit with loop ileostomy (19% versus 50% in historical controls,  $p = 0.006$ ) and preservation of the colon in 93% of patients. Further study will be necessary before any recommendations for this procedure can be made.

### Recommendations for treatment of severe complicated *Clostridium difficile* infection in adults:

- First line: vancomycin 125–500 mg po QID × 10–14 days with metronidazole 500 mg iv TID. Administer metronidazole until the patient is no longer critically ill (usually 5–7 days) (B-II-2).
- Alternative: fidaxomicin 200 mg po BID × 10 days (if severe allergy to oral vancomycin) with metronidazole 500 mg iv TID (C-III).
- In the presence of ileus or vomiting and unable to use enteral treatment, consider adding rectal administration of vancomycin (e.g., vancomycin 500 mg QID by retention enema) to the above regimens if patient is not allergic to vancomycin (C-III).
- In severe complicated CDI, urgent surgical consultation is warranted (B-II-2).

### Treatment of recurrent *Clostridium difficile* infection in adults

The recurrence of CDI poses major challenges to patients and the health care system. Recurrent CDI (rCDI) is defined as the reoccurrence of CDI within 8 weeks following

the onset of a previous episode which resolved with treatment (36,54). Approximately 20%–25% of patients experience recurrent CDI following treatment with oral vancomycin, and the risk of recurrence ranges from 27% to 50% after three episodes of CDI (10,36,55). Recurrent CDI is more common in patients over 65 years, in immunocompromised patients, in patients receiving concomitant or subsequent antimicrobial(s) and in hospitalized patients (10,56). Recurrent CDI is associated with significantly higher costs and prolonged hospitalization (57).

The mechanism of development of rCDI is multifactorial and may be related to the inability to develop adequate levels of neutralizing antibodies to *C. difficile* toxins, persistently low diversity of the colonic microbiota, persistence of *C. difficile* spores, or due to reinfection among susceptible individuals (58–60). Approximately 84% of rCDI is due to the same strain type as the initial episode (61). Currently, there is no licensed effective treatment of rCDI.

Vancomycin continues to be used for treatment of the first recurrence, and for those with a second or greater recurrence, a vancomycin taper or taper—pulse therapy has been used (57,62). However, randomized controlled trials to evaluate this strategy are not available. In a retrospective subgroup evaluation of patients who received placebo in a *Saccharomyces boulardii* clinical efficacy trial for CDI, recurrence rates of CDI among patients receiving vancomycin in tapering or pulsed dosing were lower compared with patients receiving standard dose of vancomycin four times daily: 31% (9/29) for vancomycin taper; 14.3% (1/7) for pulse (vancomycin given every 2 to 3 days) and 71.4% (10/14) for vancomycin administered four times daily (57). Recently, vancomycin taper—pulse as a control arm of an FMT clinical trial showed an efficacy rate of 58% (63). Other regimens for multiple rCDI include rifaximin or fidaxomicin chaser immediately following a standard duration of oral vancomycin therapy with reported recurrence rates of 13% (1/8) and 38% (3/8), respectively (64–66). Fidaxomicin taper immediately after either vancomycin taper or a 10-day course of fidaxomicin, administered once daily for 7 days followed by once every other day for 7 to 26 days showed efficacy of 83% (10/12) (65). Table 2 summarizes the treatment of rCDI.

### Recommendations for treatment of recurrent *Clostridium difficile* infection in adults:

- Treat the first recurrence of CDI with vancomycin 125 mg po QID for 14 days (B-II-2).
- Alternative for first recurrence of CDI: fidaxomicin 200 mg po BID for 10 days (A-I).

**Table 3:** Randomized controlled trials of fecal microbiota transplantation

	<b>Hota (63)</b>	<b>Lee (71)</b>	<b>Van Nood (73)</b>	<b>Cammarota (74)</b>	<b>Youngster (75)</b>	<b>Kelly (76)</b>	
<b>Number of patients</b>	16	178	16	20	20	22	
<b>Route of administration</b>	Enema	Enema	ND tube	Colonoscopy	NG-10 Colonoscopy-10	Colonoscopy	
<b>No. of FMTs and response rate (%)</b>	1 (44)*	1 (55) 2 (84)	1 (81) 2 (94)	1 (65) ≥2 (90)	1 – NG (60) 1 – Colonoscopy (80)	2 – NG/NG (80) 2 – Colonoscopy and NG (100) <sup>†</sup>	1 (91)
<b>FMT type</b>	Fresh	Fresh and frozen	Fresh	Fresh	Frozen	Fresh	
<b>Follow-up (weeks)</b>	17	13	10	10 weeks after last infusion	8	8	

\* FMT for acute episode of rCDI

† 2nd FMT via NG only

ND = nasoduodenal; NG = nasogastric; FMT = fecal microbiota therapy

- If a patient has had two or more recurrences, then treat with vancomycin 125 mg po QID for 10 to 14 days followed by vancomycin taper (see Table 2) (B-I).
- Peripheral neuropathy and other neurological manifestations may occur with long or repeated courses of metronidazole and hence, it should be used for recurrent disease only if vancomycin or fidaxomicin cannot be administered (C-III) (67,68).

### Fecal microbiota transplantation for recurrent *Clostridium difficile* infection in adults

An alternative to antibiotic therapy for rCDI is FMT, which transfers stool from a healthy donor to a recipient. Patients who have experienced two or more recurrences and who have failed at least one course of tapering vancomycin may benefit from FMT. The use of FMT for managing rCDI is based on the concept that patients with CDI lack protective and diverse colonic microbiota to resist colonization and replication of *C. difficile*. Following a successful FMT, the microbiota of a patient with rCDI may resemble that of a healthy donor and remains as such over time (69,70). FMT can be administered using nasoduodenal or nasojejunal tube, oral capsules, rectal tube, enema, or colonoscopy. Dose ranging studies for each individual approach have not been evaluated. As yet, no single method of delivery has been shown to be superior and the procedure has not been standardized across hospital institutions. However, based on larger randomized controlled trial data, it appears that patients may require multiple FMTs to achieve clinical response rate of over 80% (63,71). The efficacy of FMT ranges from 44% to 100% (Table 3) (63,71–76). It should be noted that the majority of the FMT randomized controlled trials excluded patients with immunocompromised conditions except for that of Lee et al (63,71,73–76). In this particular study, at the time of FMT, patients received at least one significant immunosuppressant (azathioprine, cyclosporine, infliximab, methotrexate alone or with corticosteroids) ( $n = 18$ ), received renal allograft ( $n = 5$ ), had metastatic solid tumours ( $n = 3$ ), and/or had hematologic malignancy ( $n = 4$ ) (71). Other exclusion criteria for FMT included pregnancy, evidence of severe active colitis, requirement for vasopressor agents, other gastrointestinal diseases that may cause diarrhea, and significant bleeding disorders (63,71,73–76).

The features that predict FMT outcomes are yet to be determined, but could include: specific donor and recipient factors such as age; underlying medical conditions of the recipient; prior specific anti-CDI treatment, including monotherapy versus combination antibiotic therapy; timing

of FMT in relation to the most recent episode; use of a bowel preparation before FMT to reduce intestinal concentrations of antibiotic and to remove the disrupted dysbiotic microbiota that may act as deterrents to colonization by newly introduced microbes; and finally the quality and quantity and placement of the transplanted inoculum. Despite the current high safety records of FMT, long-term safety remains unknown (77,78). Tracking long-term safety through continued follow-up with a registry of FMT recipients would be desirable.

Currently, FMT appears to be the most efficacious treatment of rCDI. However, under current provincially funded health care plans in Canada, it has not yet been well established as a standard treatment of rCDI. Health Canada has released an interim guidance document for FMT as treatment of CDI not responsive to conventional treatment, which focuses on donor screening requirements (79). The FMT procedure should be performed by a physician experienced in its preparation and delivery. The contact information of several infectious disease specialists and gastroenterologists who provide FMT is listed on the Association of Medical Microbiology and Infectious Disease (AMMI) Canada website.

### Recommendations for fecal microbiota transplantation for recurrent *Clostridium difficile* infection in adults:

- Consider FMT for patients with two or more recurrences and who have recurred after a vancomycin taper (A-II-1).

### PEDIATRIC CONSIDERATIONS FOR TREATMENT OF *CLOSTRIDIUM DIFFICILE* INFECTION

Table 4 provides a summary of the treatment recommendations for the initial episode of CDI as well as recurrences for children. Children with CDI often have a history of recent antibiotic exposure (80–84). Co-infection has been demonstrated in 12%–19% of children with CDI, with more than 70% of cases found to have another enteric pathogen present when broad molecular testing was used (81–85). The surveillance definition of CDI in the pediatric population follows adult criteria, and includes the presence of diarrhea, or at least three liquid stools within 24 hours, and a positive *C. difficile* stool test by PCR or toxigenic assay. Routine testing for *C. difficile* is discouraged among children under 12 months of age because of relatively high rates of asymptomatic colonization, which decrease over time such that children older than 2 years have similar colonization rates as hospitalized adults (81,83,86).

**Table 4:** Treatment recommendations for *Clostridium difficile* infection (CDI) in children

Clinical definition	Treatment recommendations
<b>Initial episode</b>	
Mild to moderate	One of: <ul style="list-style-type: none"> <li>• Metronidazole 30 mg/kg/day po divided QID (max 500 mg/dose) for 10 days; OR</li> <li>• Vancomycin 40 mg/kg/day po divided QID (max 125 mg/dose) for 10 days</li> </ul>
Severe, uncomplicated	<ul style="list-style-type: none"> <li>• Vancomycin 40 mg/kg/day po divided QID (max 125 mg/dose) for 10 days</li> </ul>
Severe, complicated	<ul style="list-style-type: none"> <li>• Vancomycin 40 mg/kg/day po divided QID (max 125 mg/dose) via nasogastric tube for 10–14 days. Consider addition of Intravenous metronidazole 30 mg/kg/day divided QID (max 500 mg/dose) for 10 days</li> </ul>
<b>Recurrent episodes</b>	
First recurrence, mild to moderate	One of: <ul style="list-style-type: none"> <li>• Metronidazole 30 mg/kg/day po divided QID (max 500 mg/dose) for 10 days; OR</li> <li>• Vancomycin 40 mg/kg/day po divided QID (max 125 mg/dose) for 10 days</li> </ul>
First recurrence, severe, uncomplicated	<ul style="list-style-type: none"> <li>• Vancomycin 40 mg/kg/day po divided QID (max 125 mg/dose) for 10 days</li> </ul>
Second or subsequent recurrences	<ul style="list-style-type: none"> <li>• Vancomycin as a prolonged tapered and/or pulsed regimen e.g., 40 mg/kg/day (max 125 mg/dose) po divided QID for 10–14 days; same dose po TID for 7 days; same dose po BID for 7 days; same dose once daily for 7 days, and then every 2 or 3 days for 2–8 weeks)</li> <li>• Consider fecal microbiota transplantation for recurrence following a vancomycin taper</li> </ul>

The general principles of management of CDI in the pediatric population are to discontinue antibiotics (as concomitant use has been associated with disease recurrence), provide supportive care, and institute specific therapy against CDI if there is no improvement after discontinuation of antibiotics; spontaneous resolution has been demonstrated in up to 50% of children (80,82,87). Complications of CDI are infrequent among children compared with adults, and have been associated with certain comorbid conditions, including immune suppression and gastrointestinal disease (82,88).

#### Treatment of the initial mild to moderate episode of *Clostridium difficile* infection in children

There is little evidence of comparative effectiveness of metronidazole and vancomycin in the initial management of pediatric CDI. Metronidazole has been the preferred initial therapy for mild CDI in an immunocompetent host, as noted in a survey of pediatric infectious diseases physicians across North America (89). However, in a retrospective study across 42 pediatric hospitals in the United States, oral vancomycin was being increasingly prescribed for the first inpatient episode of CDI as monotherapy in nearly half of episodes, or in combination with

metronidazole (90). The increasing use of enteral vancomycin as first-line therapy occurred despite stable low rates of severe complicated clinical outcomes, including the need for ICU-level care, colectomy or increased hospital length of stay. Oral vancomycin has been suggested as initial therapy in patients with underlying gastrointestinal tract disease, given higher rates of treatment failure of metronidazole as compared with vancomycin, particularly with severe CDI, as seen in two retrospective cohorts in the United States (84,91). The optimal strategy for mild CDI is unclear for children with other underlying chronic medical conditions such as malignancy and immune suppression, who may be at higher risk for developing complications from CDI (84,88).

#### Recommendations for treatment of the initial mild to moderate episode of *Clostridium difficile* infection in children:

One of:

- i. Metronidazole 30 mg/kg/day po divided QID (max 500 mg/dose) × 10 days (A-II-2); OR
- ii. Vancomycin 40 mg/kg/day po divided QID (max 125 mg/dose) × 10 days (A-II-2)

### Treatment of severe uncomplicated *Clostridium difficile* infection in children

There are no pediatric studies that compare these two agents. Therefore, the recommendations are drawn from adult data described above, including a randomized controlled trial which supports the use of vancomycin over metronidazole in patients who present initially with severe CDI (30). In a survey of pediatric infectious disease clinicians in the United States, most used vancomycin, either alone or in combination with metronidazole, as the preferred strategy for severe CDI; however approximately one-third of respondents still reported use of metronidazole alone for severe disease (89).

#### Recommendations for treatment of severe uncomplicated *Clostridium difficile* infection in children:

- Vancomycin 40 mg/kg/day po divided QID (max 125 mg/dose) × 10 days (B-I).

### Treatment of severe complicated *Clostridium difficile* infection in children

Complications following CDI in children are rare. In practice, the definition of severe complicated CDI has followed the adult-based SHEA/IDSA guidelines, as an episode of CDI associated with hypotension or shock, ileus, or toxic megacolon, although some pediatric studies have included the need for ICU admission as an additional criterion (23,84,91). Severe complicated CDI has been reported to occur in less than 5% of most pediatric cohorts (88,91–93). However, the criteria specified by adult-based guidelines have also been shown to have poor reliability, particularly laboratory markers, in discriminating complicated from uncomplicated disease in children (92). Clinical symptoms, including signs of peritonitis, emesis and fever, may be more predictive (92). There is no preferred antibiotic regimen for the treatment of severe complicated CDI in children, with reports of oral vancomycin prescribed alone or in combination with metronidazole (91,92).

### Treatment of recurrent *Clostridium difficile* infection in children

There are no pediatric studies examining recurrent CDI, and so definitions and recommendations are guided by adult studies. Antimicrobial treatment options are metronidazole, vancomycin, and fidaxomicin; rifaximin has not yet been approved for use in patients younger than 18 years. It is reasonable to re-treat with the same antibiotic that was used for the initial episode, including metronidazole for mild CDI. However, it is not a preferred option for a second recurrence due to the potential for systemic toxicity,

particularly neuropathy, as compared with vancomycin and fidaxomicin, which are not absorbed when orally administered. Similarly, vancomycin is preferred if the recurrence is severe. Beyond a second recurrence, alternate therapies have been considered, including oral vancomycin taper, oral vancomycin in combination with metronidazole, fidaxomicin or FMT (89).

#### Recommendations for treatment of recurrent *Clostridium difficile* infection in children:

- Repeat treatment with metronidazole 30 mg/kg/day po divided QID (max 500 mg/dose) × 10 days for the first recurrence or vancomycin 40 mg/kg/day po divided QID (max 125 mg/dose) × 10 days if first recurrent episode is mild to moderate (B-III).
- Vancomycin 40 mg/kg/day po divided QID (max 125 mg/dose) × 10 days if severe disease (B-III).
- Consider alternative therapies, such as oral vancomycin taper, fidaxomicin or FMT, if ≥ 2 recurrences (C-III).

#### Fecal microbiota transplantation for recurrent *Clostridium difficile* infection in children

Since 2010, case reports and small case series have supported the use of FMT in pediatric patients with multiple CDI recurrences, with high rates of disease resolution, similar to that seen in adults (94–97). Russell et al reported a 90% cure rate following FMT by nasogastric tube or colonoscopy among children who had experienced at least three recurrences (95). Kronman et al described a similar cohort who received a 7-day pre-transplant course of vancomycin or fidaxomicin (96). There are no data on long-term safety of FMT in children and adolescents.

#### Recommendations for fecal microbiota transplantation for recurrent *Clostridium difficile* infection in children:

- There is insufficient evidence at this time to make a recommendation for FMT in the pediatric population with the current data and lack of long-term safety data (C-III).

## ANTIMICROBIAL STEWARDSHIP AND *CLOSTRIDIUM DIFFICILE* INFECTION

Hospital-associated CDI is directly linked to antibiotic exposure and can vary within a centre across wards depending on the ward-level antibiotic exposure and colonization pressure (98,99). Unfortunately, a significant proportion of antimicrobials are either unnecessarily broad-spectrum or not indicated. In a tertiary care US hospital, patients

with current or recent CDI who were receiving non-CDI antibiotics were reviewed and almost half of the non-CDI antimicrobial days were judged unnecessary (100).

### Antimicrobials and *Clostridium difficile* infection risk: Choice of antibiotic and duration of therapy

While most antibiotics have been associated with cases of CDI, there is observational evidence that the risk may not be the same for every class or drug. In their meta-analysis that included seven observational studies of patients with community acquired CDI, Brown et al identified clindamycin [Odds Ratio (OR) 16.8], fluoroquinolones (OR 5.5), and cephalosporins, monobactams, and carbapenems (OR 5.7) as the three antibiotic groups most associated with CDI. (101) While there is no antibiotic that is completely safe, penicillin (OR 2.7), macrolides (OR 2.6), trimethoprim-sulfamethoxazole (OR 1.8) and tetracyclines (OR = 0.92) are considered lower risk (101).

*Clostridium difficile* infection risk likely increases when patients are exposed to more than one antibiotic or for longer durations (102,103). In general, the risk is highest during and within the first month after the antibiotic administration; however, the risk may extend out to three months (104). Consequently, we recommend that the spectrum and duration of therapy should be minimized for the infection to be treated and that patients who develop diarrheal illnesses in the first three months after antibiotic therapy should be clinically evaluated for CDI.

### Recommendations for antimicrobial stewardship and *Clostridium difficile* infection:

- Prescribe the narrowest spectrum of antibiotic for the minimum duration required to minimize the risk of CDI (C-II-1).
- Strategize to avoid unnecessary antibiotic use (C-I).

## PROTON PUMP INHIBITORS AND CLOSTRIDIUM DIFFICILE INFECTION

While there are several indications for when PPIs are medically necessary, nearly half of the PPIs prescribed are given without evidence-based indication for continuous use (105). Several observational studies have shown the association between the PPI use and the development of CDI. In a meta-analysis of 42 observational studies involving 313,000 patients, the adjusted odds ratio for the development of CDI was 2.5 (106). While association does not prove causality, and despite the absence of a randomized controlled trial, we suggest that any *unnecessary* PPI should be stopped when patients are initiated on

antibiotics and/or develop CDI. It is outside the scope of this document to extensively review the evidence-based indications for PPIs and it is suggested that if there is doubt in any particular case, an expert opinion could be sought (107).

### Recommendations for proton pump inhibitors in patients with *Clostridium difficile* infection

The following are recommendations for PPIs in patients with *C. difficile* infection:

- Assess the necessity for new or ongoing PPI therapy against the risk of CDI (C-II-2).
- When assessing patients with a first or subsequent episode of *C. difficile* infection, actively de-prescribe *unnecessary* PPIs (A-II-2).

## ANTIMOTILITY AGENTS AND CLOSTRIDIUM DIFFICILE INFECTION

Antimotility agents have been used effectively for the treatment of traveller's diarrhea (108). However, their use for CDI lacks definitive evidence. Koo et al reviewed antimotility agents used in the treatment of CDI (109). Twenty reports were included in their systematic review with the majority being individual case reports or case series. A total of 55 patients with CDI were given an antimotility drug such as diphenoxylate-atropine, codeine, morphine, or loperamide with one report consisting of 23 patients (110). Only 32 (58.2%) were given antibiotics for CDI treatment that included metronidazole, vancomycin, rifaximin or nitazonanide. Toxic megacolon or colonic dilatation occurred in 17 (31%) of the 55 patients and notably, none of these patients had received appropriate CDI therapy at the time antimotility agents were initiated.

In a study of 82 patients with recurrent CDI, prior infection with the NAP1/027 strain and use of opiates were significant predictors of relapse (111). Opiates may hamper the elimination of the organism by slowing bowel motility and resulting in relapse.

### Recommendations for antimotility agents in patients with *Clostridium difficile* infection

The following are recommendations for antimotility agents in patients with *C. difficile* infection:

- There are insufficient data to provide a recommendation for or against the use of antimotility agents but expert opinion cautions against its use because of its physiologic effect on the gut (I-III).

## PRIMARY PROPHYLAXIS AGAINST CLOSTRIDIUM DIFFICILE INFECTION

### Probiotics

Probiotics are defined as microbial preparations of living, low pathogenicity organisms, which when administered in adequate amounts, might confer a health benefit to the host (112). Probiotics could theoretically help prevent CDI by enhanced colonization resistance, enhanced mucosal integrity and barrier function, neutralization of *C. difficile* toxins, decrease in *C. difficile* virulence (by downregulation of gene expression) or growth (through quorum sensing). A great variety of commercial probiotic formulations are available and the effect of one type of strain, or a combination of specific strains cannot be generalized to other species or strains (112).

Probiotics are generally regarded as safe. A systematic review on the safety of probiotics in patients receiving nutritional support identified only 32 cases of invasive infections in the medical literature from 1950 to 2009, all of them related to either *Saccharomyces boulardii* or *Lactobacillus rhamnosus* GG (113).

A Cochrane review published in 2013 pooled the findings of 23 RCTs including 4,213 adults and children and confirmed the findings of other meta-analyses (114–117). Probiotics were found to significantly reduce the incidence of CDI (RR 0.36; 95% CI 0.26 to 0.49—fixed-effect analysis). These results need to be interpreted with caution as only three trials among the included studies showed a statistical difference from placebo, and two of them had unusually high rates of CDI in the control group (24% and 40%). Also, pooling these studies only makes sense if the mechanism of action of all studied probiotics is essentially the same. This assumption is not warranted given the several ‘strain-associated’ potential mechanisms reported in the literature (118). Since the release of the aforementioned meta-analysis, a large multicenter UK study (PLACIDE) did not demonstrate a significant effect of a probiotic formulation (2 strains of *Lactobacillus* and two strains of *Bifidobacteria*) in 2,941 adults older than 65 years exposed to antibiotics (RR 0.71; 95% CI 0.34 to 1.47) (119). This study was limited by the low participation rate of approximately 20% which may have affected the results. In addition, the percentage of CDI among participants was at 1% instead of the anticipated 4%. This could have resulted in a negative study because the sample size was too small to detect a difference. Recently, a double-blind multicenter RCT comparing the efficacy of a *S. boulardii* formulation

to a placebo in the prevention of antimicrobial-associated diarrhea and CDI in patients receiving systemic antibiotics was stopped for futility after the enrollment of 477 patients (120). While the data on the role of probiotics for the prevention of CDI is still not yet robust, it is unlikely that these products cause harm, albeit it is uncertain that they are of any benefit.

### Recommendations for probiotics as primary prophylaxis of *Clostridium difficile* infection:

- At this time, there is insufficient evidence to support the use of probiotics for primary prevention of CDI (I-II-3).

## SECONDARY PROPHYLAXIS AGAINST CLOSTRIDIUM DIFFICILE INFECTION

Effective strategies to prevent CDI recurrences (rCDI) would be a great addition to the current CDI armamentarium. Antibiotics administered in patients receiving antimicrobials for an ongoing infection, probiotics given after completion of initial CDI treatment, and monoclonal antibodies targeting specifically toxins have all been studied in this context.

### Antimicrobials

Patients currently or recently treated for CDI may require additional antimicrobial therapy for a concomitant infection. Recently, two retrospective cohort studies have specifically addressed the use of vancomycin to prevent CDI recurrence in patients treated with systemic antimicrobials for another infection (121,122). While both were limited by several biases, they still add interesting information about the potential use of vancomycin as a prophylactic agent. In the first study, oral vancomycin prophylaxis decreased the risk of further recurrences at 90 days among patients receiving systemic antimicrobials whose current episode of CDI was a recurrence (adjusted hazard ratio 0.47; 95% CI 0.32 to 0.69;  $p < 0.0001$ ) but not in those whose CDI was an initial episode (AHR 0.91; 95% CI 0.57 to 1.45;  $p = 0.68$ ) (121). In the second, the incidence was significantly lower in patients on vancomycin prophylaxis during the 1-month follow-up period (4.2% versus 26.6%, OR 0.12; 95% CI 0.04 to 0.4;  $p < 0.001$ ) (122). In the first study, the most frequent administered dose of vancomycin was 125 mg four times daily, while 125 mg or 250 mg twice daily was used in the second study, both for an average duration of 14 days. In the study by van Hise et al, patients received vancomycin for up to 1 week after completion of the systemic antimicrobial therapy

(122). In the study reported by Carignan et al, patients were eligible if the CDI episode was within 90 days of the administration of systemic antimicrobials, while in the study by van Hise et al, the average time between prior CDI and vancomycin administration was 6 months (range 1–21) (121). The most important hurdles to bringing these results into practice are the studies' variable dosage regimens, different follow-up periods, and non-standardized eligibility criteria and the risk of bias due to study design.

### Probiotics

In 2008, a Cochrane systematic review on probiotics for treatment of CDI concluded that there was insufficient evidence to support the use of probiotics alone or as an adjunct to antibiotics in CDI therapy (123). In the review, four studies limited by their small sizes and methodological problems were included. Only one study reported significant benefit for probiotics to reduce the risk of recurrence while administered with vancomycin compared with placebo (RR 0.59; 95% CI 0.35 to 0.98) (124). Since the publication of this review, no RCT evaluating probiotics in secondary prevention of CDI has been published.

### Monoclonal antibodies

Passive immunization with the infusion of monoclonal antibodies directed at toxins A and B, actoxumab and bezlotoxumab, respectively, have been studied in randomized, placebo-controlled, double-blind phase III clinical trials in patients receiving oral standard-of-care antibiotics for primary or recurrent CDI (125). In both trials, the overall rate of rCDI at 12 weeks was significantly lower with bezlotoxumab alone by 40% with an absolute difference of approximately 11% compared with placebo (16%–17% versus 26%–28%,  $p < 0.001$ ) (125). Patients who received actoxumab had higher rates of rCDI (26%) and serious adverse events compared with bezlotoxumab. Bezlotoxumab has been approved by the FDA (October 2016), but is not currently available in Canada.

### Recommendations for secondary prophylaxis against *Clostridium difficile* infection

- Vancomycin prophylaxis may be considered for patients with a recent history of multiple recurrences or severe complicated CDI and who need re-administration of systemic antimicrobials for a new infection. Vancomycin 125 mg po BID administered during the course of their systemic antibiotic therapy and for up to 1 week after its completion is an acceptable regimen (C-III).
- Probiotics should not be administered as an adjunctive CDI treatment to prevent further recurrences (I-III).

## PHARMACOECONOMICS OF *CLOSTRIDIUM DIFFICILE* INFECTION

An estimated 37,900 cases of *C. difficile* infection occur annually in Canada, of which 27% are recurrent episodes, costing Canadians approximately \$281 million CAD each year (126).

Currently, metronidazole and oral vancomycin remain the mainstay of treatment of CDI in Canada. While fidaxomicin and FMT have emerged as highly effective CDI treatments, the up-front costs and barriers to access have adversely affected their uptake. Below, key findings from cost-effectiveness analyses regarding treatment of initial and recurrent episodes of CDI are summarized.

### Initial episode of *Clostridium difficile* infection

Among seven studies examining the cost-effectiveness of various treatments of the first episode of CDI (metronidazole, vancomycin, fidaxomicin, FMT), fidaxomicin appears to be cost-effective as first-line treatment of CDI, particularly in patients at high risk for recurrence (127–133). However, the relative cost benefits of each treatment option remain controversial as results vary by study and study assumptions and methodologies are heterogeneous. Notably, variable payer perspectives and willingness-to-pay thresholds were used, and therefore may be interpreted disparately in different jurisdictions. It is worth highlighting that two Canadian studies, including a 2012 review by the Canadian Agency for Drugs and Technologies in Health—an organization independent from the pharmaceutical industry—did not find fidaxomicin cost-effective (134,135). Among other limitations, generic oral vancomycin was not available at the time of these studies and the use of compounded intravenous vancomycin was not consistently considered in this review.

### Recurrent *Clostridium difficile* infection

Analyses from various jurisdictions suggest that FMT by colonoscopy or enema are cost-effective and possibly cost-saving for patients with rCDI (136–139). Where FMT is not available, vancomycin, vancomycin taper, or fidaxomicin may be the preferred choice. These studies face numerous limitations, including lack of quality data to support parameter estimates for recurrence risk after vancomycin taper and assumptions that hospitalized patients are treated on general wards, or that patients remain out of hospital for the entire model length. All of the models assume a constant risk of CDI recurrence over time and model time horizons are variable, allowing different number of

recurrences to be included in the analysis. Hospitalization costs differ significantly between studies. Since no established utility measure exists for CDI, utility is defined differently in each study. Finally, costing data for FMT is obtained from variable sources and largely underestimate the infrastructure, supplies, personnel and follow-up required for the procedure. Given that FMT has not yet been standardized to achieve optimal results according to route of administration, further exploration of the cost-utility of this particular intervention is required in the future. Future system-based efficiencies, such as use of frozen FMT from universal donors, may drastically decrease the overall cost of FMT.

As costs for fidaxomicin, vancomycin and emerging treatments of CDI decrease over time, there will be a need to repeat these analyses. Furthermore, more studies conducted by independent agencies, free of bias from the pharmaceutical industry, are needed. Finally, few cost-effectiveness studies and economic analyses on CDI treatment have taken into account the Canadian health care environment, severely limiting the ability to translate these data to action (127,134,135,139).

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