Clostridium difficile-associated diarrhea in adults

Susan M. Poutanen, Andrew E. Simor

Abstract

CLOSTRIDIUM DIFFICILE IS THE MOST IMPORTANT CAUSE of nosocomial diarrhea in adults. Illness may range from mild watery diarrhea to life-threatening colitis. An antecedent disruption of the normal colonic flora followed by exposure to a toxigenic strain of *C. difficile* are necessary first steps in the pathogenesis of disease. Diagnosis is based primarily on the detection of *C. difficile* toxin A or toxin B. First-line treatment is with oral metronidazole therapy. Treatment with oral vancomycin therapy should be reserved for patients who have contraindications or intolerance to metronidazole or who fail to respond to first-line therapy.

Clostridium difficile was first described in 1935,[1] but its association with disease was not identified until 1978.[2,3] It is now recognized to be an important nosocomial pathogen that may be associated with considerable morbidity and attributable mortality. When exposed to *C. difficile*, some patients become asymptomatic carriers of the organism, whereas others contract *C. difficile*-associated diarrhea, which may range from mild watery diarrhea to life-threatening pseudomembranous colitis. In this review, we summarize the current state of knowledge regarding the epidemiology, pathogenesis, clinical features, diagnostic tests, treatment options and preventive measures for *C. difficile* diarrhea in adults.

Epidemiology

Based on surveillance conducted in 1997, the incidence of nosocomial *C. difficile* diarrhea in Canadian hospitals is estimated to range from 38 to 95 cases per 100 000 patient-days and from 3.4 to 8.4 cases per 1000 admissions.[4] These rates are comparable to those reported in studies conducted outside of Canada.[5] *C. difficile*-associated colitis has been identified as the direct cause of death in 1%–2% of affected patients, and the estimated annual cost per year per facility for readmissions due to nosocomial *C. difficile* diarrhea is $128 200.[6] The incidence of community-acquired *C. difficile* diarrhea appears to be substantially lower than rates observed in hospitals, with an estimate of 7.7–12 cases per 100 000 person-years.[7,8] The estimated prevalence of *C. difficile* colonization varies depending on the patient population studied. Among hospital inpatients the prevalence of culture positivity ranges from 7% to 11%.[9,10] In long-term

care facilities, the estimated prevalence is slightly lower, ranging from 5% to 7%.[11,12] Among ambulatory adults, the prevalence is even lower, generally less than 2%.[13,14]

The primary reservoirs of *C. difficile* include colonized or infected patients and contaminated environments and surfaces within hospitals and long-term care facilities.[10,15–18] The hands of hospital personnel caring for patients with *C. difficile* often become colonized with the organism, facilitating transmission among hospital inpatients.[10] In one study, the risk of colonization was found to increase in direct proportion to the length of hospital stay, ranging from 1% among patients admitted for less than 1 week to as high as 50% among patients admitted for more than 4 weeks; this suggests that ongoing exposure to *C. difficile* occurs throughout the hospital stay.[19]

Mature colonic bacterial flora in a healthy adult is generally resistant to *C. difficile* colonization.[20,21] However, if the normal colonic flora is altered, resistance to colonization is lost. Thus, any factor associated with alteration of the normal enteric flora increases the risk of *C. difficile* colonization after exposure to the organism. The most common risk factor isf exposure to antibiotics, especially those with broad-spectrum activity such as penicillins, cephalosporins and clindamycin.[22] Exposure to antineoplastic chemotherapy or immunosuppressive agents has less commonly been described as a risk factor.[23–25] Increasing age and severe underlying illness have been determined to be independent risk factors and may reflect age-related or disease-related changes in fecal flora.[26–28] Gastrointestinal surgery and use of nasogastric tubes, stool softeners, gastrointestinal stimulants, antiperistaltic drugs, antacids and enemas have also been associated with an increased risk of colonization.[26–28]

Not everyone colonized with the organism experiences *C. difficile* diarrhea. In fact, studies have shown that colonization with *C. difficile* protects against the development of symptomatic disease.[19,29,30] Shim and associates reported that diarrhea developed in only 1% of 192 patients asymptomatically colonized with *C. difficile* on admission to hospital compared with 3.6% of 618 patients not colonized with the organism on admission (p = 0.02).[29] The risk of diarrhea is also related to the virulence of the infecting *C. difficile* strain[21] and to the immune response to the organism's toxins. A prospective study by Kyne and associates showed that patients who were recently colonized with *C. difficile* and who had a high serum antibody response to *C. difficile*

toxin A were usually protected against diarrhea and remained asymptomatic carriers.[30] In contrast, patients who had low serum antibody responses to toxin A had a much greater risk of diarrhea. These findings suggest that antibody response to toxin A protects against the development of *C. difficile* diarrhea.

The epidemiology of *C. difficile* infection in neonates and infants is distinct from that in older children and adults. Neonates are more likely to carry toxigenic strains of *C. difficile* asymptomatically in the gastrointestinal tract, although the rate of colonization and the proportion of colonized infants with detectable toxin decrease with age.[14,31] It has been proposed that immature neonatal colonic flora permits *C. difficile* colonization,[21] and the relative lack of disease despite the presence of toxin is thought to relate to the immaturity of enterocytes lacking toxin A receptors.[32] The source of *C. difficile* in neonates is believed to be either the mother's vaginal flora or the health care environment.[33,34] In older children, day-care reservoirs for acquisition of *C. difficile* have been described.[35]

Pathogenesis

C. difficile is an anaerobic gram-positive spore-forming bacillus. The ability of *C. difficile* to form spores is thought to be a key feature in enabling it to persist in patients and the physical environment for long periods and thereby facilitating its transmission. *C. difficile* is transmitted through the fecal–oral route. The pathogenesis of the bacillus is shown in Fig. 1. Based on hamster models, most ingested vegetative cells are killed in the stomach, with only 1% of the inoculum passing into the small bowel.[21,36] *C. difficile* spores, however, are acid resistant and readily pass through the stomach; they may germinate in the small bowel upon exposure to bile acids. A number of virulence factors, including flagellae and hydrolytic enzymes produced by the organism, have been associated with the development of disease.[37,38] However, the best characterized and most important virulence factors are the *C. difficile* exotoxins, toxins A and B.[39–41]

Toxins A and B are both cytotoxic for a number of different cell types (B is a significantly more potent cytotoxin than A), both cause increased vascular permeability by opening tight junctions between cells, and both cause hemorrhage.[39,40] They both also induce the production of tumour necrosis factor-alpha and proinflammatory interleukins, which contribute to the associated inflammatory response and pseudomembrane formation.[40] Colonic pseudomembranes have a distinct appearance, with inflamed mucosa studded with adherent raised white and yellow plaques. Histologically the pseudomembranes are composed of neutrophils, fibrin, mucin and cellular debris.

Only toxigenic strains are associated with the development of *C. difficile* diarrhea. In adults who are asymptomatic carriers of *C. difficile*, these toxins are found less frequently.[14] Toxin A is thought to play a more critical role t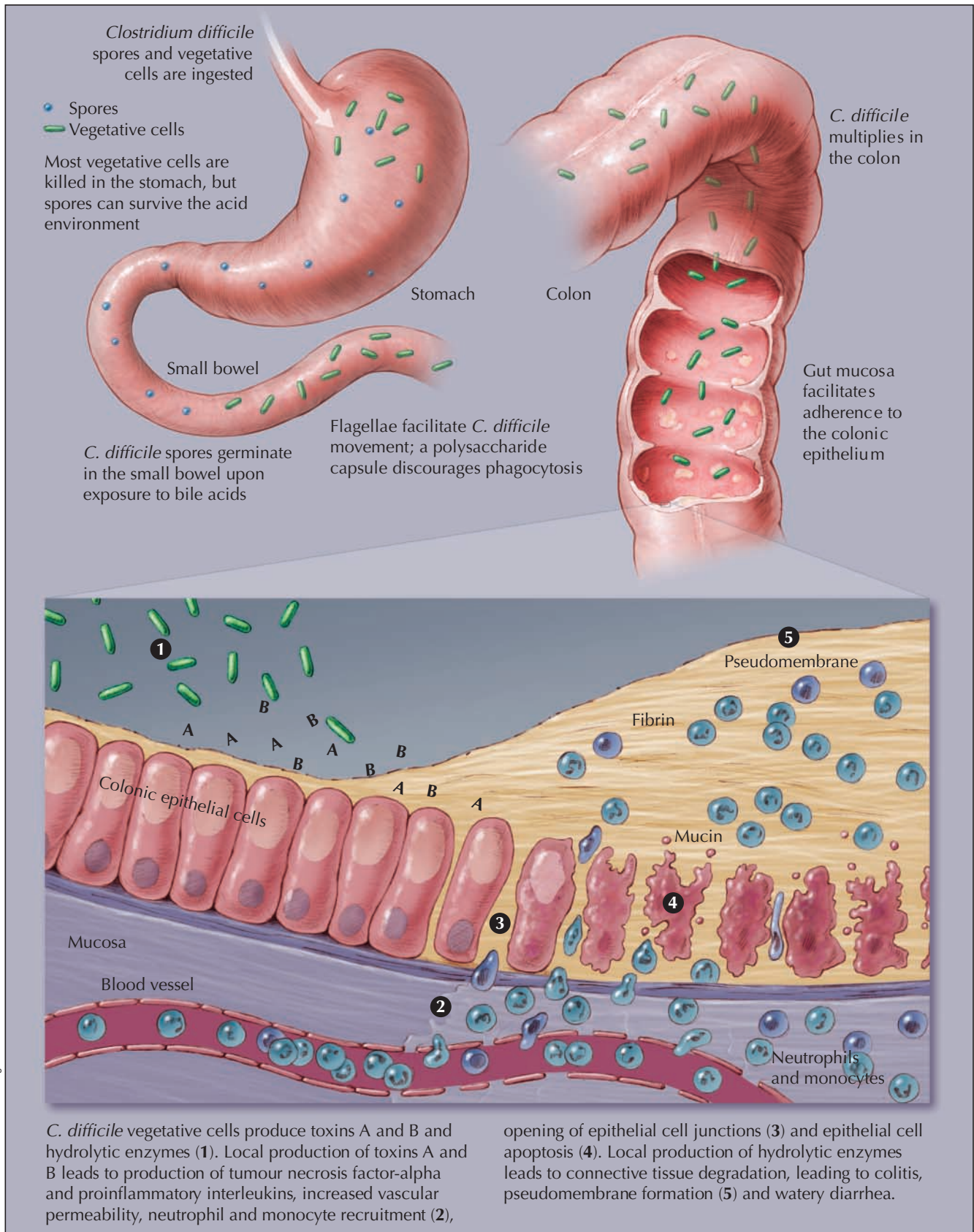han toxin B in the pathogenesis of *C. difficile* diarrhea because only it is associated with extensive tissue damage and fluid accumulation in experimental animal models.[39,41] Toxin B, on the other hand, has no noticeable direct enterotoxic activity and is thought to play a role only after the gastrointestinal wall has been damaged by toxin A.[40,41] However, as toxin A-negative/toxin B-positive virulent *C. difficile* strains have been described, it is clear that toxin A is not essential for virulence.[42,43]

In summary, at least 3 events must occur in the pathogenesis of *C. difficile* diarrhea: alteration of the normal fecal flora, colonic colonization with toxigenic *C. difficile* and growth of the organism with elaboration of its toxins (Fig. 2).

Clinical presentation

The incubation period from ingestion of *C. difficile* to onset of symptoms has not been determined. However, time from antibiotic exposure to onset of symptoms has been as short as 1 day to as long as 6 weeks or even longer.[44,45] Illness associated with *C. difficile* ranges from mild diarrhea to life-threatening colitis.[45,46] Typical clinical features include watery diarrhea, lower abdominal pain and systemic symptoms such as fever, anorexia, nausea and malaise. Leukocytosis and occult colonic bleeding frequently occur, but grossly bloody stools are uncommon. Diffuse or patchy colitis, with or without pseudomembranes, can be seen on colonic endoscopy.[45] Fulminant colitis occurs among 1%–3% of patients and is characterized by signs and symptoms of severe toxicity with fever and diffuse abdominal pain and distention.[47–49] Although diarrhea may be present, severely ill patients may have little or no diarrhea as a result of toxic dilatation of the colon (toxic megacolon) and paralytic ileus that may result from loss of colonic muscular tone.[45,49] Complications include colonic perforation and peritonitis.[45,48] Mortality associated with toxic megacolon is high, ranging from 24% to 38%.[49–52]

Recurrent diarrhea is seen in 5%–40% of patients receiving treatment for *C. difficile* diarrhea.[53–56] Kyne and associates showed that independent risk factors for recurrent *C. difficile* diarrhea include age greater than 65 years, increased severity of underlying disease and exposure to additional antibiotics after treatment.[54] Controlling for these factors, they also showed that a low serum antibody response to toxin A during an initial episode of *C. difficile* diarrhea is associated with an increased risk of recurrence. Up to almost half of recurrences have been shown to be caused by reinfection rather than by relapse, which suggests that reexposure to *C. difficile* from other patients or from the environment is a major source of recurrent symptoms.[55,56] In those with true relapse, however, recurrence of symptoms is most likely caused by the intraluminal persistence of *C. difficile* spores that germinate after antibiotic therapy is discontinued.[57] Relapse due to antibiotic resistance is not thought to be common, given the high intraluminal concentrations of antibiotics that can be achieved and the relatively rare occurrence of antimicrobial resistance in vitro.[58]

Clostridium difficile spores and vegetative cells are ingested

- Spores
- Vegetative cells

Most vegetative cells are killed in the stomach, but spores can survive the acid environment

Stomach

Colon

Small bowel

C. difficile spores germinate in the small bowel upon exposure to bile acids

Flagellae facilitate *C. difficile* movement; a polysaccharide capsule discourages phagocytosis

C. difficile multiplies in the colon

Gut mucosa facilitates adherence to the colonic epithelium

5

Pseudomembrane

Fibrin

1

B

A A A A B

A B B B

A B

A

Colonic epithelial cells

Mucin

4

Mucosa

3

Blood vessel

2

Neutrophils and monocytes

C. difficile vegetative cells produce toxins A and B and hydrolytic enzymes (**1**). Local production of toxins A and B leads to production of tumour necrosis factor-alpha and proinflammatory interleukins, increased vascular permeability, neutrophil and monocyte recruitment (**2**), opening of epithelial cell junctions (**3**) and epithelial cell apoptosis (**4**). Local production of hydrolytic enzymes leads to connective tissue degradation, leading to colitis, pseudomembrane formation (**5**) and watery diarrhea.

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Fig. 1: Pathogenesis of *Clostridium difficile*-associated diarrhea in adults.

Diagnosis

The diagnosis of *C. difficile* diarrhea should be considered in any patient with nosocomial diarrhea, especially if fever is also present. Abdominal imaging studies, including CT scans, may reveal "thumbprinting" of colonic mucosa, which suggests the presence of mucosal edema, but these changes are not specific for pseudomembranous colitis due to *C. difficile*. Direct visualization of colonic mucosa using either sigmoidoscopy or colonoscopy is required to determine the presence of pseudomembranous colitis. However, *C. difficile* colitis or diarrhea may occur without pseudomembrane formation, and colitis may be missed if only proximal disease is present. In general, sigmoidoscopy and colonoscopy should be avoided in fulminant colitis because of the risk of toxic megacolon and perforation.

A summary of the laboratory methods available for the diagnosis of *C. difficile* diarrhea is shown in Table 1. Diagnosis is generally based on the detection of toxin A or toxin B. The tissue culture cytotoxicity assay detecting the presence of *C. difficile* cytotoxin (toxin B) in stool filtrate is considered to be the "gold standard" for diagnosis because of its high specificity (99%–100%).[59,60] The sensitivity of this test is 80%–90%.[61,62] Performance of the test requires a tissue culture facility, and results are usually not available for at least 48 hours. Nonspecific cytopathic effects may be ob-
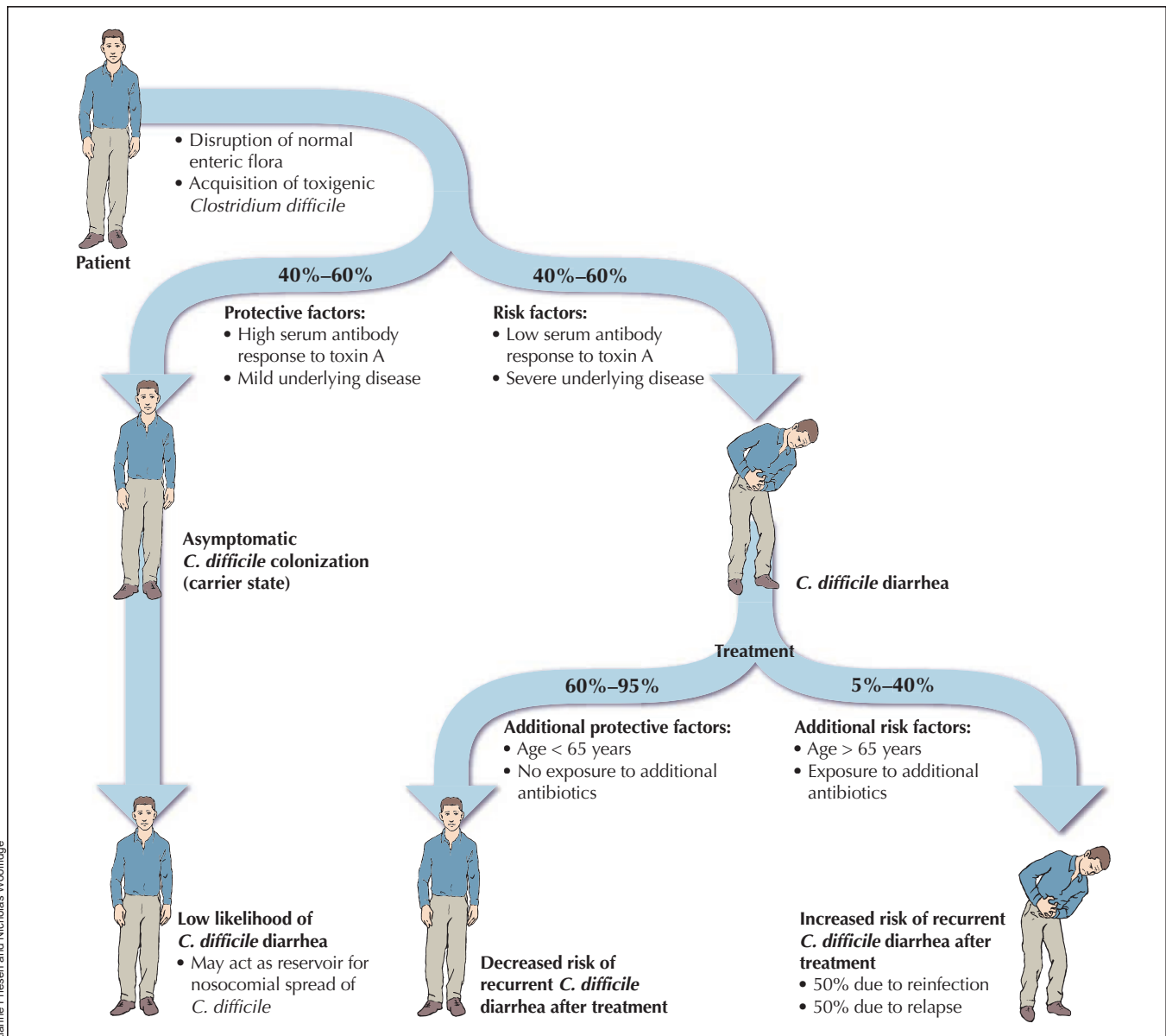

Fig. 2: Factors contributing to the development of *Clostridium difficile* colonization and diarrhea [adapted, with permission, from Johnson S, Gerding DN. *Clostridium difficile*-associated diarrhea. *Clin Infect Dis* 1998;26:1027-36, published by the University of Chicago Press, Infectious Diseases Society of America; 1998].

served in approximately 2% of cases, which makes interpretation of test results impossible.[60]

Rapid enzyme immunoassays have been developed for the detection of toxin A or both toxins A and B from stool filtrates.[61–64] Test kits able to detect both toxins are more sensitive because they are also able to identify disease caused by toxin A-negative/toxin B-positive strains of *C. difficile*. One of the main advantages of these immunoassays is their rapidity, with results available within hours. However, these tests have reduced sensitivity (65%–85%) and specificity (95%–100%) as compared with the cytotoxicity assay.[61,62]

Stool culture for detection of the organism is generally less useful because of the potential for asymptomatic carriage of *C. difficile* strains that are nontoxigenic.[14] Stool culture associated with detection of toxigenicity is potentially a more useful diagnostic test, with improved sensitivity (> 90%) and specificity (> 98%).[62,64] The procedure is labour-intensive and results are not available for at least 72–96 hours. Therefore, few laboratories routinely do stool cultures for *C. difficile*. However, stool culture does have the advantage of enabling strain typing for investigation of an outbreak.[65]

A latex agglutination test that detects the presence of a common clostridial protein, glutamate dehydrogenase, is available. The test is rapid and simple to perform but does not have adequate sensitivity (58%–68%) or specificity (90%–96%) for the accurate diagnosis of *C. difficile* diarrhea.[64,65] Recently, polymerase chain reaction (PCR) methods for the detection of *C. difficile* toxin A or B, or both, have been developed with excellent sensitivity (92%–97%) and specificity (100%) as compared with the tissue culture cytotoxicity assay.[66–68] However, standardization of PCR assays for *C. difficile* toxin detection has not been completed and commercial PCR assays are not currently available.

The processing of a single stool specimen for toxin detection at the onset of symptoms is generally sufficient to establish the diagnosis.[65,69,70] It is recommended that tests for *C. difficile* or its toxins be done only on diarrheal (unformed) stool specimens unless an ileus is present.[65,70] There is no value to testing stools of asymptomatic patients, including follow-up for "test-of-cure," unless an outbreak is being investigated.

Treatment

Treatment guidelines and recent reviews of recommended treatment for *C. difficile* diarrhea have been published and are summarized in Box 1.[53,57,65,70,71] The most important first step in treatment is cessation of the inciting agent, most commonly antibiotics, if this is deemed to be medically appropriate. For mild disease, this is often sufficient for full recovery.[70,72] For more severe disease, antimicrobial therapy directed against *C. difficile* is required. Oral metronidazole therapy (250 mg 4 times daily or 500 mg twice daily) given for 10–14 days is recommended as the initial treatment of choice.[65,70] Vancomycin (125 mg orally 4 times daily [for 10–14 days]) is the recommended second-line therapy.[65,70,73] Metronidazole and vancomycin are comparable with regard to efficacy and relapse rates.[74,75] Given the higher cost of oral vancomycin therapy and concern about selection for vancomycin-resistant enterococci,[76] metronidazole is preferred as the initial agent of choice.[65,70,71] Vancomycin should be reserved for patients with contraindications or intolerance to metronidazole or for those who fail to respond to metronidazole. Alternative antibiotic therapies for *C. difficile* diarrhea include oral therapy with teicoplanin (not available in Canada), bacitracin (not available in Canada) or fusidic acid, although these agents have not been studied as extensively as metronidazole and vancomycin.[74,77–79] In addition to specific antimicrobial therapy, supportive therapy with hydration and correction of electrolyte abnormalities is important in patients with *C. difficile* diarrhea. Antiperistaltic drugs should be avoided because they may precipitate toxic megacolon.[65,70]

Controlled clinical trials are lacking for patients with fulminant colitis who may not tolerate oral therapy. Administration of metronidazole intravenously or administration of vancomycin by nasogastric tube or rectal enema has been described in small case series.[57,71,80,81] Intravenous administration of vancomycin is not recommended because the drug is not excreted into the colon.[57] Intravenous immunoglobulin therapy has been used with success in a small number of patients with fulminant disease.[82] Surgical intervention is indicated for patients who are not responding to

Table 1: Laboratory tests available for the diagnosis of *Clostridium difficile*-associated diarrhea[59–64]

Test	Advantages	Disadvantages
C. difficile cytotoxin assay	Excellent specificity (99%–100%)	Decreased diagnostic sensitivity (80%–90%) Test results not available until after 48 h Requires tissue culture facility Detects only toxin B
Immunoassay for detection of toxin A or toxins A and B	Good specificity (95%–100%) Test results available within 4 h Technically simple	Reduced sensitivity (65%–85%) as compared with cytotoxin assay
Stool culture to isolate *C. difficile* with subsequent cytotoxin assay of isolate	Excellent sensitivity (> 90%) and specificity (> 98%) Enables typing of strain for outbreak investigation	Results not available for at least 72–96 h Labour-intensive Requires tissue culture facility

medical treatment or when colonic perforation or toxic megacolon is suspected.[51,52,83]

Unfortunately, recurrent *C. difficile* diarrhea occurs in about 5%–20% of patients after treatment with either metronidazole or vancomycin.[53,55,70] Metronidazole remains the drug of choice for treatment of an initial recurrence even if this was the original drug used.[57,65,70] For patients with multiple relapses, tapered and pulsed antibiotic therapy with metronidazole or vancomycin has been used.[57,84,85] Treatment with rifampin in combination with vancomycin[86] or with anion-binding resins such as colestipol or cholestyramine has been found to be helpful for some patients.[87] Adjunctive therapy with probiotic agents such as *Saccharomyces boulardii*[88–90] and *Lactobacillus GG*[91] has also been found to be effective in the management of a relatively small number of patients with recurrent *C. difficile* diarrhea. Further evaluation of treatment modalities for recurrent *C. difficile* colitis is required.

Preventive measures

Comprehensive guidelines and review articles summarizing strategies for the prevention of nosocomial transmission of *C. difficile* and for the prevention of *C. difficile* diarrhea have been published.[65,92,93] Prevention of nosocomial transmission of *C. difficile* depends on careful attention to handwashing, isolation and barrier precautions, and cleaning of the physical environment throughout the duration of symptomatic disease. Hand hygiene and glove use have been shown to be effective in preventing nosocomial transmission of *C. difficile*.[94,95] Because clostridial spores may be relatively resistant to alcohol and other antiseptic agents, it has been recommended that hands be washed with soap and water after glove removal during outbreaks of *C. difficile*-associated infections.[96] The use of private rooms with implementation of enteric or contact precautions has been successful in limiting transmission of *C. difficile* in hospital and long-term care settings.[97–101] Because this measure has generally been introduced along with other infection control measures, it is not known how effective it would be if used alone.

The physical hospital environment of patients with *C. difficile* infection is often contaminated and has been implicated as a reservoir for transmission of the organism to other patients.[100] Therefore, meticulous cleaning of surfaces and equipment and disinfection with agents able to eradicate *C. difficile* and its spores, such as a diluted hypochlorite solution, have been recommended.[70,92,100]

Strategies aimed at preventing the development of *C. difficile* diarrhea include antibiotic restriction, the use of probiotics, and passive and active immunization. Antibiotic restriction has been shown to be associated with decreased rates of nosocomial *C. difficile* diarrhea, and therefore programs encouraging the proper use of antibiotics are an important preventive strategy.[101–103] The use of probiotic agents throughout the duration of antibiotic use as a means of preventing *C. difficile* diarrhea in high-risk patients has been evaluated as a possible preventive therapy, with mixed results.[104–106] *C. difficile* toxin vaccines have been developed, and their safety and immunogenicity are currently being evaluated.[107,108]

Box 1: Recommended treatment of *Clostridium difficile*-associated diarrhea in adults[53,57,65,70,71]

First-line treatment

Discontinuation of antibiotics if possible

Metronidazole orally (250 mg 4 times daily or 500 mg twice daily) for 10–14 d (give metronidazole intravenously if patient is unable to take medications orally)

Alternative treatment

Vancomycin orally (125 mg 4 times daily) for 10–14 d

Treatment of recurrent disease

Repeat treatment with metronidazole or vancomycin

Bacitracin (25 000 U orally 4 times daily)

Adjunctive treatment with *Saccharomyces boulardii* (500 mg orally twice daily) or *Lactobacillus GG* (20×10^9 colony-forming units/d)

Adjunctive therapy with cholestyramine (4 g 3 times daily)

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Correspondence to: *Dr. Andrew E. Simor, Department of Microbiology, Sunnybrook and Women's College Health Sciences Centre, B121–2075 Bayview Ave., Toronto ON M4N 3M5; fax 416 480-6845; andrew.simor@sw.ca*