Clostridium difficile is emerging as a major infectious disease threat worldwide. The incidence of C. difficile infection (CDI) has exponentially increased globally, and the profile of patients at risk has changed in the past decade. Severe CDI outbreaks due to new, hypervirulent strains have emerged and inflicted significant morbidity on low-risk patients. In the United States, CDI rates have doubled, with 76.9 episodes of CDI per 10,000 hospital discharges in 2005. The alarming prevalence of CDI was exemplified in a recent report from the Association of Professionals in Infection Control and Epidemiology, who identified that more than 12 of every 1000 inpatients in the United States have been infected and are experiencing symptoms of CDI. Therefore, it is not surprising that CDI colitis has been identified as the direct cause of death in 1%–2% of affected patients, with the estimated annual cost per year per facility for nosocomial CDI estimated at $128,200. Containment and treatment of individuals afflicted with CDI was estimated at more than $3 billion in the United States alone. It is critical that health care providers understand this emerging infectious disease and develop strategies to limit its destructive impact on the population.

HISTORY

In 1935, Hall and O'Toole, in an attempt to understand the development of normal bacterial flora in neonates, identified a new anaerobe, which they initially called Bacillus difficilis. Interestingly, this bacterium was not clinically infectious in newborns but was pathogenic in guinea pigs via a fierce exotoxin. It was not until 1977 that Bartlett and colleagues identified that this anaerobic bacterium was a potent human pathogen and the etiologic agent responsible for antibiotic associated pseudomembranous colitis. The bacillus was aptly moved to the genus Clostridium, secondary to its obligate anaerobic status and its capability of producing endospores. The species name “difficile” remained owing to the difficulty involved in its isolation and study. Since then, C. difficile has evolved and is recognized as an important nosocomial pathogen, inflicting significant morbidity in infected individuals.

DISEASE CHARACTERISTICS

The virulence of C. difficile varies by patient. In its most benign cases C. difficile is associated with no symptoms, and individuals serve only as a reservoir for the disease. Symptomatic patients often report only mild abdominal pain and diarrhea. Others experience leukocytosis, fever, copious volumes of diarrhea and severe abdominal pain. Fulminant colitis develops in approximately 3% of these patients and is associated with a profound inflammatory response and considerable morbidity. The pertinent features of the various clinical presentations are summarized in Box 1.

To appreciate the spectrum of clinical disease caused by this microbe, it is important to understand its biology and the pathogenesis of disease. C. difficile is an anaerobic, gram-positive bacillus. It reproduces by the process of binary fission and is motile through the presence of peritrichous flagella. C. difficile exists
in 1 of 2 forms: a vegetative form (sensitive to oxygen) and a spore form (heat-stable and able to survive in a variety of environments). In its vegetative state the bacterium is able to use nutrients to grow and divide. However, when conditions become unfavourable (e.g., acidic environment, high temperature), this microbe is able to enter a dormant state and form a highly resistant spore. The ability of C. difficile to form these endospores is a key survival feature that allows it to persist both in patients and on inanimate objects (where it can survive up to 2 yr), making it very difficult to eradicate and easy to transmit. Interestingly, when the bacterium is faced with stress and unfavourable conditions, its ability to adhere to human intestinal cells increases, making colonization easier. Its ability to form spores enables its survival through the human digestive system and out into the oxygenated environment until it returns to its human host and vegetative state.

The natural habitat for this organism is the microflora of human intestines. Around 3% of healthy adults and up to 70% of infants have C. difficile bacteria in their guts. Natural gut flora acts as a barrier that protects against colonization by this microbe. While this organism also exists in the gastrointestinal system of pets and livestock, human CDI is not considered a zoonotic or food-borne disease. CDI is not considered a zoonotic or food-borne disease. In its vegetative state the bacterium is able to use nutrients to grow and divide. However, when conditions become unfavourable (e.g., acidic environment, high temperature), this microbe is able to enter a dormant state and form a highly resistant spore. The ability of C. difficile to form these endospores is a key survival feature that allows it to persist both in patients and on inanimate objects (where it can survive up to 2 yr), making it very difficult to eradicate and easy to transmit. Interestingly, when the bacterium is faced with stress and unfavourable conditions, its ability to adhere to human intestinal cells increases, making colonization easier. Its ability to form spores enables its survival through the human digestive system and out into the oxygenated environment until it returns to its human host and vegetative state.

The most common risk factor for colonization to antibiotics, particularly those with broad-spectrum activity (e.g., clindamycin, penicillin, some cephalosporins). Other described risk factors include immunosuppressive agents, increasing age, severe underlying illness, gastrointestinal surgery and use of antiperistaltic and antacid medications.

After colonization, C. difficile generates and releases its main virulence factors: 2 large clostridial exotoxins, toxins A and B. These toxins are encoded by the tcdA and tcdB genes. Toxins A and B act as potent exotoxins that work by binding to human intestinal epithelial cells and inducing inflammation, mucopurulent secretions and damage to mucosal structures. The process begins with toxin A binding to the apical side of the cell, which, after internalization, causes cytoskeletal changes that result in disruption of tight junctions and loosening of the epithelial barrier. This disruption allows both toxins to then cross the epithelium, where toxin B binds preferentially to the basolateral cell membrane. Both toxins are cytotoxic and induce the release of various immunomodulatory mediators. Toxin A works specifically by activating and recruiting important inflammatory mediators (interleukin [II]-6, IL-8, IL-1, tumour necrosis factor [TNF]-α) to the site of colonization, while toxin B demonstrates direct cytotoxic effects. Only toxigenic strains of C. difficile are able to produce clinically symptomatic CDI. In the asymptomatic carrier state, these toxins are found less frequently. Further, asymptomatic carriers show a propensity to produce a protective IgG response to the C. difficile enterotoxin. Toxin A, although not essential for virulence, plays a more critical role than toxin B in the development of C. difficile diarrhea, as animal models have demonstrated it is solely associated with tissue damage and fluid accumulation in intestinal cells. Toxin B has no direct enterotoxic effect and plays a role after the intestinal wall has been damaged by toxin A. Interestingly, a recent study examining the change in CDI epidemiology has identified the existence of a new hypervirulent and epidemic strain of C. difficile. It has been suggested that the

**Box 1. Clinical presentation and features of Clostridium difficile infection**

**Asymptomatic carrier state**
- Up to 20% of patients are colonized with CDI but do not have any clinical symptoms of CDI
- Individuals serve as an important reservoir for environmental contamination
- Host immune response to CDI may play a role in determining individuals’ carrier state

**C. difficile diarrhea**
- Mild to moderate nonbloody, watery diarrhea with or without abdominal cramps
- Symptoms usually begin during or shortly after antibiotic therapy
- Diarrhea resolves with discontinuation of antibiotics
- Toxins can be detected from fecal specimens
- Endoscopy results are often normal

**C. difficile colitis**
- Fever, malaise, abdominal pain, high-volume watery diarrhea in which stools can have some trace blood
- Leukocytosis is common
- Patchy erythematous colitis without pseudomembranes visible on endoscopy scan
- Pseudomembranous colitis (PMC)
  - Systemic illness, including abdominal pain, tenderness, fever and severe diarrhea that may be bloody
  - Severe leukocytosis and hypoalbuminemia can be seen
  - Pseudomembranes (raised yellow plaques on colonic mucosa), most commonly in rectosigmoid area visible on endoscopy scan
  - Increased colonic thickening visible on computed tomography scan

**Fulminant colitis**
- Occurs in approximately 3% of patients
- Associated with serious complications (perforation, prolonged ileus, toxic megacolon, death)
- Systemic inflammatory condition involving severe abdominal pain with or without diarrhea, high fever, chills, hypotension, tachycardia and marked leukocytosis
- Surgical intervention often necessary

CDI = C. difficile infection.
emergence of these hypervirulent strains has been driven by overuse and misuse of antibiotics. The epidemic strain (toxinotype 3, strain 027) has been shown to produce higher levels of toxins A and B (16–23 times higher) than the usual toxinotype 0. Further, this strain produces a binary toxin, CDT, which potentiates the toxic effects of toxins A and B.

**Diagnosis**

The enterotoxins produced by *C. difficile* represent the major virulence factors causing CDI. Diagnostic tools use this production to help health care providers diagnose the presence of this infectious scourge. Clinically, the diagnosis should be considered in any patient with new onset diarrhea with risk factors (primarily previous antibiotic exposure), especially if the diarrhea was contracted nosocomially. Laboratory diagnosis is made based on the detection of toxin A or B in a stool specimen. The gold standard test for diagnosis is the cytotoxin assay, which has a sensitivity of 80%–90% and a specificity of 99%–100%. This test is based on identification of toxin B in a cell culture. The main disadvantage with this test is that results take 1–3 days. To speed up results, rapid enzyme immunoassay tests have been developed to detect toxin A or both toxins A and B in the stool specimen. This enzyme-linked immunosorbent assay produces a reduced sensitivity (65%–85%) and specificity (95%–100%) compared with the cytotoxicity assay but allows results to be available within hours rather than days. Other less commonly used tests include anaerobic stool culture isolation of *C. difficile*. Stool culture for *C. difficile* is rarely performed in clinical microbiology laboratories because of inconvenience compared with the toxin assays and because the test, while very sensitive (90%–100%), fails to distinguish between toxigenic and nontoxigenic strains. This can be distinguished if a toxin assay is added as a second step in the test. A new investigational method is the polymerase chain reaction assay for *C. difficile* toxins. This test is sensitive (92%–97%) and specific (100%). Commercial availability is pending. In some situations, endoscopy has been used when a rapid diagnosis is required (e.g., a patient has ileus and cannot produce stool specimens). Sigmoidoscopy or colonoscopy is used to visualize and biopsy the colonic mucosa to diagnose pseudomembranous colitis. Endoscopy carries a risk of perforation, so it should be used judiciously. Finally, imaging, such as computed tomography, can be useful in demonstrating thumbprinting of the colonic mucosa (suggestive of edema), but these changes are not specific and cannot be used as the sole diagnostic tool.

**Treatment**

Once a diagnosis has been established treatment should be initiated for CDI. The key first step in treatment is to identify and eliminate the inciting agent (most commonly an antibiotic) as soon as possible. Thereafter supportive measures, such as fluid resuscitation and electrolyte correction should be initiated. These 2 measures are often sufficient for early mild disease. For mild to moderate cases, the mainstay of therapy is targeted antimicrobial treatment against *C. difficile*. The Infectious Disease Society of America recommends metronidazole (oral administration of 500 mg twice daily for 10–14 d) as the first line therapy. Vancomycin (oral administration of 125 mg 4 times daily for 10–14 d) is the drug of choice for severe CDI. If a prior underlying infection requires a prolonged course of antibiotics, anti-CDI therapy should be extended to 1 week past the concomitant antimicrobial’s conclusion. In patients with the most severe and complicated infections (e.g., toxic megacolon), a combination of intravenous metronidazole (500 mg 3 times daily) and oral vancomycin (500 mg 4 times daily) is recommended. The wide spectrum of illness caused by *C. difficile* is mirrored by an equally broad approach to following the disease’s progression. In patients with mild disease, serial examination, regular bloodwork and symptom reporting are the mainstays of monitoring. Patients with more severe manifestations of the disease, including increasing abdominal pain and distention or an impressive and increasing leukocytosis, may benefit from daily radiography of the abdomen to monitor for colonic dilatation, the development of toxic megacolon and perforation. Some suggest that genotyping *C. difficile* infections at disease onset may help predict disease severity. Clinicians armed with data regarding the genotype of *C. difficile* in instances of outbreak have felt that the information helped the management of these clusters, but these feelings were not reflected by clinical outcomes.

There is uncertainty regarding 2 major issues in the surgical management of CDI: timing and choice of procedure. Surgical intervention is common in severely ill patients with peritonism, perforation, necrotizing colitis or multi-organ dysfunction syndrome. Attempts to standardize timing of colectomy have been made on the basis of laboratory values (e.g., white blood cell count of 20–50 × 10^9/L, a serum lactate of 2.2–5.0 mmol/L), patient demographics (e.g., age > 74 yr), and clinical status (e.g., the need for vasoactive medications). The question of timing is further complicated by an emerging alternative procedure to colectomy: diverting loop ileostomy with colonic lavage, whose promising early results may lead to earlier operative intervention given the theoretical minimization of systemic insult owing to the decreased extent of the operation. However, the information obtained by Neal and colleagues regarding this technique is limited largely by its current versus historical cohort design.

Apart from metronidazole and vancomycin, several new therapeutic agents have been tested or are being researched as potential options. One of these is fidazomycin, a macrocyclic antibiotic that, in vitro, has demonstrated...
higher activity against C. difficile, including the hypervirulent type 027, than vancomycin. Large, multicentre randomized clinical trials continue to study the efficacy of this drug, and it appears to be a potent future weapon to combat C. difficile. In addition to studies on antimicrobial treatments for CDI, there have also been studies of the use of intravenous immunoglobulin (IVIG) in patients with severe or recurrent CDI. The IVIG contains C. difficile antitoxins, and small case series have demonstrated benefit, but comparative studies are still required before any treatment recommendations can be made. Dating back to 1958, intestinal microbiota transplantation (fecal bacteriotherapy) has been outlined as a potential treatment modality. In an attempt to restore normal intestinal flora (limiting colonization by C. difficile), microorganisms can be transplanted from healthy individuals via infusion of liquid suspension of stool. Systematic reviews have demonstrated this modality to be highly effective, and it led to resolution in 92% of patients. Clinical trials providing recommendations and guidance are still not available. Future possibilities include vaccination against C. difficile. Currently, a parenteral C. difficile toxoid vaccine, which induces high levels of antitoxin A immunoglobulin G, is in phase 2 clinical trials. Despite all of these treatment options, about 20% of patients with a single episode of CDI will relapse. Relapse is related to spore persistence and is caused by the same strain that caused the initial infection. Metronidazole remains the primary drug of choice for recurrence. If treatment with metronidazole alone fails, tapered and pulsed therapy with metronidazole and vancomycin is suggested. In addition, individuals with recurrent CDI tend to be very strong candidates for adjunctive therapy with probiotic agents, such as Saccharomyces boulardii and Lactobacillus GG. These probiotics are live microbes that help upregulate the host flora’s composition and thus out-compete C. difficile for colonizing real estate.

**PREVENTION**

Prevention strategies remain one of the most important methods that health care providers must use to limit the spread and pestilence caused by C. difficile. Clinical practice guidelines for CDI prevention were published by the Society for Healthcare Epidemiology of America and the Infectious Disease Society of America in 2010. The key points include the strict isolation of infected patients in private rooms, proper usage of gown and gloves and proper handwashing procedures for health care workers, environmental cleaning and disinfection using chlorine-based cleaning agents and implementation of antibiotic stewardship programs. Special attention should be paid to improving antibiotic usage by clinicians. A stepwise reduction in the use of clindamycin, broad-spectrum cephalosporins and fluoroquinolones, with an associated decrease in total frequency and duration of exposure, is one of the most effective methods of reducing the incidence of CDI according to the Centers for Disease Control.

Since its initial isolation in 1935, C. difficile has swiftly taken its position as one of the most common nosocomial pathogens causing significant morbidity and mortality worldwide. As we have learned from the pathogenesis of CDI, C. difficile is an extremely persistent organism with an ability to survive for long periods in a variety of environmental conditions. Further, it is highly adaptive, and in the past decade severe outbreaks due to hypervirulent strains have emerged. It is important to understand both the factors associated with the emergence of this disease and the modalities we can use to manage and prevent its effects. The injudicious use of antibiotics has been identified as one of the most important etiologic factors in promoting an antecedent disruption of normal colonic flora, which is a necessary first step in the pathogenesis of disease. Ergo, it will take a dedicated effort by all health care providers both to accept our role in promoting the proliferation of CDI and to use this knowledge to implement important strategies, such as proper handwashing and detailed antibiotic stewardship programs, to control and hopefully eliminate this emerging infectious scourge.

**CONCLUSION**

The Canadian Association of General Surgeons Clinical Practice Committee encourages Canadian surgeons to be aware of the science of C. difficile infection and its pathogenesis in order to be better equipped to deal effectively with the condition.

**References**