Clostridium difficile outbreaks: prevention and treatment strategies

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Abstract: The incidence and severity of Clostridium difficile infection (CDI) have increased dramatically over the past decade. Its treatment, however, has largely remained the same with the exception of oral vancomycin use as a first-line agent in severe disease. From 1999 to 2004, 20,642 deaths were attributed to CDI in the United States, almost 7 times the rate of all other intestinal infections combined. Worldwide, several major CDI outbreaks have occurred, and many of these were associated with the NAP1 strain. This ‘epidemic’ strain has contributed to the rising incidence and mortality of CDI. The purpose of this article is to review the current management, treatment, infection control, and prevention strategies that are needed to combat this increasingly morbid disease.

Keywords: antibiotic, antimicrobial, infectious colitis, pseudomembranous colitis, nosocomial, iatrogenic, toxin, Clostridium difficile

Introduction to Clostridium difficile outbreaks

Clostridium difficile is a Gram-positive, anaerobic, spore-forming, toxin-producing bacillus that causes antibiotic-associated diarrhea and colitis. It is transmitted via the fecal–oral route among humans. It was first isolated in 1935 by Hall and O’Toole from the stool of healthy neonates. They chose the name ‘difficile’ because of the difficulty they had in culturing this anaerobic bacterium on conventional media. At that time, it was not known to cause disease in human beings although cytotoxin production was recognized. In the late 1970s, C. difficile toxins were identified as the main causative agents in antibiotic-associated pseudomembranous colitis.

Over the past 20 years, the incidence and severity of C. difficile infection (CDI) have increased substantially. This pathogen is now associated with a far higher incidence of hospitalizations than the more widely publicized methicillin-resistant Staphylococcus aureus. CDI can cause a spectrum of disease ranging from asymptomatic carriage to mild diarrhea to pseudomembranous colitis with sepsis, toxic megacolon, organ failure, and death. The rate of US hospital discharges with CDI listed as a diagnosis doubled from 31/100,000 population in 1996 to 61/100,000 in 2003. The rate was sevenfold higher in persons >65 years of age compared to the 45–64 years age group. Mortality rates related to CDI also increased during the same time period, rising from 5.7 deaths per million population in 1999 to 23.7 deaths per million population in 2004, an increase of about 35% per year. From 1999 to 2004, CDI was reported as a cause of death in 20,642 persons in the United States, almost 7 times the rate of all other intestinal infections combined. In England, the UK Statistics Authority listed CDI as the primary cause of death in 499 people in 1999, a number that more than
triplled to 1998 in 2005 and then rose further to 3393 in 2006.4 The causes of these dramatic increases in CDI incidence and mortality seem to be multifactorial resulting from an aging hospital population with complex comorbidities, ever increasing antibiotic use, and the emergence of more virulent strains including the BI/NAP1/027/toxinotype III strain – henceforth designated as NAP1.5-7

Several outbreaks of CDI occurred in 6 different states in the United States between 2000 and 2003.7 The majority of isolates from the outbreaks belonged to the NAP1 strain of C. difficile, which was first characterized in the 1980s. A major difference in the newer NAP1 isolates when compared to earlier isolates was that the newer isolates exhibited high-level resistance to fluoroquinolones.7 A similar NAP1 CDI outbreak also occurred in Quebec, Canada, in 2004. The incidence of CDI in Quebec had increased from 6 per 1000 admissions in 1997 to 22.5 per 1000 admissions in 2004. The case-fatality rate of CDI also increased, rising from 1.5% of cases in 1997 to 6.9% in 2004.7 An analysis of 157 stool isolates from this outbreak, which included most major hospitals in the Quebec area, showed that 83% (129 isolates) of the cases were due to the new NAP1 strain. The emergence of the new NAP1 strain coincides with the rising incidence and mortality of CDI and highlights the need for better prevention and treatment strategies for this reemerging pathogen.

Natural history and clinical presentation

The life cycle of C. difficile begins in the spore form. These spores are easily transmitted as they are resistant to heat, acid, and antibiotics. The spores can remain viable for months outside of the human body. In the hospital, they can be found on bedding, furniture, medical equipment, as well as on the skin and jewelry of caregivers.8 Once ingested, the spores pass through the upper digestive tract into the intestines where they can germinate and colonize the colon. A study showed that 21% of patients receiving antibiotics and admitted to a general medical ward were colonized by this bacterium.8 Healthy individuals are usually protected from CDI by the normal bacterial flora of the gut, which resists C. difficile’s colonization and growth. Disruption of the normal microflora by antibiotics allows C. difficile to proliferate, produce toxins, and cause disease.10 C. difficile induces diarrhea and colitis through the release of two protein exotoxins, toxin A and toxin B. Greater than 60% of the population has serum and colonic antibody responses to these toxins.11,12 Low or absent concentrations of serum IgG antibody against C. difficile toxins has been shown to confer a greater risk of CDI among hospitalized patients who become colonized by this bacterium.13 Toxigenic C. difficile can be identified in more than 95% of pseudomembranous colitis cases and in 15%–25% of antibiotic-associated diarrhea cases.14,15

The NAP1 strain was first identified in the 1980s by restriction endonuclease analysis (then named BI).5,7 The recent North American and Quebec outbreaks used North American Field Pulse Type Analysis and PCR ribotyping, and it is now referred to as NAP1, ribotype 027, or BI/NAP1/027. This strain is characterized by three potential virulence determinants. The first is a possible enhancement of toxin A and toxin B production. The two toxin genes are found on the pathogenicity locus – a 5-gene region that includes the genes for toxin A (tcdA) and toxin B (tcdB) as well as three ancillary or regulatory genes (tcdC, tcdE, and tcdR) (Figure 1). The genes for toxins A and B are regulated by tcdR (positive regulator) and tcdC (negative regulator). The outbreak strains from Quebec and the United States carry deletion mutations in the tcdC inhibitory gene. The resulting loss of this inhibitory gene product has been postulated to increase toxin production. However, more recent data challenge this conclusion.16 The second important factor in the NAP1 outbreak strain is high-level fluoroquinolone resistance (marked resistance to gatifloxacin, moxifloxacin, and levofloxacin). Such resistance was not seen in the earlier isolates from the 1980s and the 1990s.5,7 These fluoroquinolone antibiotics are used commonly in the hospital setting as first-line treatment for community-acquired pneumonia, urinary tract infection, and gastrointestinal infection. It is thought that the widespread use of these antibiotics is partly to blame for recent NAP1 CDI outbreaks. Analysis of risk factors in the Quebec outbreak showed that the odds ratio (OR) for fluoroquinolone use in patients with CDI when compared to control subjects was 3.9. Restricting and reducing the use of fluoroquinolones may be helpful in preventing and managing NAP1 outbreaks. A third potential virulence factor in this new strain is the presence of binary toxin. Binary toxin is encoded by cdtA and cdtB in a separate region called the CDT locus. It is thought that binary toxin might have an additive enterotoxic effect with toxins A and B, but its role, if any, in the pathophysiology of CDI remains unclear.

C. difficile diarrhea and colitis usually present in patients who are undergoing antibiotic therapy (Figure 2). The most notorious antibiotics leading to this illness are clindamycin, ampicillin, amoxicillin, cephalosporins, and fluoroquinolones. It has been reported that up to 96% of
patients with symptomatic CDI received antibiotics within 2 weeks of the onset of diarrhea. Other predisposing factors leading to disease include advanced age, nursing home residence, and hospitalization. Recent data show that the use of acid suppressants are also associated with an increased risk of CDI. In the hospital, the most common presenting symptom of CDI is diarrhea, with the passage of frequent loose or watery stools. Occult blood and mucus can be seen but hematochezia and/or melena are rare. Patients can present with more serious signs and symptoms including colonic ileus or toxic megacolon.

The ileus prevents diarrhea from occurring so these patients can present with minimal or no diarrhea leading to delays in diagnosis. The only clues to the diagnosis of CDI in these cases may be fever, leukocytosis, and abdominal pain associated with diffuse abdominal tenderness to palpation and/or abdominal distention. Some patients may present with more fulminant disease, which can lead to shock, toxic megacolon, and/or multiorgan failure. The overall estimated case fatality rate of CDI is 2%. CDI can be diagnosed based on clinical suspicion (usually diarrhea in a patient with current or recent antibiotic use) ideally supported by the demonstration of toxinogenic *C. difficile* or *C. difficile* toxins in the stool. The most widely used diagnostic tests are enzyme immunoassays (EIAs) to detect *C. difficile* toxins A and B. These EIAs are rapid (2–4 hours), relatively inexpensive, and convenient but show limited sensitivity with frequent falsely negative results. Accordingly, more sensitive tests including assays for clostridial glutamate dehydrogenase (used as an initial sensitive screening test with subsequent confirmation using a more specific assay), tissue culture cytotoxicity, and PCR are under evaluation as alternatives to toxin EIAs.

**Management and therapeutic strategies: efficacy of metronidazole and vancomycin as first choice of treatment**

The immediate goal of CDI therapy is to alleviate the active symptoms of diarrhea and colitis. The ultimate goal of treatment is the restoration of the normal bacterial flora of the gut and elimination of CDI. The ideal treatment for CDI
would not require the use of antibiotics. Patients diagnosed with acute CDI should have all unnecessary antibiotics stopped. In 1974, Tedesco et al reported that up to 10% of patients receiving clindamycin suffered from pseudomembranous colitis.10 When clindamycin was discontinued, all patients recovered from their illness. However, many patients who suffer from CDI require antibiotic therapy to combat the growth of C. difficile and possibly also to treat serious coexisting infections.

The mainstays of treatment for CDI for the past 30 years have been metronidazole or oral vancomycin. Metronidazole is considered as first-line therapy for patients with mild to moderately severe CDI. Oral vancomycin has been reserved for patients who did not respond to or tolerate metronidazole, for patients with multiple recurrences of CDI, or for patients with severe disease. The published treatment failure rates of metronidazole and vancomycin before the year 2000 were similar (2.5% and 3.5%, respectively). After 2000, the published treatment failure rates of metronidazole rose to 18.2%, while that of vancomycin remained low at 2.8%.26–28 This rise in treatment failure with metronidazole has coincided with the recent dramatic increases in CDI incidence and severity. These issues resulted in an ongoing debate in the medical community as to whether vancomycin is superior to metronidazole and should, therefore, be used as first-line therapy for CDI despite concerns about higher drug cost and possibly increased nosocomial vancomycin resistance, particularly in enterococci.30,31

In 2007, Zar et al reported the results of a randomized, double-blind, placebo-controlled trial of oral vancomycin versus metronidazole for the treatment of CDI. The study showed an overall treatment response rate of 84% (66/79 patients) in the metronidazole group and 97% (69/71 patients) in the vancomycin group. What was most novel and interesting in the study was that subjects were prospectively stratified based on CDI disease severity. In patients with mild disease, the overall response rate was slightly better in the vancomycin group (98%) than in the metronidazole group (90%), but the difference did not reach statistical significance (P = 0.36). Conversely, the response rate in subjects with severe disease was only 76% in the metronidazole group compared to 97% in the vancomycin group (P = 0.02).30 These data support the continued use of metronidazole in patients with mild CDI but indicate that oral vancomycin should be used as first-line therapy for patients who present with severe infection. Unfortunately, there is no widely accepted method to define mild or severe CDI, and further studies are needed to validate predictive rules to identify the patients most likely to respond to oral vancomycin. However, the authors propose the scheme illustrated in Table 1.

Table 1 Classification and treatment of initial Clostridium difficile infection

<table>
<thead>
<tr>
<th>Severity</th>
<th>Clinical manifestations</th>
<th>Treatment</th>
</tr>
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<tbody>
<tr>
<td>Carrier</td>
<td>No discernible clinical symptoms or signs</td>
<td>No treatment is indicated</td>
</tr>
<tr>
<td>Mild to moderate</td>
<td>Mild diarrhea &lt; 12 stools/day</td>
<td>Discontinuation of predisposing antibiotics</td>
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<td></td>
<td>Afebrile</td>
<td>Hydration</td>
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<td></td>
<td>Mild to moderate abdominal discomfort or tenderness</td>
<td>Monitor clinical status</td>
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<tr>
<td></td>
<td>Nausea with rare or absent vomiting</td>
<td>Isolation</td>
</tr>
<tr>
<td></td>
<td>Leukocytosis &lt; 20,000</td>
<td>Oral metronidazole 500 mg 3 times daily or intravenous metronidazole 500 mg 3 times daily if not tolerating oral intake</td>
</tr>
<tr>
<td>Severe</td>
<td>Severe diarrhea &gt; 12 stools/day</td>
<td>Oral vancomycin 125 mg 4 times daily if intolerant of metronidazole</td>
</tr>
<tr>
<td></td>
<td>Pseudomembranous colitis</td>
<td>As above plus</td>
</tr>
<tr>
<td></td>
<td>Severe abdominal pain</td>
<td>Oral vancomycin 125 mg 4 times daily in place of oral metronidazole</td>
</tr>
<tr>
<td></td>
<td>Nausea or vomiting</td>
<td>Consider addition of intravenous metronidazole 500 mg 3 times daily</td>
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<tr>
<td></td>
<td>Ileus</td>
<td>Intravenous metronidazole 500 mg 3 times daily if not tolerating oral intake</td>
</tr>
<tr>
<td></td>
<td>In intensive care unit</td>
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</tr>
<tr>
<td></td>
<td>Leukocytosis &gt; 20,000</td>
<td></td>
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<tr>
<td>Fulminant</td>
<td>Toxic megacolon</td>
<td>Consider IVIg</td>
</tr>
<tr>
<td></td>
<td>Peritonitis</td>
<td></td>
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<tr>
<td></td>
<td>Renal failure</td>
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<td></td>
<td>Respiratory distress</td>
<td></td>
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<tr>
<td></td>
<td>Hemodynamic instability</td>
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Abbreviations: BUN, blood urea nitrogen; IVIG, intravenous immunoglobulin.
The standard initial therapy for mild CDI is to discontinue all antibiotics and monitor the patient’s progress. For mild CDI that persists, when other antibiotics cannot be discontinued or when patients are frail, then metronidazole 500 mg orally 3 times daily (or 250 mg orally 4 times daily) is often used for 10–14 days (Table 2). In patients who are unable to tolerate oral administration, parenteral or rectal administration can be used and leads to similar systemic and colonic drug levels. The initial starting dose for vancomycin is 125 mg orally 4 times daily for 10–14 days. Oral vancomycin is not degraded or absorbed by the gut and reaches the colon intact, which enables it to achieve high luminal concentrations with minimal toxicity. On the other hand, intravenous vancomycin is not secreted into the gut and is, therefore, not suitable for the treatment of CDI. In patients who cannot tolerate oral administration of vancomycin, intravenous metronidazole is the drug of choice. Vancomycin (500 mg 4 times daily) as rectal enemas or via a nasogastric tube can be used to supplement intravenous metronidazole in patients with very severe CDI, who are unable to tolerate oral vancomycin.24,25,32

A difficult problem with CDI is recurrent infection, which occurs in ~15%–30% of patients who were successfully treated with an initial course of metronidazole or vancomycin.33,34 The clinical features of recurrence are similar to the initial occurrence with the presence of diarrhea occurring usually within 2 weeks after discontinuation of therapy. However, recurrences can occur up to 3 months after stopping the initial antibiotic treatment. Patients with mild symptoms can be treated conservatively with symptomatic management. Patients who require antibiotics are typically treated with a second course of the same antibiotic used to treat the initial attack, and this approach has a success rate of about 60%. Probiotics (such as *Lactobacillus* spp. or *Saccharomyces boulardii*) may be used as an adjunctive therapy and may have some, limited efficacy in preventing recurrence.33 Patients who are intolerant to metronidazole should be placed on oral vancomycin at a dose of 125 mg 4 times daily and should be treated for a 14-day course. Unfortunately, despite successful treatment of a first recurrence 45% of these patients will have a repeat occurrence. Multiple recurrences are usually treated with a prolonged tapering course of oral vancomycin (Table 2). A suggested therapy for a second recurrence is the tapered and pulsed dosing of oral vancomycin over 51 days (Table 2). There are no established guidelines for the treatment of further recurrences, but other agents, such as intravenous immunoglobulins, rifaximin, probiotics, or fecal transplantation, have all been reported to be useful in uncontrolled studies.33,35–37 A newer promising treatment for prevention of recurrent CDI was recently published by Lowy et al.38 This was a randomized, double-blind, placebo-controlled trial of two human monoclonal antibodies against *C. difficile* toxins A (CDA1) and B (CDB1). The antibodies were administered in conjunction with metronidazole or vancomycin in patients receiving treatment for symptomatic CDI. The rate of recurrence was only 7% among patients treated with monoclonal antibodies versus 25% in the placebo group (*P* ≤ 0.001). The recurrence rate for patients infected with the BI/NAP1/027 strain was 8% for the monoclonal antibody group versus 32% in the placebo group (*P* = 0.06). Once commercially available, this monoclonal antibody will likely be used in patients at high risk for recurrent CDI. Risk factors for recurrent CDI include low serum IgG antitoxin, a prior recurrence, older age, severe underlying medical conditions, or a requirement for concomitant antibiotic treatment for additional infections.34,39

**Table 2** Suggested approaches to therapy

<table>
<thead>
<tr>
<th>Initial episode</th>
<th>Mild to moderate infection</th>
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<tbody>
<tr>
<td>Metronidazole at a dose of 500 mg orally 3 times daily for 10–14 days</td>
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<tr>
<td>Severe infection or unresponsiveness to or intolerance to metronidazole</td>
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<tr>
<td>Vancomycin at a dose of 125 mg orally 4 times daily for 10–14 days</td>
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<table>
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<tr>
<th>First recurrence</th>
<th>Mild to moderate infection</th>
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<tbody>
<tr>
<td>Metronidazole at a dose of 500 mg orally 3 times daily for 10–14 days</td>
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</tr>
<tr>
<td>Severe infection or unresponsiveness to or intolerance to metronidazole</td>
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<td>Vancomycin at a dose of 125 mg orally 4 times daily for 10–14 days</td>
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<table>
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<th>Second recurrence</th>
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<tbody>
<tr>
<td>Vancomycin in tapered and pulsed doses</td>
</tr>
<tr>
<td>125 mg daily 4 times daily for 14 days</td>
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<tr>
<td>125 mg daily 2 times daily for 7 days</td>
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<tr>
<td>125 mg once daily for 7 days</td>
</tr>
<tr>
<td>125 mg every 2 days for 8 days (4 doses)</td>
</tr>
<tr>
<td>125 mg once every 3 days for 15 days (5 doses)</td>
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| Third recurrence | Vancomycin at a dose of 125 mg orally 4 times daily for 14 days, followed by rifaximin at a dose of 400 mg twice daily for 14 days |
| Other options for recurrent infection |
| Intravenous immunoglobulin at a dose of 400 mg/kg of body weight once every 3 weeks for a total of 2 or 3 doses |
| Therapy with other microorganisms, including ‘fecal transplantation’ |

Notes: A probiotic such as *Saccharomyces boulardii* or *Lactobacillus* species may be added during the final 2 weeks of the vancomycin taper and for at least 4 weeks thereafter (preferably 8 weeks). However, the efficacy of probiotics in preventing recurrent *C. difficile* infection is unclear.

Infection control and prevention strategies
The ultimate goal in combating disease is prevention and/or eradication. Previous studies have suggested the efficacy of specific infection-control measures in reducing the incidence of CDI. These include hand hygiene, contact precautions, environmental cleaning and disinfection, and restriction of antimicrobial use. Nonetheless, the recent epidemics of CDI bring to light the need for better preventive measures. C. difficile vaccines are in development but are not ready for use in the population. Therefore, the current focus remains on infection control.

In June 2000, a C. difficile outbreak occurred at a teaching hospital in Pittsburgh, PA. This outbreak resulted in 26 colectomies and 18 deaths. In response, a C. difficile prevention bundle was instituted and was followed by a 78% decrease in the rate of CDI as well as a decrease in the number of severe CDI cases. The prevention bundle consisted of education, increased and early case finding, expanded infection-control measures, development of a CDI management team, and antimicrobial management. The education component consisted of a standardized education module with printable handouts for patients and providers. Nurses were given the authority to order testing for CDI, which allowed increased case finding. An e-mail alert system was also instituted, which encouraged attending physicians to test patients who were at high risk of having CDI. Expanded infection-control measures included environmental cleaning with bleach, electronic flags and alerts, hand hygiene with soap and water, prolonged duration of contact precautions beyond resolution of diarrhea, and infection-control audits. Finally, a formal antimicrobial management program was instituted, which required the prior approval of certain high-risk antibiotics by infectious diseases physicians and pharmacists.

A similar bundle approach was recently instituted at a teaching hospital in Boston, MA. This study was an observational before–after study of adult patients admitted to a tertiary university-affiliated hospital during a 4-year period from January 2004 to December 2008. The intervention included an educational campaign, a prevention bundle, and a treatment bundle. The educational campaign taught all hospital personnel about the increasing incidence and severity of CDI and encouraged everyone to increase their level of suspicion for this diagnosis. The campaign encouraged hospital personnel to promptly initiate diagnostic testing, isolation precautions (including hand washing), and treatment for those diagnosed with CDI. The prevention bundle gave specific responsibilities to physicians, physician assistants, nurse practitioners, floor nurses, microbiology staff, infection-control practitioners, and environmental services personnel (Table 3). The bundle also included specific infection-control practices: 1) Contact Precautions Plus’ that included emphasizing hand washing after every encounter with a patient with CDI and cleaning rooms with hypochlorite-based disinfectant after a patient with CDI was discharged. 2) Laboratory notification procedures that included verbal notification to floor nurses, e-mail alerts to hospital infections preventionists when a patient had a positive toxin assay and steps to be taken in coordinating infection control, and environmental services that aimed to decrease the transmission of C. difficile between patients. 3) A treatment bundle was created to standardize the treatment of patients with severe CDI and to provide guidelines for when to consider surgical consultation. The incidence rate of health care-associated CDI decreased by 40% from 1.1 cases per 1000 patient days preintervention to 0.66 cases per 1000 patient days postintervention. This reduction was sustained over a 21-month period.

Hand hygiene is an important component of most hospital infection control and prevention programs. In many hospitals in the United States, the use of alcohol-based hand gels now far exceeds hand washing with soap and water as the primary hand hygiene method. One reason for the increased use of alcohol-based hand gels is that they are quick and effective. Proper hand hygiene is crucial in preventing the transmission of C. difficile in the hospital setting. In 1989, McFarland et al showed that 59% of hospital personnel caring for patients with a positive C. difficile culture carried the organism on their hands. It is well known that alcohol-based hand gels do not kill the C. difficile spores. A recent study by Oughton et al evaluated different hand hygiene methods for efficacy in removing C. difficile. The study examined 10 volunteers with hands experimentally contaminated by nontoxigenic C. difficile. The results showed that the greatest reduction of C. difficile colony counts occurred by hand washing with soap and water, while the use of alcohol-based handrub was equivalent to no intervention. It is difficult to determine whether the increased usage of alcohol-based gels has played a role in the increasing incidence of C. difficile. Regardless, the current data provide preliminary support for the use of soap and water over hand gels for hospital personnel who are in contact with a C. difficile-infected patient.

Another important vector for the transmission of C. difficile is through the hospital environment.
Table 3 Clostridium difficile Infection (CDI) checklist

Prevention checklist
- When an MD, PA, NP, or RN suspects a patient has CDI:
  - Physician, Physician Assistant, or Nurse Practitioner:
    - Initiate Contact Precautions Plus
    - Order stool C. difficile toxin testing
    - Discontinue non-essential antimicrobials
    - Discontinue all anti-peristaltic medications
  - Registered Nurse:
    - Obtain stool sample for C. difficile toxin test
    - Place patient in single-patient room
    - Place Contact Precautions Plus sign on patient’s door
    - Ensure that gloves and gowns are easily accessible from patient’s room
    - Place dedicated stethoscope in patient’s room
    - Remind staff to wash hands with soap and water following patient contact
  - Microbiology Laboratory Staff Person:
    - Call relevant patient floor with positive C. difficile toxin test results
    - Provide daily list of positive test results for Infection Control
  - Infection Control Practitioner:
    - Check microbiology results daily for positive C. difficile toxin results
    - Call relevant floor to confirm that patient with positive C. difficile toxin results is in a single-patient room and that the Contact Precautions Plus sign is on the patient’s door
    - Flag the patient’s C. difficile status in the hospital’s clinical information system or in the patient’s paper chart
    - Alert housekeeping that the patient is on Contact Precautions Plus
  - Environmental Services Staff Person:
    - Prior to discharge cleaning, check for Contact Precautions Plus sign on the patient’s door
    - If Contact Precautions Plus sign is on the door, clean the room with a bleach-based cleaning agent
    - Confirm for supervisor that bleach-based cleaning agent was used for discharge cleaning for every patient on Contact Precautions Plus

Treatment checklist
- When an MD, PA, or NP diagnoses mild CDI:
  - All of the following criteria are present: diarrhea (=<6 BM/day), fever, WBC < 15,000, no peritoneal signs, and no evidence of sepsis
  - Physician, Physician Assistant, or Nurse Practitioner:
    - Initiate oral metronidazole at dose 500 mg every 6 hours
    - If no clinical improvement by 48–72 hours after diagnosis, treat patient as moderate CDI
    - Continue therapy for at least 14 days total and at least 10 days after symptoms have abated
- When an MD, PA, or NP diagnoses moderate CDI:
  - At least one of the following criteria is present: diarrhea (>12 BM/day), fever 37.5–38.5°C, WBC 15,000–25,000, or frankly visible stable lower gastrointestinal bleeding
  - Physician, Physician Assistant, or Nurse Practitioner:
    - Initiate oral vancomycin at dose 250 mg every 6 hours
    - If no clinical improvement by 48 hours, add IV metronidazole at dose 500 mg every 8 hours
    - Consider obtaining infectious disease consultation
    - Consider obtaining abdominal CT scan
    - Continue therapy for at least 14 days total and at least 10 days after symptoms have abated
- When an MD, PA, or NP diagnoses severe CDI:
  - At least one of the following criteria is present: diarrhea (>12 BM/day), fever >38.5°C, WBC > 25,000, hemodynamic instability, marked and continuous abdominal pain, ileus, absence of bowel sounds, evidence of sepsis, or intensive care unit level of care required
  - Physician, Physician Assistant, or Nurse Practitioner:
    - Obtain immediate infectious disease consultation
    - Obtain immediate general surgery consultation
    - Obtain abdominal CT scan
    - Initiate oral metronidazole at dose 500 mg every 6 hours together with IV metronidazole at dose 500 mg every 6 hours
    - Following consultation with general surgery regarding its use, consider rectal vancomycin
    - Ask general surgery service to assess the need for colectomy

Hospital interventions to decrease the incidence and mortality of healthcare-associated C. difficile infections. Notes: After the institution of this checklist along with other interventions, there was a 40% reduction in the incidence of CDI at this Boston hospital. Copyright © 2009, University of Chicago Press. Reproduced with permission from Abbott SK, Yokoe DS, Lipsitz SR, et al. Proposed checklist of hospital interventions to decrease the incidence of healthcare-associated Clostridium difficile infection. Infect Control Hosp Epidemiol. 2009;30(11):1062–1069.12

Abbreviations: MD, medical doctor; PA, physician assistant; NP, nurse practitioner; RN, registered nurse; BM, bowel movement; WBC, white blood cell count; CT, computed tomography; IV, intravenous.

C. difficile can be found in the hospital on floors, bedrails, windowsills, commodes, toilets, call buttons, blood pressure cuffs, electronic thermometers, and bed sheets.48 Therefore, disinfection of the contaminated hospital environment is essential to prevent the transmission of this nosocomial pathogen. Quaternary ammonium-based disinfectants are used commonly in the hospital setting but are not sporicidal against C. difficile.48,49 Disinfectants containing unbuffered hypochlorite (bleach), on the other hand, are sporicidal.49,50 In 1988, Kaatza et al reported on the use of hypochlorite as a disinfectant during a C. difficile outbreak. The bacterium was recovered from 31% of environmental cultures obtained on the hospital wards. These wards were then disinfected with unbuffered hypochlorite, and the outbreak subsequently ended.51 A more recent study by Fawley et al compared the effects of five different cleaning agents against epidemic and nonepidemic C. difficile strains. This study showed that only chlorine-based germicides were able to inactivate C. difficile spores.52 These studies support the use of chlorine-based disinfectants for preventing the transmission of C. difficile.

Another potential prevention measure in the fight against C. difficile could be the restriction of acid-suppressive agents. Recent literature suggests that there is an association
between the use of proton pump inhibitors (PPIs) and CDI.\textsuperscript{19,20} and multiple large studies now support this finding.\textsuperscript{53–55} Cunningham et al showed that PPI use within the preceding 8 weeks prior to exposure was associated with an increased risk of \textit{C. difficile} diarrhea, OR of 2.5, and 95% confidence interval (CI) of 1.5–4.2.\textsuperscript{20} In 2008, Aseeri et al reported similar results in a case control study, where CDI was associated with the use of PPI with an OR of 3.6 and 95% CI of 1.7–8.3.\textsuperscript{56} The pathophysiology behind this association is not well understood, as \textit{C. difficile} spores are known to be acid-resistant. \textit{C. difficile} should be able to pass through the stomach despite its acidic environment, so it is unclear as to how acid suppression might increase the risk of developing infection. Hypotheses include \textit{C. difficile}–permissive changes in intestinal flora with increasing pH\textsuperscript{57} or potentially that the use of acid suppressants is a marker for comorbidity, a well-established risk factor for CDI.\textsuperscript{58,59}

The role of probiotics in the prevention of \textit{C. difficile} remains unclear.\textsuperscript{60,61} There are many studies in the literature regarding probiotics in the prevention of antibiotic-associated diarrhea, but fewer studies looking at probiotics in the prevention of CDI. In 2004, Plummer et al reported a double-blind, placebo-controlled trial examining the role of probiotics (\textit{Lactobacillus} and \textit{Bifidobacterium}) in the prevention of CDI.\textsuperscript{62} In this study, 150 consecutive patients receiving antibiotic therapy were randomized to receiving the probiotic or placebo. The results showed that, on the basis of developing diarrhea, only 2.9% of stool samples in the probiotic group were positive for \textit{C. difficile}-associated toxins versus 7.25% in the placebo-controlled group. Despite this finding, the total number of patients who tested positive for \textit{C. difficile} was actually higher in the probiotic group (n = 11) than in the placebo group (n = 9), so the effect of the probiotic in this study is uncertain. \textit{S. boulardii} does not appear to be effective in primary prevention of CDI.\textsuperscript{33,63} At this time, there is insufficient evidence to support the widespread use of probiotics for the primary prevention of CDI. Larger randomized control trials are needed to support its use.

**Conclusion**

The incidence and severity of CDI has increased over the past decade, and this infection is associated with an increased mortality due to an aging population, increased antibiotic use, and increased bacterial virulence. Despite this increasing severity, the mainstay of treatment has changed very little. Metronidazole is appropriate for mild to moderately severe CDI, while vancomycin is now recommended as first-line therapy for severe infection. Immune-based therapies, such as vaccines and passive immunotherapies, show promise but further studies need to be done. At this time, the focus of the medical community should be on prevention strategies. Infection-control programs are essential and should be multifaceted to control the increasing incidence of this morbid disease.

**Disclosure**

The authors report no conflicts of interest in this work.

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