**Abstract**

- **Objective:** To report recent changes in the epidemiology of *Clostridium difficile*-associated diarrhea (CDAD) and to discuss its diagnosis, treatment, and prevention.
- **Methods:** Qualitative review of the literature.
- **Results:** CDAD continues to be a major problem in the health care setting. A new virulent strain of *C. difficile* has been associated with several notable hospital outbreaks. This strain, called BI/NAP1, produces 16 to 23 times the amount of toxin A and B produced by standard strains and has been associated with more severe CDAD and increased mortality. In addition to previously identified predisposing factors, risk factors for CDAD associated with this new strain include age > 65 years and fluoroquinolone use. For initial treatment of mild to moderate CDAD, metronidazole is still recommended; however, vancomycin is now recommended as initial therapy in moderate to severe disease. Studies of new drugs for treatment of CDAD are currently in process. Recurrent diarrhea remains a frequent complication of CDAD, but studies are necessary to define the best approach for treatment of recurrent disease.
- **Conclusion:** A new strain of *C. difficile* has emerged that causes more severe disease and treatment failures with standard therapies. New, more effective treatment options are urgently needed.

*Clostridium difficile*-associated diarrhea (CDAD) continues to be a major problem in hospitals and other health care facilities. The emergence of a new strain of *C. difficile*, typed as restriction endonuclease group BI, pulse field gel electrophoresis type NAP1, and toxinotype III (BI/NAP1), is particularly concerning. This strain produces 16 to 25 times the toxin of standard strains and has been associated with more severe disease and increased mortality [1,2]. This article reviews the pathogenesis, epidemiology, clinical presentation, diagnosis, treatment, and prevention of CDAD with an emphasis on the new virulent BI/NAP1 strain.

**Pathogenesis**

First described by Hall and O'Toole [3] in 1935, *C. difficile* is a spore-forming anaerobic gram-positive rod. It was identified as the cause of antibiotic-associated pseudomembranous colitis in 1978 [4,5]. When a susceptible host develops altered colonic flora related to contact with antibiotics or chemotherapy drugs and is exposed to *C. difficile* by fecal-oral transmission [6,7], acid-resistant *C. difficile* spores pass intact into the disrupted gastrointestinal tract where they germinate, proliferate, and release exotoxins A and B. Vegetative forms can transmit infection in achlorhydric patients [8].

*C. difficile* toxins A and B adhere to receptors on the colonic epithelial cell brush border and cause colonic damage via inactivation of Rho proteins, resulting in actin filament disintegration, cytoskeleton disruption, and cell death [9–11]. Toxin A also causes intestinal fluid secretion and promotes chemotaxis and inflammation with resultant pseudomembrane formation [12]. Although toxin B does not affect permeability, fluid secretion, or neutrophil migration, it is more potent than toxin A in damaging the human colonic mucosa [13].

The recently described *C. difficile* strain, BI/NAP1, demonstrates a 16- to 23-fold increased production of toxins A and B compared with historical controls and causes more severe disease [1,2]. The increased toxin production is thought to be secondary to a partial deletion in the tcdC gene, a down-regulator of toxins A and B [14]. The BI/NAP1 strain also produces a binary toxin, but its role in pathogenesis is unclear [15].

The pathologic appearance of the CDAD-affected colon ranges from normal to mild hyperemia to scattered ulcerations to diffuse pseudomembrane formation (Figure 1). Microscopically, when pseudomembranes are present, the mucosal surface contains ulcers with neutrophilic infiltrates and an overlying pseudomembrane (Figure 2).

**Epidemiology**

*C. difficile* can be found as part of the intestinal flora of 3% of healthy persons and in up to 20% to 40% of hospitalized patients. *C. difficile* has been implicated as the cause of 10% to 25% of antibiotic-associated diarrhea and 95% of pseudomembranous colitis. *C. difficile* has the ability to sporulate,
which allows for its survival in a variety of harsh environments [16,17].

Over the past 10 years, many centers in the United States and Canada have reported increasing incidence and severity of CDAD in hospitalized patients. A U.S. hospital noted an increase from 6.8 cases/1000 discharges between 1989 and 1999 to 11.6 cases/1000 discharges in 2000 [18]. Hospitals in Quebec reported an increased incidence of CDAD from 35.6/100,000 population in 1991 to 156.3/100,000 in 2003 [19]. Data from the Centers for Disease Control and Prevention revealed that hospital discharge diagnosis of CDAD increased significantly from 31/100,000 population in 1996 to 61/100,000 in 2003 [20]. The increased incidence was disproportionately higher in persons aged older than 64 years, with approximately 150 discharges/100,000 population in 1996 to more than 300 discharges/100,000 population in 2003. In addition, all-cause 30-day mortality following CDAD increased from 4.7% in 1991 to 13.8% in 2003, and 1-year attributable mortality has been reported as high as 17% in Canadian studies [19,21]. Other studies have noted lower attributable mortality (1.5%) but elevated all-cause mortality (15.2%), reflecting multiple comorbidities in populations at risk for CDAD [22].

Outbreaks of single strains of *C. difficile* in hospitals have been reported previously [23,24]. The recent increased incidence and severity of CDAD in areas of Canada, the United States, and Europe has been linked to the presence of a single hypervirulent clone of *C. difficile*, BI/NAP1. As discussed above, more severe colitis may be the result of hyperproduction of *C. difficile* toxins A and B by the BI/NAP1 strain [1,14,25].

Hospital patients, including asymptomatic carriers, and the hospital environment are the major reservoir for *C. difficile*.

The duration of hospitalization directly correlates with the acquisition of *C. difficile*; the rate of acquisition of *C. difficile* was 13% in patients hospitalized for 1 to 2 weeks, but this increased to 50% in patients hospitalized for more than 4 weeks [23]. Antimicrobial exposure is a nearly universal risk factor for development of CDAD (Table 1) [16,17,23,26]. Third-generation cephalosporins, (eg, cefotaxime, ceftazidime) have been commonly implicated; however, any antibiotic class may increase the risk of CDAD [23,26]. Longer duration of antibiotic therapy and use of multiple antimicrobial agents have also been associated with increased risk of CDAD [26]. The BI/NAP1 strain of *C. difficile* is resistant to fluoroquinolones [25]. Therefore, exposure to fluoroquinolones is a leading risk factor when evaluating for CDAD caused by BI/NAP1 [1,27–29].

Other risk factors for the development of CDAD in hospitalized patients include severity of illness, interventions that alter the usual gastrointestinal barriers to infection (eg, use of proton pump inhibitors, gastrointestinal surgery, and nasogastric tubes), and age [16,17,23,26]. In recent reports of outbreaks of CDAD due to the BI/NAP1 strain, age older than 65 years was a predominant factor associated with occurrence of infection, severity of disease, and mortality [19–21]. In addition, severe CDAD has also been reported in healthy persons and peripartum women not usually considered to be at risk for CDAD. CDAD should be considered in patients without antibiotic exposure or other risk factors when presenting with severe diarrhea [30]. Proton pump inhibitor exposure has also been implicated in increased risk for community-associated CDAD [31].
Clinical Presentation

Clinical manifestations of C. difficile infection range from an asymptomatic carrier state to fulminant colitis with toxic megacolon [32]. Severity of disease depends on host factors and virulence of the infecting strain of C. difficile [33]. The majority of hospitalized patients infected with toxigenic strains of C. difficile become asymptomatic carriers; 63% were asymptomatic carriers in a study of 83 patients with hospital-acquired C. difficile [34].

Symptomatic CDAD can be separated into diarrhea without colitis, colitis without pseudomembranes, pseudomembranous colitis, and fulminating colitis [35]. Recent outbreaks of CDAD associated with the BI/NAP1 strain in Canada, the United States, and Europe have been characterized by more severe disease [1,14]. Symptoms typically begin 5 to 10 days after initiation of antibiotic therapy but can occur as early as 1 day after initiation or as late as 10 weeks after stopping antibiotics [35].

The mildest form of CDAD is characterized by 3 to 4 watery stools per day and crampy abdominal pain without fever or other systemic complaints. Typically, there is minimal abdominal tenderness on examination and the patient does not appear ill. Diarrhea often resolves after cessation of antibiotics, and treatment with metronidazole or vancomycin is rarely required [33]. When mild, CDAD may be difficult to distinguish from diarrhea that is an adverse effect of antibiotics.

C. difficile colitis without pseudomembranes presents as a systemic illness with fever, malaise, abdominal pain, nausea and vomiting, and up to 20 watery stools per day with signs of dehydration [33]. Pseudomembranous colitis presents with similar symptoms, but colonoscopy reveals pseudomembranes [33]. Patients with C. difficile colitis with or without pseudomembranes may present with hemoccult-positive stools and, rarely, hematochezia [33].

The most severe form of C. difficile disease, fulminant colitis, occurs in approximately 2% to 3% of cases and can lead to complications, including ileus, toxic megacolon, perforation, and death [36]. Patients present with diffuse abdominal pain and distension, diarrhea, dehydration, and hypotension. On examination, these patients often have high fevers and abdominal tenderness. Peritoneal signs, including guarding and rebound tenderness, suggest bowel perforation. Laboratory findings include a high white blood cell (WBC) count (up to 40,000/mm³) and azotemia. As symptoms worsen and the patient develops an ileus or toxic megacolon, stool output may paradoxically decrease [37]. Occasionally, C. difficile colitis presents as an acute abdominal syndrome or toxic megacolon without diarrhea [38]. The BI/NAP1 strain appears to be associated with higher rates of pseudomembranous colitis, toxic megacolon, and death [19,21].

Unusual presentations of C. difficile colitis include small bowel enteritis [39], protein-losing enteropathy [40], and infections in patients with inflammatory bowel disease [41]. Extraintestinal manifestations such as bacteremia [42], abdominal abscess [43], osteomyelitis [44], and Reiter’s syndrome [45] are rare.

Diagnosis

CDAD should be suspected in any patient with diarrhea who has received antibiotics within the previous 2 months [37]. However, antibiotics may be less of a risk factor in community-associated CDAD, and CDAD should be considered in those with severe diarrhea in the absence of antibiotic exposure or other traditional risk factors [30]. In addition to the clinical symptoms, laboratory tests that suggest CDAD include leukocytosis, hypoalbuminemia, and azotemia [19,37]. Approximately 50% of patients with CDAD will develop leukocytosis (15,000–16,000/mm³) and 25% will have a WBC count greater than 35,000/mm³ [46,47]. In cases of C. difficile caused by the BI/NAP1 strain, severe disease was associated with both leukocytosis and azotemia [2,19].

In patients with pseudomembranous colitis or fulminant colitis, radiologic imaging may be helpful in guiding therapy. Plain radiography is abnormal in one third of cases and may show an ileus, megacolon, thickened haustra, thumb-printing, or free air [48]. Abdominal computed tomography (CT) scans are abnormal in approximately 50% of hospitalized patients with C. difficile colitis [49]. The most common abnormality is segmental bowel thickening, but diffuse thickening and bowel perforation can also occur [49]. Although there seems to be a correlation between positive CT scans and more severe disease, specific CT findings do not appear to correlate with the need for surgical treatment [49].

While the tissue culture cytotoxicity assay is the gold standard, testing for toxins A and B remains the standard method for diagnosing C. difficile disease (Table 2) [50,51]. The cytotoxicity assay, which measures the effect of toxins A and B on fibroblasts from a stool sample, is 94% to 100% sensitive and 99% specific [52,53]. Unfortunately, this

Table 1. Risk Factors for Acquisition of Clostridium difficile–Associated Diarrhea

<table>
<thead>
<tr>
<th>Risk Factor</th>
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<tbody>
<tr>
<td>Antibiotic exposure (ie, third-generation cephalosporins, fluoroquinolones, multiple antimicrobial agents)</td>
</tr>
<tr>
<td>Duration of hospitalization</td>
</tr>
<tr>
<td>Age &gt; 65 years</td>
</tr>
<tr>
<td>Severity of illness</td>
</tr>
<tr>
<td>Gastrointestinal surgery</td>
</tr>
<tr>
<td>Nasogastric tube feedings</td>
</tr>
<tr>
<td>Proton pump inhibitors</td>
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</tbody>
</table>

Table 2. Clinical Presentation of Clostridium difficile–Associated Diarrhea

<table>
<thead>
<tr>
<th>Symptom</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal pain</td>
</tr>
<tr>
<td>Diarrhea</td>
</tr>
<tr>
<td>Fever</td>
</tr>
<tr>
<td>Malaise</td>
</tr>
<tr>
<td>Nausea</td>
</tr>
<tr>
<td>Vomiting</td>
</tr>
<tr>
<td>Leukocytosis (&gt;15,000/mm³)</td>
</tr>
<tr>
<td>Hypoalbuminemia</td>
</tr>
<tr>
<td>Azotemia (&gt;35,000/mm³)</td>
</tr>
<tr>
<td>Segmental bowel thickening</td>
</tr>
<tr>
<td>Diffuse thickening</td>
</tr>
<tr>
<td>Bowel perforation</td>
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</tbody>
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test is expensive to perform and results typically take 2 to 3 days [52]. Consequently, most laboratories now rely on enzyme-linked immunoabsorbent assay (ELISA) to detect toxin [53]. These tests are easier to perform, less expensive, and as specific as the cytotoxic assay. However, ELISA is 5% to 10% less sensitive, and repeat testing (3 stool samples) may be necessary to detect toxin [53]. ELISA tests targeting both toxins A and B are preferred by most laboratories because single toxin tests may miss infections with a C. difficile strain producing only the untested toxin [54,55].

Although useful in epidemiologic studies of outbreaks, stool culture for C. difficile cannot distinguish between toxigenic and nontoxigenic strains. Between 10% and 30% of hospitalized patients are colonized with C. difficile without disease [34]. Stool culture is also expensive and time-consuming compared with ELISA [53]. Latex agglutination tests of the stool are less sensitive (58%–92%) and specific (80%–96%) than other tests and are not recommended [53]. Gene amplification by polymerase chain reaction (PCR) has shown promise in identifying C. difficile toxin in stool and, in several studies, compares favorably with the cytotoxic assay [57–60]. In a recent study, the sensitivity and specificity of a real-time PCR assay for the detection of toxin B gene was 100% and 94%, respectively, compared with the standard cytotoxin assay [60]. Fecal leukocyte testing is specific (92%) but not very sensitive (28%–40%) (Table 2) [61].

Endoscopy is generally not recommended as a diagnostic test for C. difficile, particularly in severe pseudomembranous colitis where bowel perforation is a risk [37]. However, the following situations warrant endoscopy: (1) a rapid diagnosis is needed and test results are delayed or insensitive tests are used, (2) the patient has an ileus and stool is not available, or (3) other colonic diseases that may be diagnosed with endoscopy are being considered [37]. Colonoscopy is preferred over sigmoidoscopy because 10% of patients may have proximal colon but not rectosigmoid pseudomembranes [62].

### Treatment

Early recognition of disease and prompt treatment is important. Treatment approaches for CDAD vary for initial versus recurrent episodes and with severity of disease (Table 3). Patients with asymptomatic C. difficile should not be treated, and in those with very mild CDAD, discontinuation of antibiotic therapy may be sufficient [63]. However, in most cases, additional treatment is required. In all cases, unnecessary antibiotics should be stopped and antiperistaltic agents should be avoided, as they can promote ileus.

Oral metronidazole (500 mg 3 times/day or 250 mg 4 times/day) for 10 days has been the preferred first-line therapy for mild to moderate CDAD. Oral vancomycin (125–500 mg 4 times/day) has been recommended for patients who cannot tolerate vancomycin, are pregnant, or have severe CDAD [53]. Although metronidazole achieves moderate stool concentrations in patients with diarrhea, intracolonic metronidazole levels are minimal once diarrhea resolves [53]. In contrast, vancomycin is not absorbed and high levels are present in the colonic lumen. Randomized controlled trials in the 1980s and 1990s showed that metronidazole and vancomycin were equally effective, with

### Table 2. Sensitivity and Specificity of Selected Tests for Clostridium difficile

<table>
<thead>
<tr>
<th>Diagnostic Test</th>
<th>Sensitivity, %*</th>
<th>Specificity, %*</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytotoxicity assay</td>
<td>67–100</td>
<td>85–100</td>
<td>Tests for both toxin A and B activity (gold standard test)</td>
<td>Expensive; time-consuming (2 days)</td>
</tr>
<tr>
<td>EIA toxin test</td>
<td>63–99</td>
<td>75–100</td>
<td>Rapid, inexpensive</td>
<td>Less sensitive than cytotoxicity assay; tests detecting only 1 toxin (A or B) are much less sensitive</td>
</tr>
<tr>
<td>Culture for C. difficile</td>
<td>89–100</td>
<td>84–99</td>
<td>Very sensitive</td>
<td>Not specific for disease; time-consuming</td>
</tr>
<tr>
<td>Latex agglutination for</td>
<td>59–92</td>
<td>80–96</td>
<td>No advantage over other tests</td>
<td>Nonspecific and insensitive</td>
</tr>
<tr>
<td>C. difficile antigen</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Used in research</td>
<td>Not yet well-developed</td>
</tr>
<tr>
<td>PCR detection of toxin gene</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Very specific; diagnostic of pseudomembranous colitis</td>
<td>Insensitive; bowel perforation risk</td>
</tr>
<tr>
<td>Endoscopy</td>
<td>51</td>
<td>100</td>
<td></td>
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</tr>
</tbody>
</table>


*Compared with clinical and test-based criteria.
Mild to moderate disease
Metronidazole 250 mg 4 times daily or 500 mg 3 times daily
Adverse Effects
Metallic taste, GI upset, peripheral neuropathy
Estimated Cost of 10-Day Course, AWP*
$22 (generic)
Moderate to severe disease
(WBC count > 20,000/mm³, rising serum creatinine, fever, severe abdominal pain)
Vancomycin 125 mg or 250 mg 4 times daily
Obstruction, ileus, or perforation
Metronidazole 500 mg IV every 6 hr and/or vancomycin via nasogastric tube or enema every 8 hr; surgical consultation
Investigational therapies
Nitazoxanide 500 mg twice daily
Rifaximin 200 mg twice daily
Adverse Effects
Nausea, headache
Hypersensitivity, transaminitis, headache, GI upset
Estimated Cost
$358
$87

AWP = average wholesale price; GI = gastrointestinal; IV = intravenously; WBC = white blood cell.

approximately 90% efficacy for resolution of diarrhea and recurrence rates of 5% to 7% with metronidazole and 12% for vancomycin [64–66]. Because of cost and potential collateral effects on colonic flora, including selection for vancomycin-resistant enterococci with vancomycin use, metronidazole has been recommended as first-line therapy for CDAD [53]. However, vancomycin remains the only U.S. Food and Drug Administration–approved agent for treatment of CDAD.

Although most current strains, including the BI/NAP1 strain, remain susceptible in vitro to both metronidazole and vancomycin, recent observational studies have suggested that metronidazole may be less effective than previously reported. Among 207 patients treated with metronidazole for CDAD at a Veteran’s Affairs hospital between 2003 and 2004, the failure rate was 22% after 10 days of metronidazole and the recurrence rate was 28% within 90 days. Only 50% of patients treated with an initial course of metronidazole were cured and had no recurrence within 90 days. These outcomes were associated with a mortality rate of 27% in this population with significant comorbidities. In addition, higher mortality was seen among those with no response to initial therapy [67]. There was no evidence of an epidemic clone during the study period, and this high failure rate occurred despite in vitro susceptibility to metronidazole.

During an epidemic of severe CDAD in Canada, use of vancomycin as initial treatment was associated with a 79% lower rate of complicated colitis or death when compared with metronidazole [19]. In addition, the rate of recurrence within 60 days was higher (47.2%) with metronidazole than with vancomycin (23.2%) [68]. Increased failure rates with standard therapies for CDAD have been attributed to an aging hospitalized patient population with severe underlying disease and impaired host immunity, increased antibiotic use, and hypervirulent, easily transmissible clones [29].

Given the increased virulence of CDAD associated with the BI/NAP1 strain, there is debate regarding which patients should receive initial treatment with vancomycin. In an observational study, high WBC count (> 20,000/mm³) and elevated serum creatinine were strongly associated with adverse outcomes [19]. In other studies, predictors of failure of metronidazole as initial therapy included albumin level less than 2.5 g/dL, age older than 65 years, intensive care unit stay, and continuation of other antimicrobial therapy [69,70]. Most experts recommend vancomycin orally as initial therapy in patients with a WBC count of 20,000/mm³ or greater or rising serum creatinine [19,71].

Decisions regarding when to change therapy from metronidazole to vancomycin are difficult. Historical studies suggest that expected response should include resolution of fevers by day 2 of therapy, improved diarrhea and leukocytosis by day 4 or 5 of therapy, and complete resolution of diarrhea by 2 weeks [72]. Improvement in leukocytosis, abdominal pain, and fever should precede resolution of diarrhea. However, treatment failure should not be assumed until after 6 to 7 days of therapy unless the patient’s clinical condition is worsening [53].

Among patients with fulminant CDAD, additional therapeutic approaches should be considered. Colectomy may be lifesaving in some patients with fulminant CDAD. During an epidemic in Canada, emergency colectomy was associated with decreased odds of dying (odds ratio, 0.22), especially among patients with a WBC count greater than 20,000/mm³, lactate level of 2.2 to 4.9 mmol/L, or age 65 years or older [73]. Alternate routes of administration for traditional treatment...
agents can be considered for severe disease with ileus or toxic megacolon. Although intravenous metronidazole has not been compared with oral metronidazole or vancomycin, it may be useful in cases of toxic megacolon or severe ileus [74]. Vancomycin administered via nasogastric tube or via retention enema (0.5–1 g vancomycin in 1–2 L of 0.9% normal saline every 4–12 hours) can be beneficial in severely ill patients who cannot take oral medications [75].

Investigational Agents

Because standard therapy with metronidazole and vancomycin has become less effective, new approaches to treating CDAD are being investigated (Table 3). Nitazoxanide, an antiparasitic agent that interrupts anaerobic bacterial metabolism, has activity against C. difficile, achieves high colonic concentrations, and was found to be as effective as metronidazole for mild to moderate CDAD in a randomized controlled trial [76–78]. Tlevamer, a nonabsorbable nonantibiotic polymer that binds and neutralizes C. difficile toxins A and B, was not inferior to oral vancomycin in a double-blind randomized trial [79–81]. Rifaximin has good in vitro activity against C. difficile (including epidemic strains), achieves high colonic levels, and has been found to be effective in treatment of recurrent CDAD in case series [19,82–85]. Finally, both passive immunization using pooled human immunoglobulin and active immunization using a toxoid vaccine are being studied for prevention and treatment [86–89].

Recurrence

Recurrence of CDAD due to reinfection or relapse occurs in 5% to 30% of patients, with some experiencing multiple relapses [53]. In most instances, management of a first recurrence of CDAD can be accomplished with the same agent. Observational data during a CDAD epidemic in Canada, revealed no difference in risk of a second recurrence (approximately 33%) whether metronidazole or vancomycin was used for retreatment [90]. Risk of complications including shock, megacolon, perforation, colectomy, and death was high with first recurrence (11%) but did not vary significantly based on treatment [90].

Pulsed dose or tapered doses of vancomycin are commonly prescribed for recurrent CDAD and may have advantages over standard vancomycin therapy in this setting. Vancomycin given over a protracted time with either tapering or intermittent doses theoretically clears C. difficile by killing spores as they germinate. A randomized trial of patients with recurrent CDAD compared various regimens of vancomycin: pulsed (125–500 mg every 3 days for 3 weeks), tapered (decreasing dose over 21 days), high (500 mg 4 times daily for 10 days), and standard (250 mg 4 times daily for 10 days). Recurrence occurred in 14% with pulsed dosing, 31% with tapered dosing, 43% with high-dose vancomycin, and 54% with standard dose vancomycin [91]. In addition, 22 patients with recurrent CDAD were treated with a course of tapered vancomycin therapy followed by a final pulse of vancomycin with no recurrences reported at 6 months [92].

Anion exchange resins such as colestipol and cholestyramine, which absorb C. difficile toxin, have been used as adjunctive therapy for recurrent or refractory CDAD. Trials with colestipol alone showed poor responses, similar to placebo [93]. Cholestyramine alone at 4 g three to 4 times daily resulted in a 68% response rate in older trials [94]. Anion binding resins also bind vancomycin; therefore, resins should be taken 2 to 3 hours before or after vancomycin doses [95].

Probiotics, including Saccharomyces boulardii and Lactobacillus, have been used as adjunctive therapy to reestablish normal colonic flora in patients with CDAD. A meta-analysis of 6 randomized controlled trials evaluating use of probiotics in addition to standard antibiotic therapy for treatment of CDAD showed a pooled relative risk of 0.59 for recurrence; however, trials were heterogenous and the majority of the benefit resulted from 2 small trials evaluating S. boulardii [96–98]. At this time, there is insufficient evidence for routine clinical use of probiotics in the treatment of CDAD. In addition, there are reports of fungemia and deaths in patients who received probiotics for this purpose [99]. Probiotic therapy with stool transfers administered via nasogastric tube or enema have infrequently been used for refractory cases of CDAD with some success [100].

Prevention and Control

As antibiotic exposure is the major risk factor for development of CDAD, avoiding unnecessary use of antibiotics is important for decreasing the risk of CDAD in the individual patient (Table 4). Use of prophylactic vancomycin or metronidazole has not been shown to be beneficial and may increase the risk of CDAD [12,26]. There is little evidence that antibiotic restriction in general decreases the rate of C. difficile in a single institution; however, restriction of
cephalosporins or clindamycin has been successfully used in the outbreak setting [24,26].

A key measure for the prevention of CDAD is to interrupt transmission of the organism between patients in the hospital setting. The hands of health care providers have been shown to be readily contaminated by C. difficile; hand carriage correlates strongly with environmental contamination with C. difficile [34,101]. C. difficile spores are not killed by alcohol hand sanitizers; thus, handwashing with soap and water is recommended after caring for patients with CDAD [102]. Patients with CDAD should be placed in a private room if possible, and the use of gloves and gowns is recommended when in contact with the patient or contaminated environments [53]. Given potential delays in diagnosis and fallibility of available diagnostic tests, some advocate a syndromic approach to application of contact isolation to all patients with symptoms of diarrhea rather than contact isolation for specific pathogens such as C. difficile [103]. Because of the potential for heavy contamination of the environment with spores, cleaning of the patient room is important to prevent the spread of C. difficile [17,34,101]. A 1:10 dilution of bleach has been more effective than routine disinfection in decreasing rates of CDAD. Longer contact times and sometimes multiple cleanings are required [16,17,104]. Patient care items that are used between patients (eg, electronic thermometers) may transmit spores, and therefore replacement with disposable items or cleaning with bleach between patients is recommended [53,105].

Summary

CDAD continues to be a problem in the health care setting. This problem has been compounded by a new strain of C. difficile, BI/NAP1, which is associated with more fulminant disease, particularly in elderly patients. Standard antibiotic therapy for CDAD, specifically metronidazole and vancomycin is successful; however, it is associated with significant relapse rates of up to 30% [53]. Although new therapies are on the horizon, sound infection control and practices and rational antibiotic stewardship remain the best defense against CDAD.

Corresponding author: Sandro K. Cinti, MD, Ann Arbor Veterans Affairs Healthcare System, 2215 Fuller Rd., 111-I, 8th Fl., Ann Arbor, MI 48105, scinti@umich.edu

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References

C. DIFFICILE DISEASE


