Clostridium difficile-associated disease: New challenges from an established pathogen

ABSTRACT

Clostridium difficile-associated disease (CDAD) can range from uncomplicated diarrhea to sepsis and even death. CDAD rates and severity are increasing, possibly due to a new strain. Transmission of C difficile occurs primarily in health care facilities via the fecal-oral route following transient contamination of the hands of health care workers and patients; contamination of the patient care environment also plays an important role.

KEY POINTS

A recently identified strain of C difficile that has caused numerous outbreaks of clinically severe disease in North America and Europe produces 16 times more toxin A and 23 times more toxin B than other strains.

Since nosocomial CDAD is almost always associated with antimicrobial use, one should avoid unnecessary and inappropriate antimicrobial therapy.

If a patient has CDAD, the clinician must vigilantly monitor for disease progression and follow infection control guidelines to prevent spread to other patients.

Important principles in treating CDAD include stopping the offending antimicrobial agent if possible, giving metronidazole or vancomycin orally for no less than 10 days, and following patients closely for any signs of clinical progression during therapy.
lorazepam 1 mg three times a day, and prednisone in tapering doses. He had no known drug allergies and did not use alcohol or illicit drugs.

Laboratory values: white blood cell count 100 x 10⁹/L, hematocrit 62.3%, sodium 125 mmol/L, potassium 6.6 mmol/L, CO₂ 13 mmol/L, and metabolic acidosis.

An abdominal radiographic series showed no evidence of obstruction.

The patient was admitted to the intensive care unit and received fluids and pharmacologic support for hypotension, and metronidazole (Flagyl) 500 mg intravenously. Results of computed tomography of the abdomen were consistent with toxic megacolon.

The patient underwent emergent exploratory laparotomy, which revealed a swollen, edematous colon with pseudomembranes; a subtotal colectomy and ileostomy were performed. After surgery, he was given a second dose of intravenous metronidazole plus intravenous ciprofloxacin and vancomycin per rectum. Three days after surgery, the patient developed ventricular fibrillation that did not respond to several resuscitation attempts, and he died.

Discussion
Although no testing for C difficile was performed before the patient died, histopathologic findings in the resected colon in the patient’s rectum on autopsy were consistent with pseudomembranous colitis, a condition considered pathognomonic for C difficile (FIGURE 1). Moreover, an immunohistochemical stain for Clostridium species demonstrated numerous organisms within the pseudomembranes (FIGURE 2).

Factors contributing to CDAD and death in this patient include his receiving antimicrobial agents and proton-pump inhibitors, both of which are risk factors for CDAD. Additionally, he received narcotics, which may be a risk factor for toxic megacolon owing to their antiperistaltic effects.

This tragic death of a young, otherwise healthy man illustrates the serious potential complications of CDAD and the importance of preventing and controlling it.
INCORRECT IN INCIDENCE AND SEVERITY

C difficile is a gram-positive, spore-forming anaerobic bacillus that was first linked to disease in 1978, when it was identified as the causative agent of pseudomembranous colitis. It has been associated with gastrointestinal infections ranging in severity from asymptomatic colonization to severe diarrhea, pseudomembranous colitis, toxic megacolon, intestinal perforation, and death. C difficile toxins can be found in the stool of 15% to 25% of patients with antibiotic-associated diarrhea and more than 95% of patients with pseudomembranous colitis.

In US hospitals participating in the National Nosocomial Infections Surveillance System, there were an average of 12.2 reported cases of CDAD per 10,000 patient-days in the years 1987 to 1998. Rates were significantly higher in teaching than in non-teaching hospitals (13.0 vs 11.7 cases per 10,000 patient-days), in medical than in surgical services, and in winter months than in nonwinter months.

Data from the US Centers for Disease Control and Prevention (CDC) reveal that hospitalizations with a discharge diagnosis of CDAD have significantly increased from 31 per 100,000 population in 1996 to 61 per 100,000 in 2003. Of patients who contracted CDAD in hospitals or nursing homes, 0.6% to 1.5% died, and CDAD was either the direct or indirect cause of death. CDAD has been estimated to cost an additional $3,669 to $7,234 per patient hospitalization. Moreover, the severity of observed disease may also be increasing, with an attributable 1-year mortality rate approaching 17% in one study.

Risk factors for CDAD

Antibiotic therapy. More than 90% of health-care-associated C difficile infections occur after or during antimicrobial therapy. Almost all antibiotics except for aminoglycosides have been associated with CDAD. A meta-analysis by Bigardi suggests that broad-spectrum antimicrobial agents, which have a greater effect on the normal intestinal flora, are more likely to lead to CDAD. However, several later studies found fluoroquinolones to be more strongly linked to CDAD than any other antimicrobial agents, including clindamycin and beta-lactam/beta-lactamase inhibitors. The risk is also greater when patients receive multiple antimicrobial agents and undergo a longer course of therapy.

Other risk factors (cited in at least three studies) are:
- Age greater than 65 years
- Severe underlying illness
- Nasogastric intubation
- Antiulcer medications. (There is conflicting evidence regarding the role of proton-pump inhibitors and histamine receptor antagonists in CDAD.)
- Longer hospital stay.

Specific populations appear to be at greater risk for developing CDAD than the general population. Most cases of CDAD occur in health care settings, as do most CDAD outbreaks. Among hospitalized patients, several studies have found that medical patients are at significantly higher risk of CDAD than surgical patients.

Additionally, C difficile is the most common infectious cause of acute diarrheal illness in long-term-care facilities. Even when an outbreak is not going on, the prevalence of C difficile colonization in long-term-care facilities ranges from 4% to 20%, compared with less than 3% in healthy adults. Compared with the general population, long-term care residents also are older and receive more antibiotics and antacids—all of which are known risk factors for CDAD. These additional risk factors make it difficult to determine which factors contribute most to the increased risk.

Neonates also have more C difficile colonization, with cited rates ranging from 5% to 70%. Paradoxically, neonates carrying toxigenic strains of C difficile are much less likely than adults to develop symptomatic disease. The reason, based on observations in rabbits, may be that neonates lack receptors for toxin A in their immature enterocytes.

HOW C DIFFICILE CAUSES DISEASE

For C difficile to establish itself and proliferate in the colonic mucosa, the normal flora of the
colon must be disrupted (as with antimicrobials) and \textit{C difficile} must be ingested (\textbf{FIGURE 3}). Although these events need not necessarily occur in that order,\textsuperscript{20} once both of them occur, the patient can become colonized or develop CDAD.

**Toxins are essential for disease**

It is unclear why some patients develop disease and others do not; however, toxin production is essential for disease to occur.

\textit{C difficile}'s primary virulence factors are toxins A and B, which are responsible for inflammation, fluid and mucous secretion, and mucosal damage (\textbf{FIGURE 1}), which lead to diarrhea or colitis.\textsuperscript{23}

A recently identified strain of \textit{C difficile}, designated North American pulsed-field gel electrophoresis type 1 (NAP 1), has caused numerous outbreaks of clinically severe disease in North America and Europe. NAP 1 produces 16 times more toxin A and 23 times more toxin B than other strains,\textsuperscript{29,30} possibly due to a deletion in a negative regulatory gene.\textsuperscript{30} In addition, NAP 1 produces a third toxin, known as binary toxin, although its significance is unknown. This new strain is resistant to both gatifloxacin and moxifloxacin, which is a new finding compared with historical strains.

**Colonization, immunity**

Only toxigenic strains of \textit{C difficile} produce clinical disease, but toxin production does not guarantee symptomatic progression.\textsuperscript{23} Other host factors can influence the clinical presentation, such as preexisting colonization with \textit{C difficile} and humoral immunity.

Some suggest that colonization with \textit{C difficile} can actually protect against symptomatic disease,\textsuperscript{31} due to the development of immunity. Kyne and colleagues\textsuperscript{32} demonstrated that asymptomatic carriers had significantly greater antibody responses to toxin A than those who developed nosocomial CDAD.

### CLINICAL PRESENTATION VARIES

The incubation period from ingestion of \textit{C difficile} to manifestation of disease has not been established. Symptoms can appear immediately after beginning antimicrobial therapy, or they may not develop until several weeks after it is completed.\textsuperscript{23} In one study of cancer outpatients,\textsuperscript{33} the median interval from hospital discharge to CDAD diagnosis was 20.3 days (range 2–60 days)—a considerable delay in disease onset.

The clinical presentation of \textit{C difficile} is a continuum that includes asymptomatic carriage, diarrhea, colitis, pseudomembranous colitis, and fulminant colitis.\textsuperscript{23}

**Mild disease**

Most often, CDAD presents as mild to moderate nonbloody diarrhea, sometimes accompanied by low abdominal cramping. Systemic symptoms are typically absent, and physical examination is remarkable only for mild abdominal tenderness.

**Severe disease**

Colitis, in contrast, tends to present with more severe symptoms, including profuse watery diarrhea and abdominal pain and distention. Fever, nausea, and dehydration are often present. There may be occult blood in the stool, but hematochezia is rare. Sigmoidoscopy reveals a characteristic membrane with adherent yellow plaques, usually in the distal colon, although occasionally it can be confined to the proximal colon and can be missed on examination.

Once severe or systemic symptoms develop, appropriate treatment is crucial to prevent progression to more severe disease.

Patients with severe colitis are at increased risk of developing paralytic ileus and toxic megacolon.\textsuperscript{23} These may lead to a paradoxical decrease in diarrhea. Such severe cases may also present as fulminant colitis, with an acute abdomen and systemic symptoms such as fever and tachycardia, as in our case presentation. Such complications require an immediate surgical consult. Of 11 patients with toxic megacolon, 7 (64%) needed surgery, and once patients undergo surgery for complications of CDAD, the mortality rate rises to 32% to 50%.\textsuperscript{34}

**Reinfection or relapse?**

Recurrence is one of the most frustrating and challenging complications of CDAD.

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\textbf{Quinolones may be more strongly linked to CDAD than other antibiotics}
Pathogenesis of *C. difficile*-associated disease

*Clostridium difficile* is spread via the fecal-oral route. The organism is ingested either as the vegetative form or as hardy spores, which can survive for long periods in the environment and can traverse the acidic stomach.

In the large intestine, *C. difficile*-associated disease can arise if the normal flora has been disrupted by antibiotic therapy.

In the small intestine, spores germinate into the vegetative form.

*C. difficile* reproduces in the intestinal crypts, releasing toxins A and B, causing severe inflammation. Mucous and cellular debris are expelled, leading to the formation of pseudomembranes.

Toxin A attracts neutrophils and monocytes, and toxin B degrades the colonic epithelial cells, both leading to colitis, pseudomembrane formation, and watery diarrhea.
There is no universal agreement on how to clinically distinguish whether a second episode of CDAD is a reinfection or a relapse. One definition of a relapse is a recurrence of symptoms within 2 months of CDAD diagnosis; a reinfection is a recurrence of symptoms after 2 months. However, studies of patients who were thought to have had a relapse within 2 months of a previous CDAD episode indicate that 48% to 56% were actually reinfected with a different strain of *C. difficile*.36,37

Be it a reinfection or a true relapse, 12% to 24% of patients develop a second episode of CDAD within 2 months of the initial diagnosis. If a patient has two or more episodes of CDAD, the risk of additional recurrences increases to 50% to 65%.34

These statistics highlight the importance of preventive strategies (see below).

## DIAGNOSIS

*C. difficile* should be suspected in any adult with antimicrobial-associated diarrhea, and CDAD can occur up to several months after antimicrobial treatment is ended.26,33

Only watery or loose stools should be tested for *C. difficile* because the rate of colonization is high: a positive result in a normal stool sample proves that the patient is colonized with *C. difficile* but not necessarily infected.38

The primary exception to this rule is when you suspect CDAD in a patient with intestinal

### Table 1

<table>
<thead>
<tr>
<th>Diagnostic Test</th>
<th>Turn-Around Time</th>
<th>Sensitivity</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endoscopy</td>
<td>2 hours</td>
<td>51%</td>
<td>Diagnostic of pseudomembranous colitis</td>
<td>Low sensitivity</td>
</tr>
<tr>
<td>Anaerobic culture</td>
<td>72 hours</td>
<td>89%–100%</td>
<td>Results useful for molecular typing</td>
<td>Does not distinguish toxin-producing strains</td>
</tr>
<tr>
<td>Tissue cytotoxic assay</td>
<td>48 hours</td>
<td>94%–100%</td>
<td>Detects A-B+ strains Gold standard</td>
<td>False-positives Results vary with experience of the technologist</td>
</tr>
<tr>
<td>Common antigen</td>
<td>15–45 minutes</td>
<td>58%–92%</td>
<td>Detects A-B+ strains Easy to use</td>
<td>Does not distinguish toxin-producing strains Cross-reacts with other anaerobes</td>
</tr>
<tr>
<td>Enzyme-linked immunosorbent assay (ELISA)—toxin A</td>
<td>2 hours</td>
<td>80%–95%</td>
<td>Easy to use</td>
<td>Does not detect A-B+ strains</td>
</tr>
<tr>
<td>ELISA—toxin A + B</td>
<td>2 hours</td>
<td></td>
<td>Detects A-B+ strains Increased sensitivity for low-level toxin production</td>
<td></td>
</tr>
<tr>
<td>Immunochromatographic toxin A</td>
<td>&lt; 1 hour</td>
<td>60%–85%</td>
<td>Simple to use Rapid</td>
<td>Does not detect A-B+ strains</td>
</tr>
</tbody>
</table>

ileus, which occurs in fewer than 1% of cases. Since most laboratories will not accept solid stool for C. difficile testing, the clinician should notify the laboratory of the specific circumstances of the patient.

In general, empiric therapy without testing for C. difficile is inappropriate, since only 30% of hospitalized patients with diarrhea have CDAD, even in an epidemic setting. Exceptions include severely ill or rapidly deteriorating patients at high risk for CDAD, in whom empiric therapy may be appropriate while awaiting test results.

There are a variety of tests for C. difficile, each with advantages and disadvantages (Table 1). Factors to consider when selecting a diagnostic test include turnaround time, sensitivity, specificity, cost, whether there is an ongoing outbreak, and, of course, availability.

Enzyme immunoassays, available in most clinical laboratories, are fast and require less technical expertise than tissue culture. Although the negative predictive value hinges on the sensitivity of the particular assay, in most cases one negative result is enough to rule out CDAD. Nonetheless, a high clinical suspicion may warrant repeat testing.

Anaerobic bacterial culture is the method employed least by hospitals to diagnose CDAD, owing to its cost and turnaround time of approximately 72 hours. In addition, this method’s accuracy varies considerably in different laboratories because the methods and culture media are not standardized. The primary advantage of anaerobic culture is that it lends itself to molecular typing of strains, which may be useful in an outbreak.

### TREATMENT

**Stop the inciting antibiotic**

Stopping the inciting antibiotic is the most important step in the initial treatment of CDAD. Up to 25% of patients with CDAD recover without further therapy; in a series from 1974, before there was effective therapy for CDAD, all 20 patients with pseudomembranous colitis eventually recovered after clindamycin treatment was stopped.

**Oral metronidazole for mild disease; vancomycin for severe**

In addition to stopping the inciting antibiotic, appropriate oral antimicrobial therapy directed specifically against C. difficile should be given for 10 days to treat mild to moderate CDAD.

In a study of 189 patients with CDAD, 97% responded to initial antibiotic therapy.

Although most patients in this study received oral vancomycin, several older studies comparing oral metronidazole to oral vancomycin for the treatment of CDAD indicate that metronidazole has been, at least historically, as effective as oral vancomycin and less expensive. In addition, widespread use of oral vancomycin could lead to vancomycin resistance. For these reasons, most experts recommend metronidazole as the first-line antimicrobial therapy for CDAD.

Recently, however, a prospective observational study reported that the response rate with metronidazole was only 78%—significantly lower than previously published rates of response to oral vancomycin and oral metronidazole.

In an accompanying editorial to that report, Dr. Dale Gerding commented on the significance of these and other data, taking into account the recent emergence of a more virulent strain of C. difficile as described above. He concluded that metronidazole is an appropriate first-line treatment for most cases of CDAD, provided that the clinician is vigilant about monitoring the response to therapy. He indicated, however, that an alternative first-line therapy, such as oral or intraluminal vancomycin, should be considered for patients who present with moderate or severe disease.

**CDAD can progress quickly**

Along the same lines, it is important to realize that mild CDAD can quickly progress to moderate or severe disease and that these distinctions are not always easy to make.

Specific signs and symptoms of moderate disease may include fever, profuse diarrhea, abdominal pain, and leukocytosis. Severe disease is defined as the presence of complications of colitis, such as sepsis, volume depletion, electrolyte imbalance, hypotension, peritonitis, paralytic ileus, and toxic shock syndrome.
megacolon. Some also include a white blood cell count of greater than $20 \times 10^9/L$ and elevated creatinine as indicators of severe disease.

Patients with signs of severe disease should receive oral vancomycin as initial therapy. Consider surgery if CDAD progresses

Because CDAD can progress despite appropriate therapy, the clinician should follow the patient closely to see if symptoms improve within 1 to 2 days of starting therapy. Fever should subside within 24 to 48 hours and diarrhea should resolve within 2 to 5 days. If the disease progresses after starting treatment, additional or alternative therapeutic options should be considered, including a surgical consult for any signs of toxic megacolon, peritonitis, or sepsis (TABLE 2). However, if the patient's condition does not deteriorate, one should not conclude that treatment has failed before 6 to 7 days of therapy.

If oral therapy cannot be given

In some circumstances, oral therapy cannot be given, especially in severely ill or postoperative patients. In these situations, intraluminal vancomycin has been shown to be effective. The role of intravenous metronidazole for CDAD has yet to be determined, although high concentrations of metronidazole have been found in the stool after intravenous administration.

Alternative regimens

Many alternative regimens for CDAD have been explored, including different dosing strategies for vancomycin, other antimicrobials, probiotics, bacteriotherapy, adsorbents, and immunotherapy. No regimen has proven to be significantly more effective than oral vancomycin or metronidazole for first-line therapy.

Some studies suggest, however, that treatment of recurrent CDAD with pulsed or tapered dosing of oral vancomycin may reduce recurrence rates. Some evidence also supports the use of probiotics such as *Saccharomyces boulardii* or *Lactobacillus* species in conjunction with vancomycin or metronidazole to reduce the recurrence rate of CDAD.

In 84 reported cases, fecal enemas were given to replace the microflora disrupted by *C difficile* and antimicrobials; the recurrence rate was 10%. However, there have been no randomized controlled trials of this strategy.

Adsorbents such as ion-exchange resins and polymers, which, in theory, bind the C

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<tr>
<th>DISEASE/HOST CHARACTERISTICS</th>
<th>RECOMMENDED THERAPY</th>
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<tr>
<td>Mild disease (No systemic symptoms, only mild diarrhea)</td>
<td>Metronidazole 250 mg by mouth four times a day or 500 mg by mouth three times a day for 10 days</td>
</tr>
<tr>
<td>Moderate disease (Fever, profuse diarrhea, abdominal pain, leukocytosis)</td>
<td>Vancomycin 125–500 mg by mouth four times a day for 10 days</td>
</tr>
<tr>
<td>Severe disease (Paralytic ileus, toxic megacolon, dehydration or sepsis)</td>
<td>Surgical consult plus intraluminal vancomycin</td>
</tr>
<tr>
<td>Inability to take oral medications</td>
<td>Intraluminal vancomycin with or without intravenous metronidazole</td>
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**TABLE 2** Therapeutic options for *C difficile*-associated disease
difficile toxins in the colonic lumen before they can attach to enterocytes and cause disease, have also been tried. Although studies in animals were promising, human studies have not shown currently available agents to be superior to standard therapies. In fact, cholestyramine has actually been shown to bind to vancomycin, leading to suboptimal drug levels.

Intravenous immunoglobulin has demonstrated some positive results according to case reports, but no randomized controlled trials have been done.34

Avoid antiperistaltic agents
Antiperistaltic agents should not be given, either alone or in conjunction with other therapy.5,6 This recommendation is based on anecdotal data indicating that diphenoxylate and atropine may predispose patients with CDAD to toxic megacolon. Since narcotics also have antiperistaltic effects, they too should be avoided in patients with CDAD.5,6 Narcotics may have contributed to the poor outcome of the case described at the beginning of this article.

Gauge response to therapy on signs and symptoms
Therapeutic response should be based purely on clinical signs and symptoms: a repeat toxin assay should not be done as a “test of cure,” since patients may remain colonized with toxin-producing strains following recovery.52

Do not treat asymptomatic colonization
Current therapies are ineffective for eradicating asymptomatic colonization. Vancomycin has been studied for this purpose. However, experts do not recommend treating patients colonized with C difficile as an infection control strategy.42 Its effects are not sustained and patients may be at increased risk for prolonged carriage after treatment ends.

Significant intraluminal levels of metronidazole are achieved only in the presence of diarrhea, which renders the drug ineffective for patients with asymptomatic colonization.36

■ PREVENTION

Two approaches to the prevention of CDAD include infection control, thus interrupting the horizontal spread of C difficile within health care facilities, and reducing the individual patient’s risk of acquiring the disease once exposed to the organism.38 Probiotic agents have been studied as prophylaxis in patients receiving antimicrobial agents, but no statistically significant difference in rates of CDAD has been seen.38

Contact precautions
Spread of C difficile in health care facilities has been well documented, occurring primarily person to person (from people with or without symptoms) and via contamination of the patient care environment.38,53 The most effective means of decreasing horizontal spread of C difficile has been a combination of vigilant hand hygiene and use of isolation precautions.36

The literature contains both direct and indirect evidence for contamination of health care workers’ hands in endemic and outbreak settings. Alcohol is not effective in killing C difficile spores. Therefore, if a hospital is experiencing an outbreak, it is prudent for health care workers to wash their hands exclusively with soap and water when caring for patients with known CDAD.54

The 1994 Hospital Infection Control Practices Advisory Committee (HICPAC) Guideline for Isolation Precautions in Hospitals recommends contact precautions for symptomatic patients. These include placing patients in private rooms or cohorting (grouping patients in a designated area) and donning gowns and gloves when entering the patient’s room.55 One hospital reported a 60% decrease in CDAD incidence after instituting a more stringent infection control program, including increased enforcement of contact precautions, a monthly educational program, triclosan-containing hand soap, and increased environmental cleaning.56

Bleach for environmental disinfection
Environmental contamination of C difficile is due to persistence of spores that can be highly resistant to routine disinfectants and can survive on dry surfaces for many weeks or months. The rate of surface contamination increases in proportion to the C difficile status, severity of diarrhea, and incontinence of
patients in the area. Environments of asymptomatic carriers have lower rates than those of patients with symptomatic disease.\(^{38}\)

Patient-care items such as reusable electronic rectal thermometers have been implicated in outbreaks, and dedication of single-use items to individual patients can eliminate this source of contamination.\(^{24,38}\) “High-touch” surfaces in patients’ bathrooms (eg, light switches) have also been implicated in outbreaks and should be targeted for enhanced environmental cleaning.

No well-controlled trials of disinfectants have been conducted; however, use of both unbuffered and phosphate-buffered hypochlorite solutions (bleach) has been shown to decrease rates of \textit{C. difficile} contamination, and some studies suggest that cleaning with bleach may lower CDAD rates.\(^{57–59}\) Although no disinfectants are registered with the Environmental Protection Agency with a claim for \textit{C. difficile} spore inactivation, the HICPAC Guideline for Environmental Infection Control in Healthcare Facilities recommends “meticulous cleaning followed by disinfection using hypochlorite-based germicides as appropriate.”\(^{60}\) Dilutions and schedule of mixing bleach solutions for this purpose can be found in the HICPAC guideline.

**Restrict antibiotic use?**

Since prior antimicrobial use is associated with the vast majority of patients who develop health-care-associated CDAD, restricting the use of specific antimicrobial agents would seem to be an important infection-control strategy to reduce patient risk. Unfortunately, with the exception of clindamycin restriction, few reports demonstrate success of this approach.

However, reduction of unnecessary antimicrobial use in general would reduce the risk of CDAD in all patients. Clinicians who have treated patients with severe or recurrent CDAD may gain an increased appreciation of the serious risks associated with unnecessary antimicrobial therapy.

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**REFERENCES**


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