**Clostridium difficile** Infection
Clinical Challenges and Management Strategies

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_Clostridium difficile_ has become the leading cause of nosocomial diarrhea in adults. A substantial increase has occurred in morbidity and mortality associated with disease caused by _C difficile_ and in the identification of new hypervirulent strains, warranting a high clinical index of suspicion for infections due to this organism. Prevention of infection requires a multidisciplinary approach, including early recognition of disease, effective contact isolation precautions, adherence to disinfectant policies, and judicious use of antibiotics. Current treatment approaches are based on the severity of illness. As hypervirulent strains evolve, unsuccessful treatments are more common. Complicated colitis caused by _C difficile_ may benefit from surgical intervention. Subtotal colectomy and end ileostomy have been the procedures of choice, but are associated with a high mortality rate because of late surgical consultation and use of surgery as a salvage therapy. A promising surgical alternative is creation of a diverting loop ileostomy with colonic lavage. (*Critical Care Nurse*. 2014;34[4]:24-35)

This article has been designated for CNE credit. A closed-book, multiple-choice examination follows this article, which tests your knowledge of the following objectives:

1. Identify symptoms of _Clostridium difficile_ infection (CDI)
2. Describe strategies to prevent transmission of CDI
3. Identify treatment options for CDI

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Epidemiology and Pathogenesis

Whereas other hospital-associated infections have declined since 2001, the incidence of CDI has increased. Reports from the Agency of Healthcare Research and Quality indicate that the number of CDI diagnoses at the time of hospital discharge more than doubled in the United States, from 139,000 to 301,200, from 2001 through 2005. According to Redelings et al, reported mortality rates for C difficile disease in the United States increased from 5.7 per million population in 1999 to 23.7 per million in 2004. The upward trend continues, according to a 2008 Nationwide Inpatient Sample, which recorded nearly 350,000 CDI diagnoses at the time of discharge from acute care hospitals. Currently, C difficile is estimated to be responsible for more than 500,000 infections each year, the majority of which are hospital acquired. More alarming is the 9% mortality associated with CDI compared with less than 2% for all other types of admissions. As the incidence of CDI increases, so does the severity of the infection.

The greatest concern about CDI is its progression to complicated or fulminant colitis, which is often refractory to medical management. Progression is often rapid and can lead to shock and death despite treatment. Increases in the severity of CDI may be related to its evolving virulence since 1990. Most notably, a 2003 review of 1771 cases in Quebec, Canada, later identified as an outbreak, revealed that the number of CDI cases had more than quadrupled since 1991. The marked increases in frequency and severity of this outbreak were attributed to a single, hypervirulent strain that was present in 82% of the patients in this population. The strain is known as Clostridium difficile NAB1/B1/027 or NAP-1/027, and it has been linked to changes in disease pathogenesis in both Europe and North America.

Since its emergence, NAP-1/027 has been directly linked to increased mortality due to fulminant colitis. Investigators have described several unique properties of this strain that account for fulminant colitis. The major virulence determinants of CDI are its ability to hyperproduce toxins A and B and to produce a binary toxin, which are notable in the NAP-1/027 strain. Toxin A, an enterotoxin, and toxin B, a cytotoxin, can cause disruption of the epithelial mucosal surface, leading to marked colonic inflammation. Some NAP-1/027 isolates have mutation of tcdC, the gene responsible for inhibition of toxin transcription during the bacterial growth phase. This deletion mutation in strain NAP-1/027 leads to toxin production 10 times greater than that of other less virulent strains. Another virulence factor that most likely contributes to CDI severity is the higher rate of germination of some strains of NAP-1/027. One study suggests that a higher germination rate may contribute to disease recurrence.

In summary, several features of this ribotype may contribute to its increased virulence. These include genetic divergence from other strains that enhances cell tropism, mutation in the tcdC gene that may result in a removal of log-phase repression of toxin expression, and increased sporulation. Finally, NAP-1/027 and other hypervirulent strains have high-level resistance to fluoroquinolones. Currently, this strain accounts for more than 35% of all strains recovered from patients with CDIs.

Upon entry into the cell, toxin A or toxin B targets Rho GTPases, which play a central role in, but are not limited to, organization of the actin cytoskeleton, control of the barrier function of epithelial cells, and the signaling and motility of host immune cells. Subsequent inactivation of the Rho GTPases by toxin A or B results in shrinkage of the host cell by degradation of the actin cytoskeleton, resulting in the loss of structural integrity and apoptosis. Collectively, these changes lead to the loss of the barrier function of the intestines. The normally tight junctions among epithelial cells are disrupted, allowing migration of granulocytic cells into the intestines and exacerbating the inflammatory response associated with colitis. The compromised epithelial barrier leads to increased permeability and fluid accumulation and then diarrhea. The majority of C difficile strains produce both A and B toxins, but some patients are colonized...
with non–toxin-producing strains that are nonpathogenic. These patients are asymptomatic carriers of C difficile, and CDI does not develop unless the patients are also infected with a toxin-producing strain.\textsuperscript{20}

### Risk Factors

Despite changes in C difficile pathogenicity since 1990, the most important risk factor for CDI continues to be recent administration of antibiotics (within the preceding 3 months). In a recent study by Chitnis et al,\textsuperscript{21} 64.1% of patients with community-associated CDI had received antibiotics within 12 weeks of collection of a stool specimen positive for C difficile. Kelly and Lamont\textsuperscript{22} reported the same results for up to 96% of patients. Antibiotic use alters the normal gastrointestinal flora, a change that can facilitate the colonization and proliferation of C difficile. Although all antibiotics have been linked to CDI, the ones implicated most often are clindamycin, fluoroquinolones, cephalosporins, and β-lactams.\textsuperscript{23} Historically, CDI was thought to affect elderly and immunosuppressed patients. Nowadays many other well-established risk factors are associated with CDI (eg, prolonged hospitalization, previous gastrointestinal surgery, comorbid conditions such as inflammatory bowel disease, neoplastic diseases and antineoplastic chemotherapy, solid-organ or hematopoietic cell transplant, male sex, malnutrition, postpyloric tube feeding, and low serum albumin level).\textsuperscript{24} Frequent use of broad-spectrum antibiotics is the most widely recognized modifiable risk factor.\textsuperscript{24}

Observational studies have suggested that the use of proton pump inhibitors (PPIs) may be a risk factor for both incident and recurrent CDIs. Barletta et al\textsuperscript{25} found a significant relationship between PPIs and the development of CDI. Patients in whom CDI developed were more likely to have received a PPI (76% vs 39%; \textit{P} < .001) and have had a longer duration of PPI therapy than those who did not have CDI. The probability for CDI was higher when PPI use exceeded 2 days in patients without a previous hospital admission and 1 day in patients with a previous admission (odds ratios, 1.14; 95% CI, 1.02–1.27; \textit{P} = .02). Data on PPIs and their association with CDI remain controversial, but clinicians should strongly consider restricting PPI use.

### Clinical Manifestations and Spectrum of Disease

Like most infections caused by enteric pathogens, CDI results in a wide spectrum of clinical manifestations, from no signs and symptoms (asymptomatic carriers) to peritonitis associated with colonic perforation.

Patients with mild CDI usually have crampy abdominal pain with mild to moderate diarrhea only. Patients with moderate CDI have diarrhea and any additional signs or symptoms not indicative of severe CDI. A diagnosis of severe CDI is made when a patient has 2 of the following signs and symptoms: white blood cell count greater than 15 000/μL, serum level of albumin less than 3 g/L, or abdominal tenderness.\textsuperscript{26}

Complicated CDI, sometimes referred to as fulminant colitis, is marked by severe abdominal pain, abdominal distention, worsening diarrhea, and any of the following: need for admission to the intensive care unit, hypotension, altered mental status, end organ failure (intubation, acute kidney failure, temperature > 38.5°C, white blood cell count >35 000/µL, or serum lactate level >2.2 mg/dL [to convert to millimoles per liter, multiply by 0.111]).\textsuperscript{26} Fulminant colitis occurs in 2% to 5% of patients with CDI but is associated with a mortality rate of 35% to 80%.\textsuperscript{27} A lack of diarrhea in a patient with worsening abdominal distention and systemic illness is an ominous finding and is indicative of ileus and intestinal failure. Patients may be hypotensive and require support with vasopressors and may have other signs and symptoms of end organ failure, including respiratory failure and acute kidney failure. Fortunately, colonic perforation or necrosis is quite rare. We think that colonic necrosis or perforation is not primarily associated with the disease process and occurs only as a result of the development of abdominal compartment syndrome or nonocclusive mesenteric ischemia in patients with complicated disease.\textsuperscript{27} The aforementioned criteria for classifying patients as having “complicated” disease are defined in the recent guidelines of the American College of Gastroenterology.\textsuperscript{26} The guidelines are based on a combination of multivariate analyses, findings of multiple case series, and the recommendations of the European Society of Clinical Microbiology and Infectious Diseases.\textsuperscript{26,28}

Recurrent CDI should be considered in patients who have recurrent diarrhea within a few weeks of completion of medical treatment for CDI (either vancomycin or metronidazole).\textsuperscript{29} Although the pathology is not entirely
clear, a persistently altered fecal flora and an impaired immune response to *C difficile* and its toxins may be a factor. Approximately 5% to 25% of patients treated for CDI relapse after successful treatment. Well recognized, but often less encountered, are the extracolonic manifestations of CDI. These manifestations occur in a variety of organ systems: bacteremia, small-bowel infections, reactive arthritis, and miscellaneous infectious processes, including necrotizing fasciitis, osteomyelitis, and cellulitis.

Atypical manifestations are common among older adults, making diagnosis more challenging. A fever generally indicates a more serious infection in older patients; therefore, fever may or may not be present in an elderly patient with CDI. Earlier signs and symptoms of CDI in elderly patients include acute confusion and altered mental status. Even more nonspecific indications may include lethargy, weakness, falls, anorexia, and general loss of physical functional capacity.

**Diagnosis**

The diagnosis of CDI requires accurate and rapid results for individual patient management and prevention of nosocomial transmission. Only diarrheal stool should be sent for diagnostic testing. Several laboratory tests can verify the presence of toxin-producing *C difficile*; however, marked discrepancies in test performance have been reported. Consequently, neither clear nor consistent guidelines exist. Current laboratory methods (see Table) include toxigenic culture and cell cytotoxicity neutralization assay, enzyme immunoassay for toxin (TcdA or TcdB) or common antigen (glutamate dehydrogenase), and real-time polymerase chain reaction.

Anaerobic culture of *C difficile* from stool is a sensitive test, but the result is not specific for CDI because this organism is part of the normal intestinal flora in 4% of healthy persons and 20% to 25% of *C difficile* do not produce toxins. In toxigenic culture testing, *C difficile* are isolated from stool by enriching for spores and inoculating the spores onto an anaerobic culture medium. After several days of incubation, colonies are isolated and identified. Once confirmed as *C difficile*, strains are further tested for the B toxin (TcdB) and observed for cytopathic effects. Toxigenic culture testing remains the gold standard for laboratory diagnosis because of its high sensitivity (94%-100%) and high specificity (99%). However, the process is time-consuming and labor intensive, taking up to 5 days for results, and therefore is not clinically applicable for high-volume testing.

Unlike toxigenic culture testing, the cell cytotoxicity neutralization assay specifically detects TcdB in stool specimens that have been suspended in the transport medium. The suspension is filtered to separate viruses and bacteria from the toxin, and samples of the filtrate are inoculated onto tissue culture cells with or without antibodies to TcdB. The tissue cultures are incubated and observed for neutralization or cytopathic activity. In both sets of tissue cultures (with and without antibodies), the cells inoculated with specimens negative for *C difficile* toxin B remain unchanged. Specimens positive for the toxin cause cytopathic changes in cultures that have no antibodies and no cytopathic changes (neutralization) in cultures that have the antibodies. Although the

**Table** Performance characteristics of *Clostridium difficile* laboratory tests compared with toxigenic culture

<table>
<thead>
<tr>
<th>Method</th>
<th>Sensitivity, %</th>
<th>Specificity, %</th>
<th>Positive predictive value, %&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Negative predictive value, %&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Assay time</th>
<th>Cost, $</th>
</tr>
</thead>
<tbody>
<tr>
<td>Toxigenic culture</td>
<td>94-100</td>
<td>99</td>
<td>NA</td>
<td>NA</td>
<td>2-5 days</td>
<td>~8</td>
</tr>
<tr>
<td>Cell culture neutralization assay</td>
<td>75-100</td>
<td>100</td>
<td>92</td>
<td>99</td>
<td>2-4 days</td>
<td>~5</td>
</tr>
<tr>
<td>Toxin A/B enzyme immunoassay</td>
<td>63-92</td>
<td>91-98</td>
<td>48-97</td>
<td>95-98</td>
<td>15-100 minutes</td>
<td>10-20</td>
</tr>
<tr>
<td>Glutamate dehydrogenase</td>
<td>87-90</td>
<td>94</td>
<td>63</td>
<td>99</td>
<td>15-100 minutes</td>
<td>10-20</td>
</tr>
<tr>
<td><em>C difficile</em> nucleic acid amplification</td>
<td>77-99</td>
<td>94-100</td>
<td>68</td>
<td>99</td>
<td>&lt;1-3 hours</td>
<td>25-50</td>
</tr>
</tbody>
</table>

Abbreviation: NA, not applicable.
<sup>a</sup> Based on information from Eastwood et al.<sup>31</sup>
<sup>b</sup> Assumes 10% prevalence of disease.
sensitivity of the cell cytotoxicity neutralization assay is 75% to 100%, specificity remains near 100%. This test is also criticized for its turnaround time, which is 2 to 4 days.\(^{35}\)

In an attempt to provide quicker laboratory results, many facilities have adopted an enzyme-linked immunoassay (ELISA) to detect both toxins A and B in stool samples. Results can be obtained quickly, in 2 to 6 hours. Stool is diluted and added to microwells coated with toxin A and B polyclonal antibodies. In specimens positive for toxin, the complexes of toxin and antibodies remain after washing and are detected via a colorimetric reaction. Although rapid and inexpensive, performance of immunoassays varies widely. The sensitivity of ELISA is 63% to 92%, and false-negative results are possible.\(^{36}\)

A second ELISA targets glutamate dehydrogenase (GDH), a common \textit{C difficile} antigen that is secreted into the stool.\(^{34}\) GDH is an enzyme present in microbes that converts glutamate to \(\alpha\)-ketoglutarate and vice versa. The presence of GDH is not specific to \textit{C difficile} and does not confirm the presence of a strain of \textit{C difficile}. Detection of GDH, however, can be used as an initial screening assay, because lack of the enzyme in stool is strongly predictive of the absence of \textit{C difficile}.\(^{37}\) The sensitivity most likely is 87% to 90%,\(^{31}\) which is a major limitation of this assay. GDH-positive specimens are further investigated by using any of the other laboratory studies.

Nucleic acid amplification (NAAT), the newest commercially available method for detection of \textit{C difficile}, is based on amplifying \textit{C difficile} DNA as a marker of CDI. Current NAAT methods include real-time polymerase chain reaction, DNA microarray, and loop-mediated isothermal amplification.\(^{38}\) The Food and Drug Administration has currently approved 4 assays. Tests show either a positive or a negative result in anywhere from 45 minutes to 2 hours. Sensitivity among the NAATs is 77% to 99% and specificity is 94% to 100%,\(^{33}\) and the test has clear time-related advantages. For these reasons, techniques based on real-time polymerase chain reaction are becoming the preferred diagnostic test for detection of \textit{C difficile} in many institutions.

No single test or testing strategy is significantly better than others for use in the clinical care of patients. When sensitivity, specificity, and turnaround time are considered, we advocate cytotoxicity culture assay or NAAT. Some laboratories advocate a modified 2- or 3-step algorithm with a combination of ELISA, GDH testing, and/or NAAT (see Figure).

Abdominal computed tomography (CT) has emerged as a valuable diagnostic tool in detecting complicated CDI. In a retrospective study by Imbriaco and Balthazar\(^{40}\) of patients with severe CDI, CT scans were useful in detecting signs of severe colitis: diffuse colonic thickening, multilayered appearance caused by different densities of edematous submucosa and hypermucosa (target sign), pericolic stranding, and thickened haustra with alternating bands of low and high density (accordion sign), which is thought to be specific for CDI. CT was also sensitive in detecting early stages of CDI, revealing colonic wall thickening greater than 4 mm with surrounding edema.\(^{41,42}\) The positive predictive value of CT scans for diagnosing \textit{C difficile} is as high as 88%.\(^{43}\) The results can also help rule out other differential diagnoses of abdominal pain and may assist in monitoring the efficacy of treatment.

Endoscopy has also been used to help distinguish between CDI colitis and other causes of diarrhea, but with limited success. The presence of a pseudomembrane on the colonic mucosa is pathognomonic for CDI and is manifested as an elevated white-yellow plaque composed of inflammatory cells, fibrin, and other cellular debris. Pseudomembranes, however, are only detected in 50% to 60% of patients with CDI,\(^{44}\) and false-negative rates for endoscopy can be as high as 25%.\(^{45}\) Lack of sensitivity, higher costs, patients’ discomfort, and risk of bowel perforation during the examination have made endoscopy a less appealing diagnostic tool.\(^{43}\)

**Infection Control and Prevention**

\textit{Clostridium difficile} is a challenge for infection control and prevention. Two main aspects must be considered: preventing the acquisition of \textit{C difficile} and stopping transmission of the organism and its spores to other hospitalized patients. \textit{Clostridium difficile} can spread by direct or indirect exposure to a patient or the patient’s environment. Early recognition of patients with suspected or diagnosed CDI is the primary step in prevention of spread. Subsequently, patients can be placed in contact precaution
isolation as recommended by the Hospital Infection Control Practice Advisory Panel of the Centers for Disease Control and Prevention.44 Strict adherence to contact precautions will have a marked effect on limiting the spread of infection and cross-contamination. Ideally, patients with CDI should be placed and kept in private rooms.

Incorporation of personal protective equipment consisting of a gown and gloves is critical in providing a barrier to prevent transmission of spores. Relaying a patient’s isolation status to all members of the health care team is important to accommodate the special needs of the patient.45 Prevention strategies apply to patient care equipment, instruments, and devices and the patient environment. Spores can exist for years on surfaces, leading to transmission throughout the health care environment.46 Strict environmental decontamination is key to any effective interventional strategy for interrupting the spread of this organism. Only chlorine-based disinfectants and high-concentration vaporized hydrogen peroxide are sporidial and should be used for surface disinfection of areas used for care of patients who have C difficile.45

Hand hygiene plays a critical role in the prevention and control of C difficile. Although alcohol hand gels are effective against vegetative clostridial cells, they are ineffective against the spores. In a recent study,17 30% of C difficile spores remained on the hands of health care workers after the use of 3 mL of an alcohol-based gel. Therefore, after removing their personal protective equipment, health care providers should wash their hands with soap and water to mechanically remove spores and interrupt the transmission of C difficile.

Because CDI can almost exclusively be linked to previous antibiotic use, judicious and appropriate use of antibiotics can play an important role in infection control and prevention.30 Both the level of risk associated

![Figure](image-url)
with a selective antibiotic and the number of prescribed days should be considered when evaluating the risk for CDI by a particular antibiotic. Prolonged, inappropriate use of broad-spectrum antibiotics is a critical determinant of CDI and should be avoided.\textsuperscript{46} The role of an antibiotic stewardship program is to optimize the use of the right drug, for the right purpose, and for the right duration to promote judicious use of antimicrobial agents.\textsuperscript{10}

**Medical Management**

The spectrum of CDI ranges from mild to complicated episodes, and further consideration determines whether or not it is a primary episode or a recurrence. Current treatment of CDI varies and is based on the severity of illness as well as the number of recurrences. Stopping use of all possible inciting antibiotics is recommended if warranted. If use of antibiotics must be continued to treat concurrent infections, an effort to avoid clindamycin, cephalosporins, and fluoroquinolones, as well as the drug that was used to promote CDI, is recommended. General medical treatment strategies have called for use of metronidazole or enteral vancomycin,\textsuperscript{26,47} for which 2 important considerations exist. One is that although metronidazole can be effectively delivered intravenously or orally, it will only reach a therapeutic concentration in the colon if the patient has diarrhea. The second is that vancomycin is effective only when delivered enterally (orally, enteric feeding tubes, or enema).

Treatment for CDI can be started before laboratory confirmation for patients with high pretest conditions suggestive of the infection. Metronidazole is typically recommended for mild to moderate cases of CDI at a dose of 500 mg orally 3 times per day for 10 to 14 days. However, in severe cases, vancomycin 125 mg orally 4 times per day for 10 to 14 days may be better than metronidazole.\textsuperscript{49} Patients with complicated disease, which includes patients with ileus or marked abdominal distention, should have their care escalated to include a combination of metronidazole 500 mg intravenously 3 times per day, vancomycin 125 mg orally 4 times per day, and vancomycin 500 mg in 500 mL of physiological saline as an enema 4 times per day (if ileus or abdominal distention is present).\textsuperscript{35,48} Additionally, surgical consultation is advised for patients with complicated CDI.

Fidaxomicin was recently approved by the Food and Drug Administration as an antibiotic for the treatment of CDI. Results of 2 randomized trials suggested that fidaxomicin was not less effective than vancomycin with respect to the clinical cure rate of CDI and was perhaps better than vancomycin with regards to disease recurrence.\textsuperscript{49} At this point, in part because of expense, fidaxomicin is not commonly used as a first-line therapy.

According to estimates, 20% to 30% of patients with CDI will have a recurrent episode after initial treatment, and approximately 50% of those patients will have multiple recurrences.\textsuperscript{50,51} For the first recurrence, the same regimen is recommended unless severity dictates a change from metronidazole to vancomycin. For the second and all subsequent recurrences, vancomycin is recommended in intermittent and pulsed doses. The pulsed dosing allows the clostridial spores to germinate, thus increasing susceptibility, because \textit{C difficile} organisms are susceptible to treatment only when in their full vegetative state. Furthermore, the repetitive cycle of antibiotic-free periods allows normal flora to reestablish themselves within the gastrointestinal tract, potentially reducing rates of recurrent CDI.\textsuperscript{50,51}

In patients with relapsing CDI, fecal microbiota transplant, the infusion of stool from a healthy donor into the intestines of a patient to restore normal flora, has been used as an alternative treatment.\textsuperscript{52} Gough et al\textsuperscript{53} reported that the effectiveness of this treatment varied by route of administration, volume of stool given, relation of the patient to the stool donor, and previous treatment. Overall, they reported CDI resolution with no adverse effects in 92% of patients who received a fecal microbiota transplant, suggesting that this strategy might be a possible approach for patients with refractory disease.\textsuperscript{53} Van Nood et al\textsuperscript{54} reported an 81% resolution of diarrhea associated with CDI after 1 duodenal infusion of donor feces in patients with recurrent CDI. After donor-feces infusion, patients had increased fecal bacterial diversity, similar to that of healthy donors. These therapies hold tremendous promise, particularly for patients with chronic, relapsing CDI.\textsuperscript{54} In addition, the use of probiotic agents as adjuncts in the treatment of recurrent CDI is being considered. Probiotics may be beneficial, but studies have been underpowered to show the benefits.
Surgical Management

Almost all patients with CDI respond to antibiotic therapy, but 3% to 10% progress to a complicated, fulminant state of systemic toxic effects and may require surgical intervention; only 0.17% to 3.5% of patients with CDI have surgical intervention. Although no clear indications for surgery exist, most health care providers advocate surgical intervention for patients with worsening clinical features, specifically peritonitis or any evidence of systemic shock. Total abdominal colectomy with end ileostomy has been considered the operation of choice and can marginally improve survival. Although the total abdominal colectomy with end ileostomy improves survival in patients with fulminant CDI, postoperative mortality rates remain dire: 35% to 80%. Additionally, laparotomy and subtotal or total abdominal colectomy can result in marked morbidity, with survivors often requiring permanent ileostomy. Olivas et al reported that 3 critical factors may be contributing to the unacceptably high postoperative mortality rates: surgical intervention is frequently delayed, approaching futility in context of the disease process; selection of patients is incorrect because of a lack of clearly defined guidelines; and the clinical course of CDI is difficult to predict. In addition to the problem of inappropriate selection of patients, surgeons, patients, and patients’ family members are reluctant to accept such an extensive, invasive, and morbid procedure early in the disease process when death is most avoidable. An alternative surgical strategy that is less invasive could improve patients’ acceptance of early surgical treatment and improve postoperative mortality rates.

One emerging option is laparoscopic creation of a double-barrel ileostomy for distal colonic washout. In a study reported in 2011, Neal et al sought to determine whether a minimally invasive, colon-preserving surgical approach could serve as an alternative treatment in severe CDI. All patients diagnosed with fulminant CDI (42 in all) at the University of Pittsburgh Medical Center or VA Pittsburgh Healthcare System, Pittsburgh, Pennsylvania, between June 2009 and January 2011 were treated with this novel approach. The surgical intervention involved the creation of a loop ileostomy, intraoperative colonic lavage with warmed polyethylene glycol 3350/electrolyte solution via the ileostomy, and postoperative antegrade instillation of vancomycin flushes via the ileostomy. The criterion for success was CDI resolution, and results were analyzed for historical comparison. The treatment strategy resulted in reduced mortality compared with that of the historical population (19% vs 50%; odds ratio, 0.24; \( P = 0.006 \)). Preservation of the colon was achieved in 39 of 42 patients (93%). The remaining 7% underwent a subsequent colectomy. Although the study was done at a single center and conclusions regarding broad application are limited, data suggest that in severe cases of CDI, a diverting loop ileostomy and colonic lavage are an alternative to total abdominal colectomy and result in reduced morbidity and preservation of the colon. Long-term outcomes and risk of recurrence remain to be assessed.

Conclusion

Clostridium difficile infections are the leading cause of health care–associated infectious diarrhea. The scope of the disease ranges from asymptomatic carriers to severe, or fulminant, cases in vulnerable patients with deadly results. Because of the marked morbidity and mortality rates associated with CDI, a high clinical suspicion is warranted with susceptible patients. Treatments based on severity and ranging from oral antibiotic regimens to drastic total abdominal colectomy should have clearly defined guidelines and be initiated quickly. Efforts to combat CDI should include early recognition, implementation of contact isolation precautions, proper cleansing and care of environmental factors to stop transmission, judicious hand hygiene, and focused antimicrobial stewardship programs. Earlier surgical consultation and management may improve outcomes in patients with complicated disease. Novel surgical approaches that do not involve resection of the colon may prove to be better than total abdominal colectomy. A multidisciplinary approach with the support of hospital leaders is needed to reduce the morbidity, mortality, and financial burden for patients and the health care system.

Financial Disclosures

None reported.

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References


**CCN Fast Facts**

**Clostridium difficile Infection: Clinical Challenges and Management Strategies**

**Facts**

Clostridium difficile has become the leading cause of nosocomial diarrhea in adults.

**Risk Factors**

- The most important risk factor for *C. difficile* infection (CDI) is recent administration of antibiotics. Antibiotics implicated most often are clindamycin, fluoroquinolones, cephalosporins, and β-lactams.
- Other risk factors are prolonged hospitalization, gastrointestinal surgery, inflammatory bowel disease, neoplastic diseases and chemotherapy, solid-organ or hematopoietic cell transplant, male sex, malnutrition, postpyloric tube feeding, and low serum albumin level.
- The use of proton pump inhibitors may be a risk factor; clinicians should strongly consider restricting this use.

**Clinical Manifestations**

- Patients with mild CDI have crampy abdominal pain with mild to moderate diarrhea only. Patients with moderate CDI have diarrhea and any signs or symptoms not indicative of severe CDI. Patients with severe CDI have white blood cell count >15,000/µL, serum level of albumin <3 g/L, and/or abdominal tenderness.
- Complicated CDI (fulminant colitis) is marked by severe abdominal pain, abdominal distention, worsening diarrhea, and admission to the intensive care unit, hypotension, altered mental status, or end organ failure.
- A lack of diarrhea in a patient with worsening abdominal distention and systemic illness is an ominous finding and is indicative of ileus and intestinal failure.
- A fever may indicate a more serious infection in older patients. Earlier signs and symptoms of CDI in elderly patients include acute confusion and altered mental status. Nonspecific indications may include lethargy, weakness, falls, anorexia, and loss of physical capacity.

**Diagnosis**

- Laboratory methods include toxigenic culture and cell cytotoxicity neutralization assay, enzyme immunoassay for toxin or common antigen, and real-time polymerase chain reaction.
- Many facilities use an enzyme-linked immunosorbent assay (ELISA). Although rapid and inexpensive, performance of immunoassays varies, and false-negative results are possible.
- Nucleic acid amplification (NAAT) is based on amplifying *C. difficile* DNA as a marker of CDI. Current NAAT methods include real-time polymerase chain reaction, DNA microarray, and loop-mediated isothermal amplification.
- No single test is significantly better than others. When sensitivity, specificity, and turnaround time are considered, we advocate cytotoxicity culture assay or NAAT.
- Abdominal computed tomography has emerged as a valuable diagnostic tool in detecting complicated CDI.
- Endoscopy has been used to distinguish between CDI colitis and other causes of diarrhea, but with limited success.

**Infection Control and Prevention**

- *C. difficile* can spread by direct or indirect exposure to a patient or the patient’s environment. Early recognition of patients with suspected or diagnosed CDI is key.
- Personal protective equipment consisting of a gown and gloves is critical to prevent transmission of spores.
- Although alcohol hand gels ineffective against the spores. After removing their personal protective equipment, health care providers should wash their hands with soap and water to remove spores and interrupt the transmission of *C. difficile*.

**Medical Management**

- Stop all possible inciting antibiotics.
- Metronidazole is typically recommended for mild to moderate CDI at a dose of 500 mg orally 3 times/day for 10 to 14 days.
- About 20% to 30% of patients with CDI will have a recurrent episode.
- Fecal microbiota transplant, the infusion of stool from a healthy donor into the intestines of a patient to restore normal flora, has been used as an alternative treatment.

**Surgical Management**

- Almost all patients with CDI respond to antibiotic therapy, but 3% to 10% progress to a complicated, fulminant state of systemic toxic effects and may require surgical intervention.
- Most health care providers advocate surgical intervention for patients with worsening clinical features, specifically peritonitis or any evidence of systemic shock. Total abdominal colectomy with end ileostomy has been considered the operation of choice and can marginally improve survival.
- One emerging option is laparoscopic creation of a double-barrel ileostomy for distal colonic washout. Long-term outcomes and risk of recurrence remain to be assessed.