Clostridium difficile Infection Is on the Rise

The emergence of an epidemic strain makes prevention and early diagnosis critical.

In recent years, both the incidence and severity of Clostridium difficile infection have increased, accompanied by an associated rise in mortality. This has largely been attributed to the emergence of a treatment-resistant, highly virulent strain that’s capable of causing illnesses ranging from mild diarrhea to colitis and sepsis. Hospitalized patients are considered to be at especially high risk for infection, and among inpatient cases, antibiotic treatment has been an almost universal factor; however, in the past decade C. difficile has appeared with increased frequency in populations previously considered to be at low risk, including peripartum women and healthy people in the community.

In terms of cost and lost productivity, this pathogen is a major burden to the health care system, comparable to that associated with methicillin-resistant Staphylococcus aureus. A 2008 report from the Association for Professionals in Infection Control and Epidemiology (APIC) stated that C. difficile infection is “associated with an increased length of stay in health-care facilities by 2.6 to 4.5 days and attributable costs for inpatient care have been estimated to be $2,500 to $3,500 per episode, excluding costs associated with surgical interventions. In the United States, the economic consequences related to management of this infection exceed $3.2 billion annually.”

EMERGENCE OF AN EPIDEMIC STRAIN

C. difficile is an anaerobic, spore-forming bacterial organism that is found mainly in the soil but also occurs in the natural gut flora of a small percentage of the population. First detected in the fecal material of healthy neonates in 1935, it was believed to be non-pathogenic until 1978, when it was demonstrated to be a major cause of antibiotic-associated diarrhea. According to the Centers for Disease Control and Prevention (CDC), C. difficile currently accounts for 15% to 25% of all such episodes.

In recent years, the epidemiology of C. difficile has changed dramatically. Since 2000, hospitals have seen outbreaks characterized by more severe disease and greater rates of complications. For example, data gleaned from death certificates indicate that the rate of mortality caused by C. difficile has increased from 5.7 per million in 1999 to 23.7 per million in 2004. A fact sheet issued by the CDC in 2012 linked the pathogen to 14,000 deaths per year; however, the actual figure is likely much higher, as death certificates do not necessarily list C. difficile when patients die from a complication like sepsis. The CDC’s Physicians’ Handbook on Medical Certification of Death states that, “for statistical and research purposes, it is important that the causes of death and, in particular, the underlying cause of death be reported as specifically and as precisely as possible.”

The current epidemic strain of C. difficile is more virulent and more resistant to the antibiotics traditionally used in its treatment. It has been identified variously as type BI, North American pulsed-field type 1 (NAP1), and polymerase chain reaction ribotype 027 (BI/NAP1/027), depending on the type of analysis used to identify it. BI/NAP1/027 is believed to be more pathogenic because of its high production of both an enterotoxin (toxin A) and a cytotoxin (toxin B) that cause the diarrhea and inflammation seen in infected patients. Another toxin produced by the BI/NAP1/027 strain, known as binary toxin, has also been identified and has been linked to higher fatality rates, although its role is not completely understood.

Researchers have recently finished sequencing the genomes of 150 C. difficile strains isolated from hospital patients between 1985 and 2010, allowing them to determine the evolutionary history of today’s epidemic strain and the subsequent pattern of global spread. In North America, two genetically distinct variants of the toxigenic BI/NAP1/027 strain, the first appearing in Pittsburgh around the year 2001, independently acquired resistance to fluoroquinolone...
antibiotics (a class that includes ciprofloxacin [Cipro and others] and levofloxacin [Levaquin and others]) at about the same time. Both quickly spread across the United States and abroad. The fluoroquinolone resistance seems to have been a critical factor in the worldwide spread of the pathogen and its persistence in hospitals, as these medications were prescribed widely during the 1990s. The newer strains would have had an advantage over susceptible strains, allowing them to spread unchecked.

**Risk factors and mode of transmission.** Risk factors for individual patients include antibiotic therapy, use of proton pump inhibitors, recent gastrointestinal surgery, immunosuppressed status because of disease or chemotherapy, organ transplantation, HIV infection, advanced age, and prolonged length of stay in a health care facility. The rate of *C. difficile* acquisition (that is, colonization or infection) rises to 50% among those with hospital stays longer than four weeks, compared with 13% in patients with stays up to two weeks. Although the elderly are still disproportionately affected, the CDC reports that *C. difficile*-related disease is now being diagnosed in people previously considered to be at low risk, including peripartum women, children, and otherwise healthy adults.

*C. difficile* is shed in fecal matter and the spores can persist for long periods on dry surfaces, even after terminal cleaning that takes place after the patient has died or been discharged) of a patient’s room. Spores are transferred to patients mainly via the hands of health care providers who have touched a contaminated surface or device. When a patient ingests them, the spores pass through the stomach and into the small intestine, where they germinate into their vegetative form. Colonized patients who aren’t immunosuppressed or on antibiotic therapy may remain in an asymptomatic carrier state. However, where antibiotics or other factors such as surgery or proton pump inhibitors have disrupted the natural flora of the patient’s colon, *C. difficile* is likely to proliferate. This disruption is most likely caused by broad-spectrum antibiotics, especially clindamycin (Cleocin and others); antibiotics less likely to cause *C. difficile* infections include the fluoroquinolones, aminoglycosides, antipseudomonal penicillins, metronidazole (Flagyl and others), rifampin (Rifadin), and vancomycin. However, there is ongoing controversy about which antibiotic medications are to be blamed for *C. difficile* infections. The evidence remains circumstantial: does the problem result from certain antibiotics being used routinely on geriatric units or from poor terminal cleaning on units where *C. difficile* rates are already high and the spores continually contaminate the environment? The risk of antibiotic-associated diarrhea more than doubles when antibiotic therapy exceeds three days.

Environmental contamination with *C. difficile* is a primary risk factor for a hospital-wide outbreak. It’s important to note that asymptomatic patients colonized with *C. difficile* can still contaminate the environment and the amount of spores present in the environment is directly proportional to the number of patients with *C. difficile*. Patients who share a room with a *C. difficile*-positive patient tend to acquire the organism more quickly (3.2 days) than those who don’t share a room with such patients (18.9 days).

**Symptoms of infection** may begin during antibiotic therapy or several weeks after the antibiotic is stopped. Patients first present with watery diarrhea, sometimes accompanied by cramping. More severe cases are thought to result when the toxins produced by the BI/NAP1/027 strain damage the colonic mucosa, causing an inflamed and nodular colon. *C. difficile* bacteria can normally be present in the intestines, only proliferating when a course of antibiotics removes the bacteria with which they compete. Photo by David M. Martin, MD / Science Photo Library.
pus, contributing to a buildup in the colon of cellular debris (see Figure 1). This condition can manifest as severe watery diarrhea (as often as 15 times a day), blood or pus in the stool, abdominal tenderness, nausea, loss of appetite, and fever higher than 101°F (38°C). In fulminant or severe complicated cases, inflammatory lesions and pseudomembrane formation in the colon can lead to bowel perforation, sepsis, shock, and death. 

Patient isolation should be maintained if fulminant C. difficile is suspected, as diarrhea may be absent and stool cytology negative for C. difficile toxin, but endoscopic results may reveal extensive pseudomembrane formation. 

Toxic megacolon is a life-threatening complication of C. difficile–related colitis that is relatively rare, with a reported incidence of 0.4% to 3% of all cases. It can be difficult to diagnose toxic megacolon because of its atypical presentation of acute abdomen in immunocompromised or older adult patients; therefore, presumptive diagnosis of C. difficile is warranted until diagnostic tests are conclusive. Patients with toxic megacolon usually present with significant abdominal distention due to dilation of the colon; other symptoms may include profuse diarrhea, high fever, severe abdominal pain, oliguria, tachypnea, and leukocytosis. Surgical intervention is often required to manage perforation, progressive swelling of the colon, or uncontrolled bleeding. It should be noted that colectomy is a radical and life-changing treatment, resulting in significant morbidity and prolonged hospitalization. 

**Diagnosis.** C. difficile should be the first organism suspected when a hospitalized or recently discharged patient develops diarrhea. Testing remains a challenge, however, because there’s currently no single laboratory test that’s rapid, widely available, and sufficiently sensitive and specific. Tests for C. difficile include stool culture, various tissue and immunoassays, antibody-based tests, and polymerase chain reaction. The stool culture test for C. difficile has high sensitivity but is labor intensive and time consuming, requiring special techniques for culturing anaerobic organisms (results are not available for 48 to 96 hours). Unfortunately, the test also isn’t very specific, resulting in false-positive results wherever nontoxicogenic strains of C. difficile are present. This problem can be overcome by testing isolates with an immunoassay designed to detect toxin production, a procedure known as toxigenic culture. While toxigenic culture is too slow to be clinically useful (it takes 4 to 7 days to obtain results), the high sensitivity and specificity of this test make it the gold standard against which other test modalities should be compared in clinical trials.

Until an ideal test can be developed, the Society for Healthcare Epidemiology of America (SHEA) and the Infectious Diseases Society of America (IDSA) have issued an interim recommendation that a two-step testing process be used to compensate for the low sensitivity of toxin testing alone:

- an initial screen of stool samples using a test that identifies the presence of glutamate dehydrogenase, an antigen common to both toxigenic and nontoxicogenic strains of C. difficile
- a follow-up to positive screening results with testing that identifies the presence of a C. difficile toxin, using either a cytotoxicity assay or polymerase chain reaction

When a positive cytotoxicity assay is accompanied by worsening symptoms, a computed tomographic scan may be used to confirm a diagnosis of pseudomembranous colitis or toxic megacolon. Endoscopy may also be used when pseudomembranous colitis is suspected, but it is used less often because of the risk of bowel perforation. Even when laboratory tests are negative or haven’t been performed, SHEA guidelines state that C. difficile–associated disease can be diagnosed on the basis of a positive clinical test for pseudomembranous colitis alone when diarrhea is present.

It should be noted that the routine testing of neonates is not advised, as children younger than one year have high rates of asymptomatic colonization (37% before one month, 30% from one to six months, and 14% from six to 12 months). Testing is inconclusive for children between the ages of one and two years, and other causes of disease should be sought when a child presents with diarrhea—although children older than two years have rates of C. difficile colonization similar to those seen in adults and a positive test indicates probable infection.

**TREATMENT AND PREVENTION**

If C. difficile infection is confirmed or strongly suspected, the patient’s existing antibiotic treatment should be stopped unless serious systemic infection, such as sepsis, pneumonia, or bacterial meningitis, prevents it. According to the CDC, C. difficile symptoms will resolve in about 20% of patients two to three days after discontinuation of antibiotics. Most patients, however, will require treatment with metronidazole, vancomycin, or fidaxomicin (Dificid), a recently approved narrow-spectrum antibiotic developed specifically to treat C. difficile infection. Research suggests that BI/NAP1/027 may not respond as readily to metronidazole as nontoxicogenic strains do, although there is no laboratory evidence of metronidazole resistance. However, to reduce selective pressure for vancomycin resistance, the most recent
SHEA–IDSA treatment guidelines state that metronidazole is the drug of choice for mild to moderate symptoms (the usual dosage for adults is 500 mg by mouth, three times a day for 10 to 14 days). In recurring episodes, or in initial episodes of very severe infection, vancomycin is the preferred drug (125 mg by mouth, four times a day for 10 to 14 days). Oral vancomycin is not metabolized by the liver but is excreted in the stool unchanged, meaning that it achieves high levels in the colon, which is ideal for *C. difficile* treatment. Intravenous vancomycin is not effective, however, since it does not reach high concentrations in the colon.

After treatment, reinfection is common. Studies have shown reinfection rates of 5% to 50%, but 20% is typical. Some patients have a series of relapses, extending the illness for many weeks. Fidaxomicin, the first new antibiotic to be approved for *C. difficile* infection in 30 years, appears to reduce the rate of recurrence of non–BI/NAP1/027 *C. difficile* strains, although its high cost has limited its use in hospitals. In clinical trials, fidaxomicin demonstrated selective eradication of *C. difficile* with minimal disruption to the normal, healthy intestinal flora. It should be considered for patients with recurrent *C. difficile* infection who have previously been treated with vancomycin or metronidazole and in whom a non–BI/NAP1/027 strain has been isolated; it may also be considered for recurrent infection where strain typing is not available. The recommended adult dosage of fidaxomicin is 200 mg by mouth, twice per day for 10 days; no clinical trials have been conducted in children.

For patients who develop pseudomembranous colitis or toxic megacolon, total or partial colectomy may be the only option. Mortality from fulminant *C. difficile* infection remains high despite surgical intervention. A 2007 Canadian study found a 34% mortality rate in patients with colectomy; for those who didn’t have the surgery, the rate was greater than 50%. The latest research, published in the January 31, 2013, issue of the *New England Journal of Medicine*, demonstrates that fecal microbiota transplantation reestablishes a balance of healthy intestinal flora and is more than 90% effective in the most recalcitrant of *C. difficile* cases. The procedure involves one or more infusions of fecal bacterial flora obtained from healthy donor stool, suspended in sterile saline, filtered to remove large particulate matter, and administered by enema, colonoscope, or nasogastric tube. Treatment recommendations for *C. difficile* infection in children are based on adult protocols and emphasize supportive care, as children may require aggressive IV hydration. While vancomycin is the only antibiotic approved by the Food and Drug Administration for treatment of the pediatric population, the Committee on Infectious Diseases of the American Academy of Pediatrics recommends that it not be used because of its selective pressure on vancomycin-resistant *Enterococcus*. Oral metronidazole is considered the drug of choice for children, although no clinical trials specific to pediatric populations have been conducted.  

**Prevention.** Antibiotic stewardship programs that monitor the careful use of antimicrobials can aid in controlling and preventing the spread of *C. difficile*, and several studies support the use of narrow-spectrum antibiotics, wherever possible, in reducing its incidence. If possible, patients with *C. difficile* infections should be kept in single rooms or in shared rooms with other positive patients, as the CDC emphasizes isolation precautions for preventing transmission in hospitals.

**Mortality from fulminant *C. difficile* remains high despite surgical intervention.**

First and foremost, the SHEA–IDSA guidelines stress the importance of contact precautions and good hand hygiene. Preventing cross-contamination by strictly adhering to handwashing protocol and maintaining contact isolation with the correct donning and removal of gloves and gowns remain the cornerstones for preventing the transmission of *C. difficile* from health care workers to patients. Laboratory research has demonstrated that alcohol-based hand sanitizers do not inactivate the spores of *C. difficile*, yet hospitals where alcohol rubs are the primary means of hand hygiene have not reported increases in the incidence of *C. difficile*-associated disease. In theory, there’s an advantage to using running water to physically remove spores and wash them down the drain; therefore, handwashing with soap and water should be considered after removing gloves in the setting of a *C. difficile* outbreak.

Environmental cleaning and disinfection strategies are important in all health care settings, not only in hospitals and long-term care facilities. Disinfection strategies are crucial in controlling *C. difficile* in group homes, psychiatric institutions, and any other setting where the bacteria may spread. The use of dedicated equipment (medical equipment that doesn’t leave the room after making contact with the patient or with anything in the environment, not only with feces) and the replacement of reusable equipment with disposables—or a combination of these strategies—has the potential to reduce *C. difficile* incidence.
vitro studies have demonstrated the efficacy of a wide variety of disinfectants against *C. difficile*, but there isn’t a great deal of data on their effect in the health care environment. Disinfectants containing sodium hypochlorite (bleach) can kill bacterial spores and therefore have been recommended for use in cleaning patient rooms and surfaces, especially in terminal cleaning. Since 2009, the U.S. Environmental Protection Agency has approved several disinfectants that have demonstrated sporidical action against *C. difficile*, and these products are worth consideration. Some of these solutions use sodium hypochlorite as the active sporidical ingredient, while others use peracetic acid, which offers the advantage of not bleaching fabric colors.40 For environmental cleaning recommendations and basic prevention strategies, see www.cdc.gov/hai/organisms/cdiff/Cdiff_settings.html.

Research indicates that suboptimal housekeeping practices, rather than a failure of any specific disinfectant, are to blame when environmental contamination persists after terminal cleaning of a patient’s room.41 A 21-month prospective intervention study at a Cleveland, Ohio, hospital demonstrated the efficacy of forming a dedicated daily disinfection team and implementing a standardized process for clearing rooms of *C. difficile* spores.42

The use of probiotics to prevent antibiotic-related diarrhea has been somewhat controversial and not well understood. It has been proposed that probiotics—a dietary supplement of live bacteria or yeast—may help to maintain the balance of healthy gut flora by competitively inhibiting the overgrowth of pathogens.43

A recent meta-analysis of 20 clinical trials with more than 3,800 participants found that probiotics were associated with a 66% reduction in the incidence of *C. difficile*–associated diarrhea.44 Yet it can be difficult to evaluate and apply this research because the effects of a specific probiotic strain of bacteria or yeast cannot be extrapolated to other strains. Additionally, many probiotic strains are packaged and sold as supplements with few controls on labeling and quality, rather than in a form that health care organizations can easily use.

**NURSING CONSIDERATIONS**

As frontline caregivers, nurses must take responsibility for early recognition of the signs and symptoms indicative of *C. difficile* infection including, according to the APIC, all cases of diarrhea of unknown origin in all patients.2 The takeaway message for nurses is that they must act quickly and should follow their organization’s protocols for initiating contact precautions as soon as diarrhea manifests—even before testing occurs—to reduce the spread of spores to environmental surfaces. In addition to the use of personal protective equipment (gloves, gowns) and dedicated patient care equipment that doesn’t leave the room, the APIC advises placing all patients with diarrhea in isolation until *C. difficile* is ruled out, as opposed to waiting for positive test results before initiating isolation.2

Ideally, patients suspected of or confirmed as having *C. difficile* infection should be assigned to a private room with toilet facilities en suite. When the availability of private rooms is limited, nursing staff or infection preventionists should request preferential room assignments for patients with bowel incontinence.2 In other cases, nurses may need to work closely with the infection control team to determine the best patient placement options (for example, “co-horting” or selecting a suitable roommate). Isolation precautions may be discontinued once *C. difficile* infection has been ruled out as a cause of diarrhea. For confirmed cases of infection, precautions may be discontinued when diarrhea resolves and laboratory tests are negative.2

In addition to monitoring vital signs and hydration status in patients with *C. difficile* infection, nursing care should focus on maintaining skin integrity and promoting comfort. Abdominal tenderness, pain, cramping, skin irritation, and isolation measures can all contribute to a patient’s misery. Numerous liquid bowel movements and friction from frequent cleaning can cause skin irritation that contributes to perineal dermatitis—nursing staff should be vigilant about preventing this complication.

While mandated isolation may lead to emotional distress in some patients, it is still necessary to ensure isolation in appropriate circumstances. Nursing studies on the subject have been limited but suggest that patient satisfaction can be enhanced by providing individualized information about treatment and the duration of the isolation, maintaining excellent staff communication, promoting the patient’s sense of control, and ensuring access to telephone and television.43 Nurses should also be involved in patient and family education about hygiene measures that prevent reoccurrence, particularly handwashing.

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Irena L. Kenneley is a clinical nurse specialist and an assistant professor at the Frances Payne Bolton School of Nursing at Case Western Reserve University in Cleveland, Ohio. Contact author: irena.kenneley@case.edu. The author has disclosed no potential conflicts of interest, financial or otherwise.
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