Clostridium difficile Infection Is on the Rise

In recent years, both the incidence and severity of *Clostridium difficile* infection have increased, accompanied by an associated rise in mortality.[1] This has largely been attributed to the emergence of a treatment-resistant, highly virulent strain, which is capable of causing illnesses that range from mild diarrhea to colitis and sepsis.[1] Transmission among hospitalized patients is especially high, and although antibiotic treatment was at one time an almost universal factor among inpatient cases, *C. difficile* is now showing up in populations previously considered to be at low risk. [1, 2]

In terms of cost and productivity, this pathogen is a major burden to the healthcare system, comparable to methicillin-resistant *Staphylococcus aureus* (MRSA). [2] A report published by the Association for Professionals in Infection Control and Epidemiology *(*APIC*)* states that *C. difficile* infection is "associated with an increased length of stay in healthcare 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."[2]

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 nonpathogenic until 1978, when it was demonstrated to be a major cause of antibiotic-associated diarrhea (AAD).[3] According to the Centers for Disease Control (CDC), it currently accounts for 15 to 25 percent of all AAD episodes.[4]

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 indicates that mortality rates due to *C. difficile* have increased from 5.7 per million in 1999 to 23.7 per million in 2004.[5] A fact sheet issued by the CDC in 2012 linked the pathogen to 14,000 deaths per year[6], yet 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, in its *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."[7] With this in mind, in cases of *C. difficile*-related disease, a death certificate that lists sepsis as the "immediate cause" of death on Line (a) might list *C. difficile* on Line (b) or Line (c) as "the disease, injury, or complication, if any, that gave rise to the immediate cause of death.")

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), or PCR Ribotype 027, depending on the type of analysis used to identify it. BI/NAP1/027 is believed to more pathogenic due to its high production of both an enterotoxin (toxin A) and a cytotoxin (toxin B), which cause

the diarrhea and inflammation seen in infected patients. Another toxin, known as binary toxin, has also been identified in the BI/NAP1/027 strain and has been linked to higher fatality rates, although its role is not completely understood.[8]

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. They calculated that it first appeared in Pittsburgh around the year 2001 and quickly spread across the U.S., and that another toxigenic strain evolved independently elsewhere in the U.S. around the same time. [9] Both of these strains acquired a genetic mutation that confers resistance to fluoroquinolone antibiotics, a class that includes Ciprofloxacin and Levaquin. This resistance seems to have been a critical factor in the worldwide spread of the pathogen and its persistence in hospitals, as fluoroquinolones 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 (PPIs), recent gastrointestinal surgery, immunosuppressed status due to disease or chemotherapy, transplant, HIV infection, advanced age, and prolonged length of stay in a healthcare facility. The rate of *C. difficile* acquisition rises to 50 percent in hospital stays longer than four weeks, as compared to 13 percent in patients with up to two weeks.[10] Although the elderly are still disproportionately affected, the CDC reports that *C. difficile*-related disease is now being diagnosed in people traditionally considered to be at low risk, including peri-partum women, children, and otherwise healthy people within the community.[4]

C. difficile is shed in fecal matter and the spores can persist for long periods of time on dry surfaces, even after terminal cleaning of a patient room (see Prevention section, below). Spores are transferred to patients mainly via the hands of healthcare providers who have touched a contaminated surface or device.[4] When a patient ingests them orally, the spores pass through the stomach and into the small intestine, where they germinate into their vegetative form. Colonized patients who are not immunosuppressed or on antibiotic therapy may develop and remain in an asymptomatic carrier state. However, where antibiotics have disrupted the natural flora of the patient's colon, *C. difficile* is likely to proliferate, resulting in clinical manifestations like diarrhea.[11] This disruption is most likely to be caused by broad-spectrum antibiotics like the fluoroquinolones, cephalosporins, carbapenems, and clindamycin while antibiotics with fewer propensities to cause *C. difficile* infections include the aminoglycosides, antipseudomonals, metronidazole, and vancomycin.[12] The risk of antibiotic-associated diarrhea more than doubles when antibiotic therapy exceeds three days.[13]

Environmental contamination with *C. difficile* is a primary risk factor for a hospital-wide outbreak. A CDC report states that, "The degree to which the environment becomes contaminated with *C. difficile* spores is proportional to the number of patients with *C. difficile*-associated diarrhea, although asymptomatic, colonized patients may also serve as a

source of contamination."[14] Patients who share a room with a *C. difficile*-positive patient tend to acquire the organism more quickly, after an estimated hospital stay of 3.2 days, compared with a stay of 18.9 days for other patients.[15]

Symptoms

Symptoms of *C. difficile* 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 through a profound inflammatory response, which may be evidenced clinically by an elevated WBC count.[16, 17] These cases often progress into a condition known as pseudomembranous colitis (PMC), in which the colon develops ulcerations that produce pus, contributing to a build-up of cellular debris within the colon. PMC can manifest as severe watery diarrhea (up to 15 times a day), blood or pus in the stool, abdominal tenderness, nausea, loss of appetite, and fever of over 101ºF. The resulting dehydration can lead to hypokalemia, hypoproteinemia, or renal failure and, in extreme cases, perforation may occur, leading to peritonitis or sepsis.[17]

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 percent of all cases.[18, 19] 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.[20] 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.[21]

Diagnosis

C. difficile should be the first organism suspected when a hospitalized or recently discharged patient develops diarrhea. Testing remains a challenge, however, as there is currently no single laboratory test that is 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 (PCR).

Stool culture for *C. difficile* has high sensitivity, however the test is labor intensive and time consuming, requiring special techniques for culturing anaerobic organisms (results are not available for 48 to 96 hours).[4] The test is unfortunately not very specific, resulting in false-positive results wherever non-toxigenic 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.[4] While toxigenic culture is too slow to be clinically useful (results in 4 to 7 days), the high sensitivity and specificity of this test make it the gold-standard against which other test modalities should be compared in clinical trials.[4]

Until an ideal test can be developed, the Society for Healthcare Epidemiology of America (SHEA) and the Infectious Diseases Society of America (IDSA) recommend a two-step testing process, which can help to overcome the low sensitivity of toxin testing alone:[22]

- An initial screen of stool samples using a test that identifies the presence of glutamate dehydrogenase (GDH), which is an antigen common to all strains of *C. difficile*, whether toxigenic or nontoxigenic.
- A follow-up to positive screening results with testing that identifies the presence of a *C. diff* toxin (this can be either a cytotoxicity assay or PCR).

When a positive cytotoxicity assay is accompanied by worsening symptoms, CT scan may be used to confirm a diagnosis of PMC or toxic megacolon. Endoscopy may also be used when PMC is suspected, but is used less often due to risk of perforation.[23] Even when lab tests are negative or have not been performed, SHEA guidelines state that *C. difficile*-associated disease can be diagnosed on the basis of a positive clinical test for PMC alone, when diarrhea is present.[24]

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 1 month, 30% from 1 to 6 months, and 14% from 6 to 12 months).[25] 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 by the age of three years, children have rates of colonization similar to those seen in adults and a positive test indicates probable infection.[25, 2]

Nursing Considerations

As frontline caregivers, nurses must take responsibility for the early recognition of patients who may have *C. difficile* infection – according to APIC, this includes all patients with diarrhea of unknown origin.[2] The takeaway message for nurses is that they must take action quickly, and should follow their organization's protocols for initiating Contact Precautions as soon as diarrhea manifests (i.e. even before testing occurs), in order 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 does not leave the room, 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 dedicated toileting facilities. When private rooms are limited, nursing staff or infection preventionists should request their preferential assignment to patients who are incontinent of stool.[2, 15, 22] In other cases, nurses may need to work closely with the infection control team to determine the best patient placement options (e.g. cohorting 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 the patient has gone at least 48 hours without symptoms of diarrhea. [2, 15, 22]

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.[26] 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.[27] Nursing studies showing that mandated isolation leads to emotional distress in patients have been small, but suggest that patient satisfaction can be enhanced by measures that include 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.[28, 29] Nurses should also be involved in patient and family education about hygiene measures that prevent reoccurrence, particularly handwashing.[30]

Treatment

When *C. difficile* infection is confirmed or strongly suspected, existing antibiotic treatment should be stopped wherever possible. According to the CDC, *C. difficile* symptoms will resolve in about 20 percent of patients within three days of this discontinuation.[4] Most patients, however, will require treatment with metronidazole, vancomycin, or fidaxomicin, a recently approved, narrow-spectrum antibiotic developed specifically for *C. difficile* infection. Research suggests that BI/NAP1/027 may not respond as well to metronidazole as non-toxigenic strains, although there is no laboratory evidence of metronidazole resistance.[31] 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 is 500 mg orally t.i.d for 10 to 14 days). In recurring episodes, or in initial episodes of very severe infection, vancomycin is the preferred drug (125 mg orally q.i.d. for 10-14 days).[22] Oral vancomycin is not metabolized by the liver, but is excreted in the stool unchanged – meaning it achieves high levels in the colon, which is ideal for *C. difficile* treatment.[32,33] Intravenous vancomycin is not effective, however, since it does not reach high concentrations in the colon.[27,28]

After treatment, reinfection is common and relapses occur in an estimated 20 to 25 percent of patients.[34] 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 have a reduced rate of *C. difficile* recurrence,[35] although its high cost has limited its use among hospitals. In clinical trials, fidaxomicin (trade name Dificid) demonstrated selective eradication of *C. difficile* with minimal disruption to the normal, healthy intestinal flora.[36] It should be considered for patients with recurrent *C. difficile* infection who have previously been treated with vancomycin or metronidazole and in which a non-NAP1/BI/027 strain has been isolated (it may also be considered for recurrent infection where strain typing is not available).[37] The recommended adult dosage of fidaxomicin is 200 mg orally, twice daily for 10 days; no clinical trials have been conducted in children.[38]

For patients who develop PMC or toxic megacolon, total or partial colectomy may be the only option. Mortality from fulminant *C. difficile* infection remains high despite surgical intervention.[20,39]

The latest research, published in the January 2013 issue of the New England Journal of Medicine, demonstrates that fecal microbiota transplant (FMT) is more than 90 percent effective in the most recalcitrant cases of *C. difficile* infection.[40] FMT re-establishes a balance of healthy intestinal flora, resulting in a cure.[41] The procedure involves one or more infusions of fecal bacterial flora, which has been obtained from donor stool, suspended in sterile saline, and filtered to remove large particulate matter. It is then administered through enema, colonoscope, or nasogastric tube.[36]

Treatment recommendations for *C. difficile* infection in children are based on adult protocols, with an emphasis on supportive care as children may require aggressive IV hydration. According to the American Academy of Pediatrics, oral metronidazole is considered the drug of choice for children, although no clinical trials specific to pediatric populations have been conducted.[42]

Prevention

Nurses play a critical role in preventing *C. difficile* transmission. Spores are transmitted from patient to patient via improperly sanitized hands and also through the use of contaminated shared equipment. Meticulous hand hygiene—using soap and water—and strict adherence to isolation protocols are therefore the foundation for effective *C. difficile* transmission prevention. Handwashing and strict isolation should be observed when caring for patients even after resolution of CDI symptoms, as they are still capable of shedding spores long after clinical symptoms subside. It is important for nurses to communicate with their institutional epidemiology staff to determine appropriate duration of isolation for the patient with a current or prior history of CDI on a case-by-case basis. Also, nurses must be careful to clean equipment that is shared between patients, and partner with housekeeping services to effectively clean areas of potential contamination. Typically, regular active cleansing ingredients in hospital disinfectants are quaternary ammonium compounds and do not kill spores. The Centers for Disease Control (CDC) currently recommends using hypochlorite-based germicides, such as bleach-based solutions, for cleaning *C. difficile*-contaminated environmental surfaces and equipment.

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.[43] If possible, patients with *C. difficile* infections should be kept in single rooms or cohorted with other positive patients, as the CDC emphasizes isolation precautions for preventing transmission in hospitals.[4] (A SHEA position paper regarding *C. difficile* infection in the elderly states that housing infected residents of long-term care facilities in private rooms is of unproven value, but may be useful in cases of fecal incontinence.)[44]

Yet first and foremost, the SHEA/IDSA guidelines stress the importance of contact precautions along with good hand hygiene. Preventing cross-contamination by adhering to rigid hand washing protocols and maintaining contact isolation with the correct donning and removal of gloves and gowns remains the cornerstone for preventing the transmission of *C. difficile* from healthcare workers to patients.[22]

Laboratory research has demonstrated that alcohol-based hand sanitizers do not inactivate the spores of *C. difficile*, yet hospitals using alcohol rubs as the primary means of hand hygiene have not reported increases in *C. difficile* instances.[45] Still, because a theoretical advantage exists in using running water to physically remove spores and wash them down the drain, 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 hospitals and long-term care facilities. Dedicated equipment (medical equipment that does not leave the room after making contact with the patient or anything in the environment – not just with feces) and/or replacing reusable equipment with disposables can potentially reduce *C. difficile* incidence.[22] Although all routine hospital disinfectants can destroy the living bacteria, only those containing sodium hypochlorite (bleach) can kill the spores, and these should be used for cleaning patient rooms and surfaces.[22] Since 2009, the U.S. Environmental Protection Agency (EPA) has approved several disinfectants with claims of sporicidal action against *C. difficile*, and these products are worth consideration. Some of these solutions use sodium hypochlorite as the active sporicidal ingredient, while others use peracetic acid, which offers the advantage of not bleaching fabric colors.[22]

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 room.[46] A 21-month prospective intervention study at a Cleveland hospital demonstrated the efficacy of forming a dedicated daily disinfection team and implementing a standardized process for clearing rooms of *C. difficile* spores.[47]

The use of probiotics to prevent antibiotic-related diarrhea has been somewhat controversial and not well understood. It has been proposed that probiotics – defined as living organisms that confer a health benefit on their host – may help to maintain the balance of healthy gut flora by competitively inhibiting the overgrowth of pathogens.[48] A recent meta-analysis of 20 clinical trials including 3800 participants found that probiotics were associated with a 66% reduction in the incidence of *Clostridium difficile*–associated diarrhea.[49] Yet it can be difficult to evaluate and apply this research, because the effects of a probiotic are specific to that strain of bacteria or yeast and 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 is easily used by health care organizations.[46]

For a copy of the complete SHEA/IDSA guidelines, visit http://www.cdc.gov/HAI/pdfs/cdiff/Cohen-IDSA-SHEA-CDI-guidelines-2010.pdf. For environmental cleaning recommendations and basic prevention strategies, see http://www.cdc.gov/hai/organisms/cdiff/Cdiff_settings.html.

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